

**SYNTHESIS AND REACTIONS OF LITHIATED MONOCYCLIC AZOLES
CONTAINING TWO OR MORE HETERO-ATOMS
PART IV: IMIDAZOLES[†]**

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***Abstract** - The metallation and halogen $\rightarrow$ metal exchange reactions of imidazoles (1,3-diazoles) and the reactions of the resulting organometallic derivatives, particularly lithiated derivatives, are reviewed comprehensively.*

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[†] This series of reviews is dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

I INTRODUCTION

A general introduction to this series of reviews was given in Part I.² Parts I-III cover the literature through June 1993 whilst this review covers the literature through December 1993.

The imidazole (1,3-diazole) ring system has been studied more than any of the other azole systems covered in this series presumably because many of its derivatives possess biological activity.³⁻⁹ The present review is comprehensive with respect to the discussion but omits in its Tables the examples presented in the Tables of our earlier review⁸ on this topic. A comparison between these two reviews shows that there has been considerable recent interest in metallated imidazoles. We have made no attempt to cover the metallation reactions of imidazolines. However, noteworthy are the additions of methyl- and phenyllithium to the $-C\equiv N$ - and $-C\equiv N^+(O^-)$ -bonds in 2*H*-imidazole 1-oxides, 4*H*-imidazole 1- and 3-oxides and 1,3-dioxides, and analogous imidazoline oxides.¹⁰

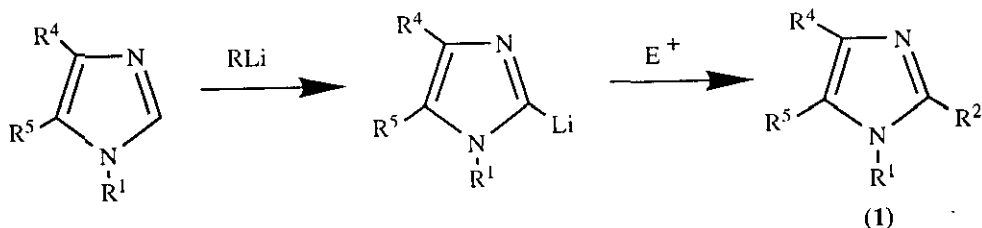
II MONOMETALLATION IN THE RING

Metallation of a ring C-atom, with the reactivity order C-2 > C-5 > C-4, is observed in imidazoles bearing suitable *N*-1 substituents, otherwise *N*-lithiated derivatives are formed.¹¹⁻¹⁶ Addition of an alkylating agent to the *N*-1 lithiated derivatives of 4(5)-substituted imidazoles leads to a mixture of *N*-alkylated products;^{13,17} the presence of hexamethylphosphorictriamide (HMPA) helps with less reactive alkylating agents.¹⁷

A number of *N*-1 protecting groups have been studied; each has its own advantages and disadvantages¹⁸⁻²¹ (see also ref. 22).

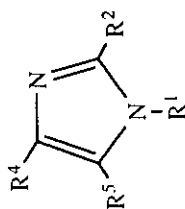
A Lithiation at position-2

Monolithiation of *N*-1 protected imidazoles occurs at position-2 even at low temperatures, most commonly -78 °C. The resulting 2-lithiated derivatives have been trapped with a variety of electrophilic quenching reagents, to give 1,2-di- or polysubstituted imidazoles (**1**) (Scheme 1) (Table I); e.g. with ketones, carbinols [**1**; R² = C(OH)R'R''] have been prepared in 50-96% yields (these are **not** listed in Table I).²³

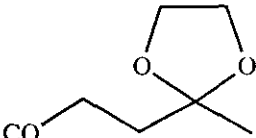
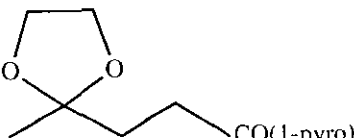
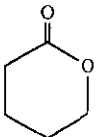
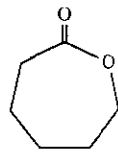


Scheme 1

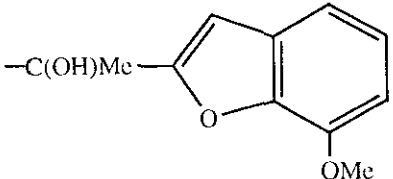
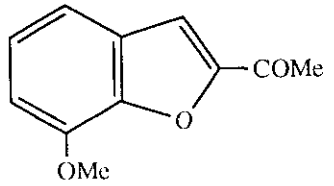
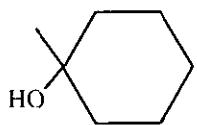
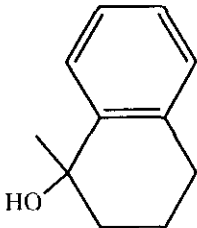
Table I
Imidazoles Synthesised from Imidazol-2-ylolithium Compounds^a

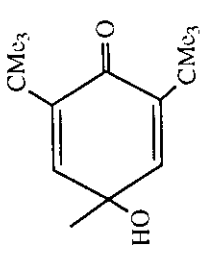
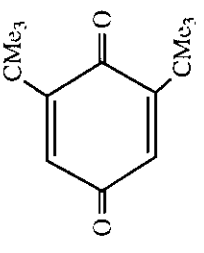
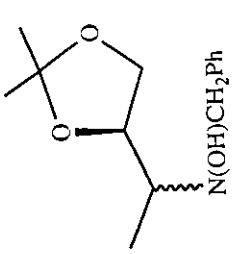
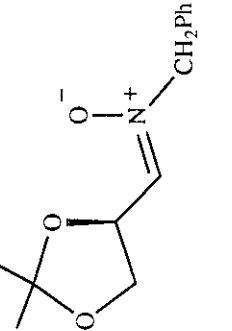
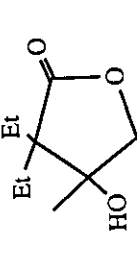
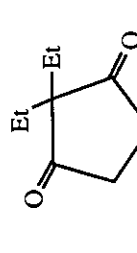


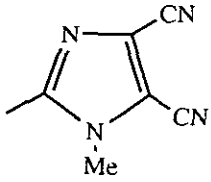
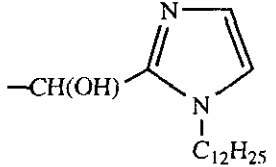
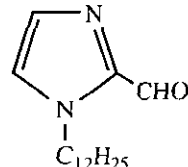
R ¹	R ²	R ⁴	R ⁵	Reagent	Yield (%)	Ref.
Me	Br	H	H	Br ₂	80	24, 25
Me	Br	H	H	NBS ^b	21	26
Me	I	H	H	I ₂	—, 86,	27, 28
Me	2-Py	H	H	ZnCl ₂ /2-PyBr ₂ /Pd(PPh ₃) ₄	93	29
Me	CHO	H	H	DMF	89 ^c	30
Me	CHO	H	H	PhNMeCHO	—	31
Me	CONMe ₂	H	H	CICONMe ₂	85	32
Me		H	H		35	33

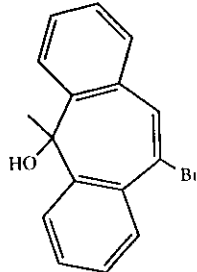
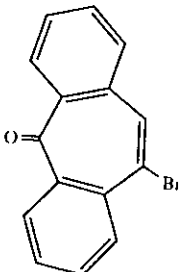
Me		H	H		79b	33-35
Me	COCHMePr	H	H	1-PyroCOCHMePr	89b	33, 34
Me	COC ₆ H ₁₃	H	H	C ₆ H ₁₃ COCl	58	33
Me	COC ₆ H ₁₃	H	H	C ₆ H ₁₃ CO ₂ Me	68	33
Me	COC ₆ H ₁₃	H	H	1-PyroCOC ₆ H ₁₃	100b	33, 34
Me	COC ₆ H ₁₁ -c	H	H	cyclohexylCO ₂ Me	45.5	33
Me	COC ₆ H ₁₁ -c	H	H	1-PyroCOcyclohexyl	100b	34
Me	COCH=CHPh	H	H	1-PyroCOCH=CHPh	62b	33, 34
Me	COCH ₂ CHMe(CH ₂) ₂ CH=CMe ₂	H	H	Me ₂ C=CH(CH ₂) ₂ CHMeCH ₂ CO ₂ Me	27.5	33
Me	CO(CH ₂) ₂ CH(OH)Ph	H	H	1-PyroCO(CH ₂) ₂ CH(OH)Ph	86b	33, 34
Me	CO(CH ₂) ₃ OH	H	H		75	33
Me	CO(CH ₂) ₅ OH	H	H		76	33
Me	COPh	H	H	PhCOCl	68	33

Me	COPh	H	H	PhCO ₂ Me	42	33
Me	COPh	H	H	PhCN	—	36
Me	COPh	H	H	1-PyroCOPh	100 ^b	34
Me	COC ₆ H ₃ (OCH ₂ O)-3,4	H	H	3,4-(OCH ₂ O)C ₆ H ₃ CO ₂ Me	42	33
Me	COC ₆ H ₃ (OCH ₂ O)-3,4	H	H	1-PyroCOC ₆ H ₃ (OCH ₂ O)-3,4	100 ^b	33, 34
Me	CO(2-Mim) ^b	H	H	(MeO) ₂ CO	93	32
Me	CO(2-Mim) ^b	H	H	(EtO) ₂ CO	76	37
Me	CO(4-Py) ^b	H	H	4-PyCN	5 ^d	36
Me	CO(4-Py) ^b	H	H	1-PyroCO(4-Py)	84	33, 34
Me	CH(OH)(CH ₂) ₅ Me	H	H	Me(CH ₂) ₅ CHO	70	35
Me	CH(OH)CH ₂ CHMe(CH ₂) ₂ Pr- <i>iso</i>	H	H	<i>iso</i> -Pr(CH ₂) ₂ CHMeCH ₂ CHO	88	35
Me	CH(OH)C ₆ H ₁₁ -c	H	H	cyclohexylCHO	76	35
Me	CH(OH)Ph	H	H	PhCHO	74-77	38
Me	CH(OH)C ₆ H ₄ NMe ₂ -4	H	H	4-Me ₂ NC ₆ H ₄ CHO	74-77	38
Me	CH(OH)C ₆ H ₃ (OMe) ₂ -3,4	H	H	3,4-(MeO) ₂ C ₆ H ₃ CHO	74-77, 86	38, 35
Me	CH(OH)(3-In) ^b	H	H	indole-3-CHO	63	39
Me	C(OH)Me ₂	H	H	Me ₂ CO	96	40
Me	C(OH)(Pr- <i>iso</i>) ₂	H	H	(<i>iso</i> -Pr) ₂ CO	78	40
Me	C(OH)MeC ₆ H ₁₃	H	H	MeCOC ₆ H ₁₃	84.5	35

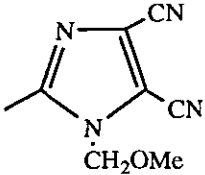
Me	C(OH)MePh	H	H	PhCOMe	92, 88	35, 40
Me	C(OH)Me(thien-2-yl)	H	H	thien-2-ylCOMe	83	40
Me	C(OH)Me(2-furyl)	H	H	2-furylCOMe	87	40
Me		H	H		79	35
Me	C(OH)BuPh	H	H	PhCOBu	82	35
Me	C(OH)Ph ₂	H	H	Ph ₂ CO	90	35
Me	C(OH)(2-Mim) ₂ ^b	H	H	ClCO ₂ Me	–	41,42
Me		H	H	cyclohexanone	85	40
Me		H	H	1-tetralone	90	35

Me		H	H		-	43
Me	SMe	H	H	Me ₂ S ₂	55	44
Me	SBu- <i>tert</i>	H	H	(<i>tert</i> -Bu) ₂ S ₂	41	45
Me	SPh	H	H	Ph ₂ S ₂	89	45
Me		H	H		81 (<i>syn:anti</i> -88:12) 76 (<i>syn:anti</i> -21:79)§	46
Me	SnMe ₃	H	H	Me ₃ SnCl	-, 73	47, 48 (see also ref. 49)
Me	I	H	Cl	I ₂	70	50
Me		H	Cl		-	51
Me	I	H	I	I ₂	59	24

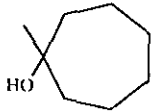
Me		CN	CN	CuCl ₂ /O ₂ /H ₃ O ⁺	54 ^c	52
C ₁₂ H ₂₅	CHO	H	H	DMF	80	53
C ₁₂ H ₂₅		CH ₂ OTHPb	H		32 ^f	53
CH ₂ Ph	D	H	H	D ₂ O	88	54
CH ₂ Ph	Me	H	H	MeI	13	54
CH ₂ Ph	I	H	H	2-O ₂ NC ₆ H ₄ I	35	54
CH ₂ Ph	C ₆ H ₄ NO ₂ -2	H	H	2-O ₂ NC ₆ H ₄ I	9	54
CH ₂ Ph	CHO	H	H	PhNMeCHO	—	31
CH ₂ Ph	COC ₆ H ₄ Cl-3	H	H	3-ClC ₆ H ₄ COCl	6	54
CH ₂ Ph	COC ₆ H ₄ Cl-4	H	H	4-ClC ₆ H ₄ COCl	14	54
CH ₂ Ph	COC ₆ H ₄ Cl-4	H	H	4-ClC ₆ H ₄ CHO	13 ^g	54
CH ₂ Ph	CH(OH)C ₆ H ₄ Cl-4	H	H	4-ClC ₆ H ₄ CHO	9	54
CH ₂ Ph	C(OH)Ph ₂	H	H	Ph ₂ CO	74, 2	55, 18
CH ₂ Ph	C(OH)PhC ₆ H ₄ Cl-2	H	H	2-ClC ₆ H ₄ COPh	8	18

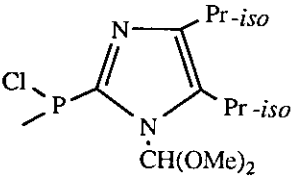
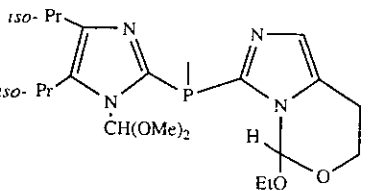
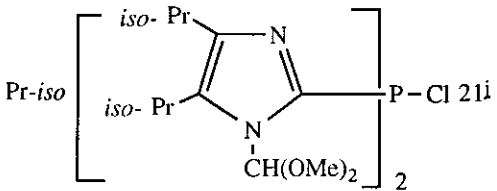
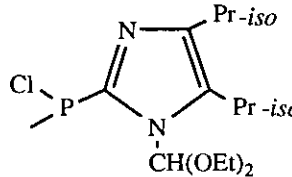
CH ₂ Ph	C(OH)PhC ₆ H ₄ Cl-4	H	H	4-ClC ₆ H ₄ COPh	12	18
CH ₂ Ph	C(OH)PhC ₆ H ₄ OMe-4	H	H	4-MeOC ₆ H ₄ COPh	37	18
CH ₂ Ph	C(OH)PhC ₆ H ₄ CF ₃ -4	H	H	4-F ₃ CC ₆ H ₄ COPh	21	18
CH ₂ Ph	C(OH)(C ₆ H ₄ F-4) ₂	H	H	(4-FC ₆ H ₄) ₂ CO	21	18
CH ₂ Ph	C(OH)(C ₆ H ₄ Cl-4) ₂	H	H	(4-ClC ₆ H ₄) ₂ CO	20	18
CH ₂ Ph		H	H		50	18
CH ₂ Ph	SMe	H	H	Me ₂ S ₂	31	54
CH ₂ Ph	SPh	H	H	Ph ₂ S ₂	38	54
CH ₂ Ph	CH(OH)Ph	Ph	Ph	PhCHO	73	55
CH ₂ Ph	C(OH)MePh	Ph	Ph	PhCOMe	80	55
CH ₂ Ph	C(OH)Ph ₂	Ph	Ph	Ph ₂ CO	72	55
CH ₂ C ₆ H ₄ Cl-4	C(OH)Ph ₂	H	H	Ph ₂ CO	7	18
CH ₂ C ₆ H ₄ Cl-4	C(OH)(C ₆ H ₄ Cl-4) ₂	H	H	(4-ClC ₆ H ₄) ₂ CO	5	18
CH ₂ (1-Bzt) ^b	COPh	H	H	PhCO ₂ Et	30	56
CH ₂ (1-Bzt) ^b	CH(OH)C ₆ H ₄ Me-4	H	H	4-MeC ₆ H ₄ CHO	74	56
CH=CH ₂	C(OH)PhC ₆ H ₄ Pr- <i>iso</i> -4	H	H	4- <i>iso</i> -PrC ₆ H ₄ COPh	71	18
CH=CH ₂	C(OH)PhC ₆ H ₄ Bu- <i>tert</i> -2	H	H	2- <i>tert</i> -BuC ₆ H ₄ COPh	61	18

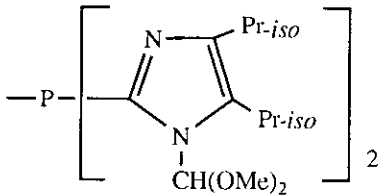
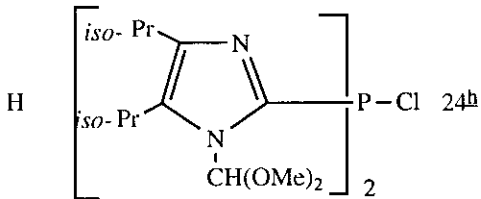
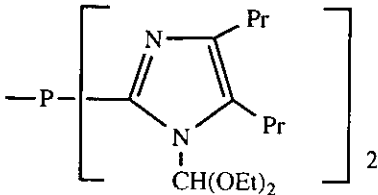
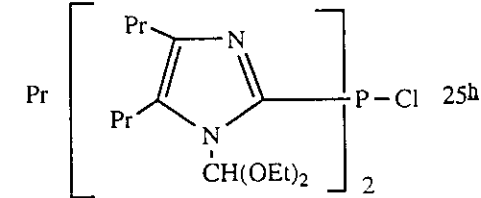
CH=CH ₂	C(OH)PhC ₆ H ₄ Bu- <i>tert</i> -4	H	H	4- <i>tert</i> -BuC ₆ H ₄ COPh	81	18
CH=CH ₂	C(OH)PhC ₆ H ₄ CF ₃ -4	H	H	4-F ₃ CC ₆ H ₄ COPh	52	18
CH=CH ₂	C(OH)(C ₆ H ₄ Bu- <i>tert</i> -4) ₂	H	H	(4- <i>tert</i> -BuC ₆ H ₄) ₂ CO	80	18
CH=CH ₂	C(OH)(C ₆ H ₄ Cl-4) ₂	H	H	(4-ClC ₆ H ₄) ₂ CO	60	18
CH ₂ CH=CH ₂	C(OH)PhC ₆ H ₄ Cl-4	H	H	4-ClC ₆ H ₄ COPh	43	18
CH ₂ CH=CH ₂	C(OH)(C ₆ H ₄ Cl-4) ₂	C ₆ H ₄ Cl-4	H	(4-ClC ₆ H ₄) ₂ CO	36	18
CH ₂ CH=CH ₂	C(OH)(C ₆ H ₄ Cl-4) ₂	Me	Me	(4-ClC ₆ H ₄) ₂ CO	10	18
CH ₂ OMe	CHO	H	H	DMF	—	14
CH ₂ OMe	C(OH)Ph ₂	H	H	Ph ₂ CO	78	18
CH ₂ OMe	C(OH)PhC ₆ H ₄ Bu- <i>tert</i> -2	H	H	2- <i>tert</i> -BuC ₆ H ₄ COPh	50	18
CH ₂ OMe	C(OH)PhC ₆ H ₄ F-4	H	H	4-FC ₆ H ₄ COPh	74	18
CH ₂ OMe	C(OH)PhC ₆ H ₄ Cl-4	H	H	4-ClC ₆ H ₄ COPh	47	18
CH ₂ OMe	C(OH)PhC ₆ H ₄ CF ₃ -3	H	H	3-F ₃ CC ₆ H ₄ COPh	64	18
CH ₂ OMe	C(OH)PhC ₆ H ₄ CF ₃ -4	H	H	4-F ₃ CC ₆ H ₄ COPh	81	18
CH ₂ OMe	C(OH)PhC ₆ H ₄ OH-4	H	H	4-TMSOC ₆ H ₄ COPh ^{b,f}	35	18
CH ₂ OMe	C(OH)PhC ₆ H ₄ SMe-4	H	H	4-MeSC ₆ H ₄ COPh	90	18
CH ₂ OMe	C(OH)C ₆ H ₃ Cl ₂ -2,4	H	H	2,4-Cl ₂ C ₆ H ₃ COPh	78	18
CH ₂ OMe	C(OH)C ₆ H ₃ Cl ₂ -2,6	H	H	2,6-Cl ₂ C ₆ H ₃ COPh	46	18
CH ₂ OMe	C(OH)(C ₆ H ₄ F-4) ₂	H	H	(4-FC ₆ H ₄) ₂ CO	53	18
CH ₂ OMe	C(OH)(C ₆ H ₄ Cl-4) ₂	H	H	(4-ClC ₆ H ₄) ₂ CO	50	18

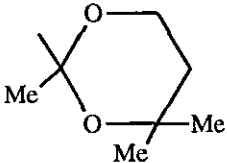
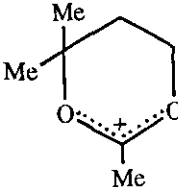
CH ₂ OMe	C(OH)(C ₆ H ₄ CF ₃ -4) ₂	H	H	(4-F ₃ CC ₆ H ₄) ₂ CO	15	18
CH ₂ OMe	C(OH)(C ₆ H ₄ OH-4) ₂	H	H	(4-TMSOC ₆ H ₄) ₂ CO ^{b,f}	26	18
CH ₂ OMe	C(OH)(C ₆ H ₄ OMe-4) ₂	H	H	(4-MeOC ₆ H ₄) ₂ CO	87	18
CH ₂ OMe	C(OH)(C ₆ H ₄ OCH ₂ OMe-4) ₂	H	H	(4-MeOCH ₂ OC ₆ H ₄) ₂ CO	25	18
CH ₂ OMe	C(OH)(C ₆ H ₃ Cl ₂ -2,4) ₂	H	H	(2,4-Cl ₂ C ₆ H ₃) ₂ CO	48	18
CH ₂ OMe	C(OH)(C ₆ H ₄ Bu- <i>tert</i> -4)(C ₆ H ₄ Cl-4)	H	H	4- <i>tert</i> -BuC ₆ H ₄ COC ₆ H ₄ Cl-4	51	18
CH ₂ OMe	C(OH)(C ₆ H ₄ F-4)(C ₆ H ₄ Cl-4)	H	H	4-FC ₆ H ₄ COC ₆ H ₄ Cl-4	51	18
CH ₂ OMe	C(OH)(C ₆ H ₄ F-4)(C ₆ H ₃ Cl ₂ -2,4)	H	H	4-FC ₆ H ₄ COC ₆ H ₃ Cl ₂ -2,4	60	18
CH ₂ OMe	C(OH)(C ₆ H ₄ Cl-4)(4-Py) ^b	H	H	4-PyCOC ₆ H ₄ Cl-4 ^b	60	18
CH ₂ OMe	SPh	H	H	Ph ₂ S ₂	76	22
CH ₂ OMe	SiMe ₂ Bu- <i>tert</i>	H	H	<i>tert</i> -BuMe ₂ SiCl	94	32
CH ₂ OMe	C(OH)(C ₆ H ₄ Cl-4) ₂	Me	Me	(4-ClC ₆ H ₄) ₂ CO	53	18
CH ₂ OMe	SiMe ₃	Cl	Cl	Me ₃ SiCl	—	57
CH ₂ OMe	C(OH)PhC ₆ H ₄ SMe-4	C ₆ H ₄ Cl-4	H	4-MeSC ₆ H ₄ COPh	25	18
CH ₂ OMe	C(OH)(C ₆ H ₄ Cl-4) ₂	C ₆ H ₄ Cl-4	H	(4-ClC ₆ H ₄) ₂ CO	35	18
CH ₂ OMe		CN	CN	CuCl ₂ /O ₂ /H ₃ O ⁺	27 ^c	50
CH ₂ OEt	I	H	H	I ₂	90	58
CH ₂ OEt	2-Py- ^b	H	H	ZnCl ₂ /2-PyBr/Pd(PPh ₃) ₄	93	29

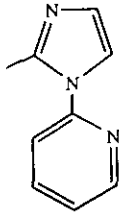
CH ₂ OEt	I	<i>iso</i> -Pr	<i>iso</i> -Pr	I ₂	87	58
CH ₂ OBu- <i>tert</i>	D	H	H	D ₂ O	100	59
CH ₂ OBu- <i>tert</i>	Me	H	H	MeI	94	59
CH ₂ OBu- <i>tert</i>	CHO	H	H	HCO ₂ Me	78	59
CH ₂ OBu- <i>tert</i>	CH(OH)Ph	H	H	PhCHO	88	59
CH ₂ OBu- <i>tert</i>	C(OH)Ph ₂	H	H	Ph ₂ CO	96	59
CH ₂ OCH ₂ Ph	D	H	H	D ₂ O	100	59
CH ₂ OCH ₂ Ph	CHO	H	H	HCO ₂ Me	81	59
CH ₂ OCH ₂ Ph	C(OH)Ph ₂	H	H	Ph ₂ CO	82	59
CH ₂ OCH ₂ Ph	C(OH)PhC ₆ H ₄ Cl-4	H	H	4-ClC ₆ H ₄ COPh	30	18
CH ₂ OCH ₂ Ph	CHO	I	I	DMF	5-10	60
CH ₂ O(CH ₂) ₂ OMe	D	H	H	D ₂ O	100	59
CH ₂ O(CH ₂) ₂ OMe	Me	H	H	MeI	97	59
CH ₂ O(CH ₂) ₂ OMe	CHO	H	H	HCO ₂ Me	70	59
CH ₂ O(CH ₂) ₂ OMe	CO ₂ Et	H	H	ClCO ₂ Et	63	59
CH ₂ O(CH ₂) ₂ OMe	C(OH)Ph ₂	H	H	Ph ₂ CO	83	59
CH ₂ O(CH ₂) ₂ SiMe ₃	I	H	H	I ₂	90	58
CH ₂ O(CH ₂) ₂ SiMe ₃	Me	H	H	MeI	94	61
CH ₂ O(CH ₂) ₂ SiMe ₃	CHO	H	H	DMF	96	62
CH ₂ O(CH ₂) ₂ SiMe ₃	CH(OH)(2-furyl)	H	H	2-furylCHO	82	61

CH ₂ O(CH ₂) ₂ SiMe ₃		H	H	cycloheptanone	72	61
CH ₂ O(CH ₂) ₂ SiMe ₃	OH	H	H	(Me ₃ SiO) ₂	98	63
CH ₂ O(CH ₂) ₂ SiMe ₃	OH	H	H	(PhCO ₂) ₂ O	91	63
CH ₂ O(CH ₂) ₂ SiMe ₃	CPh(NHCOMe)CONHOMe	H	H	MeCON=CPhCONHOMe	46b	61
CH ₂ O(CH ₂) ₂ SiMe ₃	CHO	H	Me	DMF	89	62
CH ₂ O(CH ₂) ₂ SiMe ₃	Me	CH ₂ Pr- <i>iso</i>	H	MeI	64	61
CH ₂ O(CH ₂) ₂ SiMe ₃	CHO	CH ₂ Pr- <i>iso</i>	H	DMF	85	61
CH ₂ O(CH ₂) ₂ SiMe ₃	COC ₆ H ₁₁ -c	CH ₂ Pr- <i>iso</i>	H	cyclohexylCOCl	42	61
CH ₂ O(CH ₂) ₂ SiMe ₃	COMe	CH ₂ Pr- <i>iso</i>	H	MeCOCl	20	61
CH ₂ O(CH ₂) ₂ SiMe ₃	COMe	CH ₂ Pr- <i>iso</i>	H	Ac ₂ O	40	61
CH ₂ O(CH ₂) ₂ SiMe ₃	CH(OH)Ph	CH ₂ Pr- <i>iso</i>	H	PhCHO	99	61
CH ₂ O(CH ₂) ₂ SiMe ₃	CH(C ₆ H ₁₁ -c)NHCH ₂ Ph	CH ₂ Pr- <i>iso</i>	H	c-C ₆ H ₁₁ CH=NCH ₂ Ph/ BF ₃ ·OEt ₂	87	61
CH ₂ O(CH ₂) ₂ SiMe ₃	D	Ph	H	D ₂ O	100	61
CH ₂ O(CH ₂) ₂ SiMe ₃	CH(OH)C ₆ H ₁₁ -c	Ph	H	cyclohexylCHO	86	61
CH ₂ O(CH ₂) ₂ SiMe ₃	CH(OH)CH=CHPh	Ph	H	PhCH=CHCHO	100	61
CH ₂ O(CH ₂) ₂ SiMe ₃	SPh	Ph	H	Ph ₂ S ₂	95	61
CHMeOEt	Me	H	H	MeI	91	20
CHMeOEt	CHO	H	H	DMF	90	20

CHMeOEt	C(OH)Ph ₂	H	H	Ph ₂ CO	88	20
CHMeOEt ¹	NO ₂	C ₆ H ₃ Cl ₂ -3,4	Ph	N ₂ O ₄	—	64
CHMeOEt	NO ₂	C ₆ H ₄ OEt-4	C ₆ H ₄ F-4	N ₂ O ₄	—	64
CHMeOEt	NO ₂	C ₆ H ₄ F-4	3-Py ^b	N ₂ O ₄	—	64
CH(OMe) ₂		Pr-iso	Pr-iso	1/2 PCl ₃	—	65
CH(OMe) ₂ ¹		Pr-iso	Pr-iso		65i	40
CH(OEt) ₂	C(OH)Me ₂	H	H	Me ₂ CO	76i	40
CH(OEt) ₂	C(OH)MePh	H	H	Ph ₂ S ₂	8	22
CH(OEt) ₂	SPh	H	H	—	—	65
CH(OEt) ₂		Pr	Pr	1/2 PCl ₃	—	65

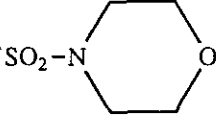
CH(OEt) ₂		H		24h	65	
CH(OEt) ₂		Pr		25h	65	
CMe(OEt) ₂	C(OH)(C ₆ H ₄ Cl-4) ₂	H	H	(4-ClC ₆ H ₄) ₂ CO	60h	66
THP ^b	SCF ₃	Ph	Ph	F ₃ CSCl	31h	67
THP ^b	SCF ₃	Ph	Ph	(F ₃ CS) ₂	—	68
THP ^b	SCF ₃	Ph	C ₆ H ₃ Cl ₂ -3,4	(F ₃ CS) ₂	—	68
THP ^b	SCF ₃	C ₆ H ₄ F-4	C ₆ H ₄ F-4	F ₃ CSCl	—	67
THP ^b	SCF ₃	C ₆ H ₄ F-4	C ₆ H ₄ F-4	(F ₃ CS) ₂	—	68
THP ^b	SCF ₃	C ₆ H ₄ F-4	C ₆ H ₄ OMe-4	(F ₃ CS) ₂	—	68
THP ^b	SCF ₃	C ₆ H ₄ OMe-4	C ₆ H ₄ OMe-4	(F ₃ CS) ₂	—	68
THP ^b	SCF ₂ CF ₃	C ₆ H ₄ F-4	C ₆ H ₄ F-4	(F ₃ CCF ₂ S) ₂	—	68
THP ^b	NO ₂	C ₆ H ₄ F-4	C ₆ H ₄ F-4	N ₂ O ₄	—	64

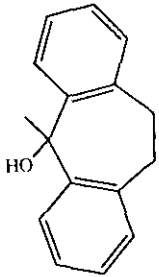
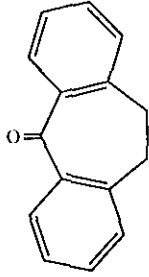
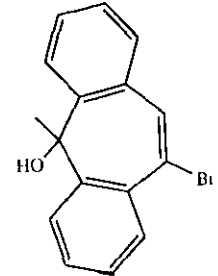
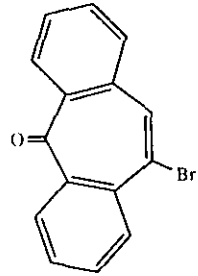
THP ^b	NO ₂	C ₆ H ₄ OMe-4	C ₆ H ₄ OMe-4	N ₂ O ₄	—	64
THP ^b	NO ₂	C ₆ H ₄ F-4	thien-2-yl	N ₂ O ₄	—	64
CH ₂ NMe ₂	Bu	H	H	BuI	76 ^h	21
CH ₂ NMe ₂	CHPrBu	H	H	BuBr	27 ^h	21
CH ₂ NMe ₂	COC ₆ H ₄ Me-4	H	H	4-MeC ₆ H ₄ CO ₂ Et	65 ^h	21
CH ₂ NMe ₂	CONHBu- <i>tert</i>	H	H	<i>tert</i> -BuNCO	62 ^h	21
CH ₂ NMe ₂	CH(OH)C ₆ H ₄ Me-4	H	H	4-MeC ₆ H ₄ CHO	60 ^h	21
CH ₂ NMe ₂	C(OH)Ph ₂	H	H	Ph ₂ CO	72 ^h	21
(CH ₂) ₃ N=CPh ₂	COPh	H	H	PhCOCl		69
(CH ₂) ₃ N=CPh ₂	COC ₆ H ₄ F-4	H	H	4-FC ₆ H ₄ COCl	71-90	69
(CH ₂) ₃ N=CPh ₂	COC ₆ H ₄ OMe-4	H	H	4-MeOC ₆ H ₄ COCl		69
CPh ₃	C(OH)Ph ₂	H	H	Ph ₂ CO	37	18
CPh ₃	SPh	H	H	Ph ₂ S ₂	99 ^c	22
CPh ₃	Me	Br	H	MeI	63	22
CPh ₃	NO ₂	Me	H	PrONO ₂	50 ⁱ	70 [see also ref. 71]
Ph	CO(4-Py) ^b	H	H	4-PyCN	40	36
Ph		H	H	 ClO ₄ ⁻	85	72, 73

2-Py ^d	C(OH)Ph ₂	H	H	Ph ₂ CO	46	74
2-Py ^d		H	H	CuCl ₂	18	74
SO ₂ NMe ₂	2-Py ^b	H	H	ZnCl ₂ /2-PyBr/Pd(PPh ₃) ₄	60	29
SO ₂ NMe ₂	CHO	Ph	H	DMF	—	75
SO ₂ NMe ₂	CHO	C ₆ H ₃ Cl ₂ -2,4	H	DMF	—	75
SO ₂ NMe ₂	CHO	CH(OTMS)C ₆ H ₂ Cl ₃ -2,4,6	H	DMF	—	75
SO ₂ NMe ₂	CO ₂ Et	Ph	H	ClCO ₂ Et	—	57
SO ₂ NMe ₂	CO ₂ Et	Cl	Ph	ClCO ₂ Et	—	57
SO ₂ NMe ₂	CO ₂ Et	Cl	(CH ₂) ₃ Cl	ClCO ₂ Et	—	57
SO ₂ NMe ₂	CN	H	H	PhOCN	69	76
SO ₂ NMe ₂	CN	Me	H	TosCN	—	75
SO ₂ NMe ₂	CN	Bu- <i>tert</i>	H	TosCN	50	76
SO ₂ NMe ₂	CN	CH ₂ OH	H	TosCN	—	77
SO ₂ NMe ₂	CN	CH ₂ OR (various)	H	TosCN	—	77
SO ₂ NMe ₂	CN	CHR ¹ OR (various)	H	TosCN	—	77
SO ₂ NMe ₂	CN	CHMe(OTMS)- C ₆ H ₂ Cl ₃ -2,4,6	H	PhOCN	83	76

SO ₂ NMe ₂	CN	CR ¹ R ² OR (various)	H	TosCN	—	77
SO ₂ NMe ₂	CN	CH ₂ SPh	H	TosCN	—	77
SO ₂ NMe ₂	CN	CH ₂ NMeCOC ₆ H ₄ Cl-4	H	TosCN	—	77
SO ₂ NMe ₂	CN	CH ₂ NMeSO ₂ C ₆ H ₄ Cl-4	H	TosCN	—	77
SO ₂ NMe ₂	CN	CF ₃	H	TosCN	—	75
SO ₂ NMe ₂	CN	CH=CHC ₆ H ₄ Cl-4	H	TosCN	—	75
SO ₂ NMe ₂	CN	Ph	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ F-2	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ F-3	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ F-4	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ Cl-2	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ Cl-3	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ Cl-4	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ Br-4	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ Br-4	H	PhOCN	72	76
SO ₂ NMe ₂	CN	C ₆ H ₄ CF ₃ -2	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ CF ₃ -3	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ CF ₃ -4	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ OMe-4	H	TosCN	—	75
SO ₂ NMe ₂	CN	C ₆ H ₄ CN-4	H	TosCN	—	75

SO ₂ NMe ₂	CN	C ₆ H ₃ Me ₂ -2,4	H	TosCN	–	75
SO ₂ NMe ₂	CN	C ₆ H ₃ F ₂ -2,4	H	TosCN	–	75
SO ₂ NMe ₂	CN	C ₆ H ₃ Cl ₂ -2,4	H	TosCN	–, 75	75, 76
SO ₂ NMe ₂	CN	C ₆ H ₃ Cl ₂ -3,4	H	TosCN	–	75
SO ₂ NMe ₂	CN	C ₆ H ₂ Cl ₃ -2,3,4	H	TosCN	–	75
SO ₂ NMe ₂	CN	C ₆ H ₂ Cl ₃ -2,4,5	H	TosCN	–	75
SO ₂ NMe ₂	CN	C ₆ H ₂ Cl ₂ CN-2,4,3	H	TosCN	–	75
SO ₂ NMe ₂	CN	thien-2-yl	H	TosCN	50	76
SO ₂ NMe ₂	CN	5-chlorothien-2-yl	H	TosCN	–	75
SO ₂ NMe ₂	CN	2,5-dichlorothien-3-yl	H	TosCN	–	75
SO ₂ NMe ₂	CN	CH(OMe) ₂	H	TosCN	–	78
SO ₂ NMe ₂	CN	CH(OMe) ₂	H	PhOCN	70	76
SO ₂ NMe ₂	CN	COC ₆ H ₃ Cl ₂ -2,6	H	TosCN	–	75
SO ₂ NMe ₂	CN	COC ₆ H ₄ Me ₃ -2,4,6	H	TosCN	–	75
SO ₂ NMe ₂	CN	COC ₆ H ₂ Cl ₃ -2,4,6	H	(CN) ₂	–	75
SO ₂ NMe ₂	CN	CN	H	TosCN	–	75
SO ₂ NMe ₂	CN	SPh	H	TosCN	–	75
SO ₂ NMe ₂	CN	SCH ₂ Ph	H	TosCN	–, 58	75, 76
SO ₂ NMe ₂	CN	SO ₂ NR ₂ (various)	H	TosCN	–	75, 79
SO ₂ NMe ₂	CN	H	Me	TosCN	–	75
SO ₂ NMe ₂	CN	C(OEt)Ph ₂	Me	TosCN	–	75

SO ₂ NMe ₂	CN	CH ₂ O(pyran-2-yl)	Me	TosCN	—	77
SO ₂ NMe ₂	CN	CPh ₂ OEt	Me	TosCN	75	77
SO ₂ NMe ₂	CN	H	Ph	TosCN	—	75
SO ₂ NMe ₂	SPh	H	H	Ph ₂ S ₂	56	22
SO ₂ NMe ₂	SiMe ₃	H	H	Me ₃ SiCl	—	80
SO ₂ NMe ₂	SiEt ₃	H	H	Et ₃ SiCl	—	81
SO ₂ NMe ₂	SiMe ₂ Bu- <i>tert</i>	H	H	<i>tert</i> -BuMe ₂ SiCl	90, 91, —	32, 82, 83
	CN	C ₆ H ₃ Cl ₂ -2,4	H	TosCN	—	75
SO ₂ C ₆ H ₄ Me-4	C(OH)(C ₆ H ₄ Cl-4)C ₆ H ₁₁ -c	H	H	4-ClC ₆ H ₄ COcyclohexyl	25	18
SO ₂ C ₆ H ₄ Me-4	C(OH)PhC ₆ H ₄ Cl-2	H	H	2-ClC ₆ H ₄ COPh	40	18
SO ₂ C ₆ H ₄ Me-4	C(OH)PhC ₆ H ₄ Cl-4	H	H	4-ClC ₆ H ₄ COPh	29	18
SO ₂ C ₆ H ₄ Me-4	C(OH)PhC ₆ H ₄ Br-4	H	H	4-BrC ₆ H ₄ COPh	50	18
SO ₂ C ₆ H ₄ Me-4	C(OH)PhC ₆ H ₄ Me-4	H	H	4-MeC ₆ H ₄ COPh	55	18
SO ₂ C ₆ H ₄ Me-4	C(OH)(C ₆ H ₄ F-4) ₂	H	H	(4-FC ₆ H ₄) ₂ CO	29	18
SO ₂ C ₆ H ₄ Me-4	C(OH)(C ₆ H ₄ Cl-4) ₂	H	H	(4-ClC ₆ H ₄) ₂ CO	26	18
SO ₂ C ₆ H ₄ Me-4	C(OH)(C ₆ H ₄ Br-4) ₂	H	H	(4-BrC ₆ H ₄) ₂ CO	43	18

SO ₂ C ₆ H ₄ Me-4		H	H		10	18
SO ₂ C ₆ H ₄ Me-4		H	H		12	18
SiMe ₃	SiMe ₃	H	H	Me ₃ SiCl	62	84

^a With BuLi unless stated otherwise. ^b The following abbreviations have been used: 1-Pyro = pyrrolidin-1-yl; 2-Mim = 1-methylimidazol-2-yl; 2-Mom = 1-methoxymethylimidazol-2-yl; 2-Eom = 1-ethoxymethylimidazol-2-yl; 2-, 3-, and 4-Py = pyrid-2(3 and 4)-yl; 3-In = indol-3-yl; 1-Bzt = benzotriazol-1-yl; TMS = trimethylsilyl; THP = tetrahydropyran-2-yl; NBS, NCS, NIS = *N*-halogenosuccinimide (X = Br, Cl, I). ^c With LDA. ^d Minor product of the reaction. ^e In the presence of Et₂AlCl. ^f Yield after removal of THP or TMS protecting group. ^g Other products (see Scheme 7). ^h After removal of 1-protecting group. ⁱ In this case the 2-lithiated imidazole employed was that derived from the cyclic amide of 4(5)-hydroxyethylimidazole. ^j Generated *in situ* and used in further synthesis.

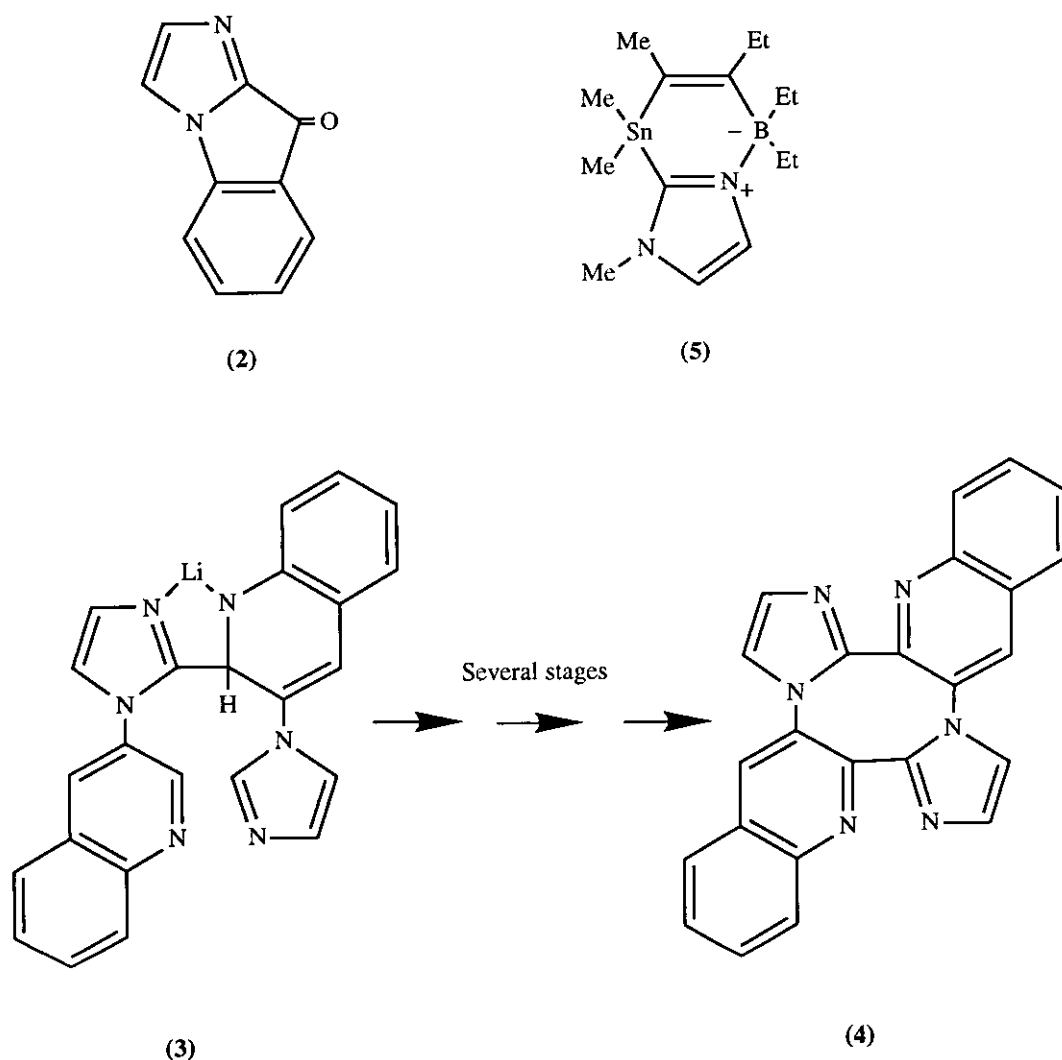
Butyllithium is most commonly used as the metallating reagent whilst lithium diisopropylamide (LDA) is the reagent of choice when the imidazole carries substituents prone to nucleophilic attack. Ethereal solvents [diethyl ether (Et₂O), tetrahydrofuran (THF), or dimethoxyethane (DME)] are normally used. Lithium naphthalenide has been used to "metallate" 1-methylimidazole⁸⁵ but it does not find general use; e.g. it does not metallate 1-phenylimidazole. In view of the ease of C-2 metallation of imidazoles the addition of chelating reagents, such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA), to enhance basicity of the organolithium reagent is not usually necessary. The ease of C-2 deprotonation is exemplified with substrates capable also of halogen → metal exchange.

4-(And 5)-chloro (the Cl-atom is exchangeable if position-2 is blocked) and 4-bromo derivatives (Br-atom exchangeable with positions-2 and -5 blocked) are metallated in position-2 (Table I). Thus, e.g., 4-chloro-*N,N*-dimethyl-5-phenylimidazole-1-sulfonamide is lithiated at position-2 (BuLi/THF/-70 °C), quenching with ethyl chloroformate gives the ethyl 2-carboxylate (Table I).⁵⁷

By judicious choice of reaction conditions it is possible to metallate imidazoles at position-2 which carry functional groups also capable of reacting with the reagent. Thus, e.g. with one mol. equiv. of butyllithium (THF/-100 °C) it is possible to selectively C-2 metallate 4,5-dicyano-1-methylimidazole;¹⁵ see also refs. 52 and 75 (addition of TMEDA is reported to help). At -80 °C complications arise as a result of attack of the butyllithium on one of the cyano groups. Quenching the C-2 anion is only possible with electrophilic reagents which react at -100 °C. It is preferable to prepare this anion *via* bromine → lithium exchange (Section IV.A). Deprotonation of 4,5-dicyano-1-methylimidazole with LDA (THF/-80 °C) gives the C-2 anion which proceeds to yield oligomers by its attack on the cyano groups of other molecules.¹⁵ With two mol. equiv. of butyllithium followed by quenching with water 4,5-dicyano-1-methylimidazole yields a butyl ketone.

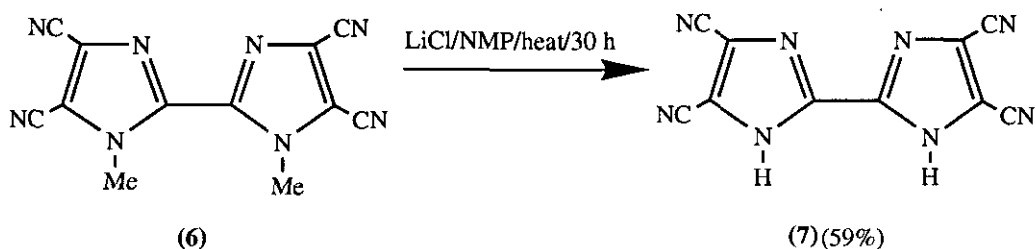
Whilst 1-phenylimidazole-2-carboxylic acid is obtained when 1-phenylimidazole is treated successively with one mol. equiv. of butyllithium and carbon dioxide, when this reaction is repeated using three mol. equiv. of butyllithium, compound (2) is produced through carbonation of a dilithiated species.⁸⁶ The 2-lithiated derivative of 1-(quinol-3-yl)imidazole (LDA/THF) reacts with starting material as it forms, to give the product (3) (Scheme 2) of azomethine bond addition which can be transformed to the macrocyclic dimer (4) by further 2-lithiation, intramolecular bond addition, hydrolysis, and oxidation.^{87,88}

Condensation of 1-methylimidazol-2-ylolithium with (*E*)-2-dimethyl(chloro)stannyl-3-diethylborylpent-2-ene [Me₂Sn(Cl)MeC=CEtBEt₂] gives rise to the bicyclic compound (5) (83% yield).⁸⁹



Scheme 2

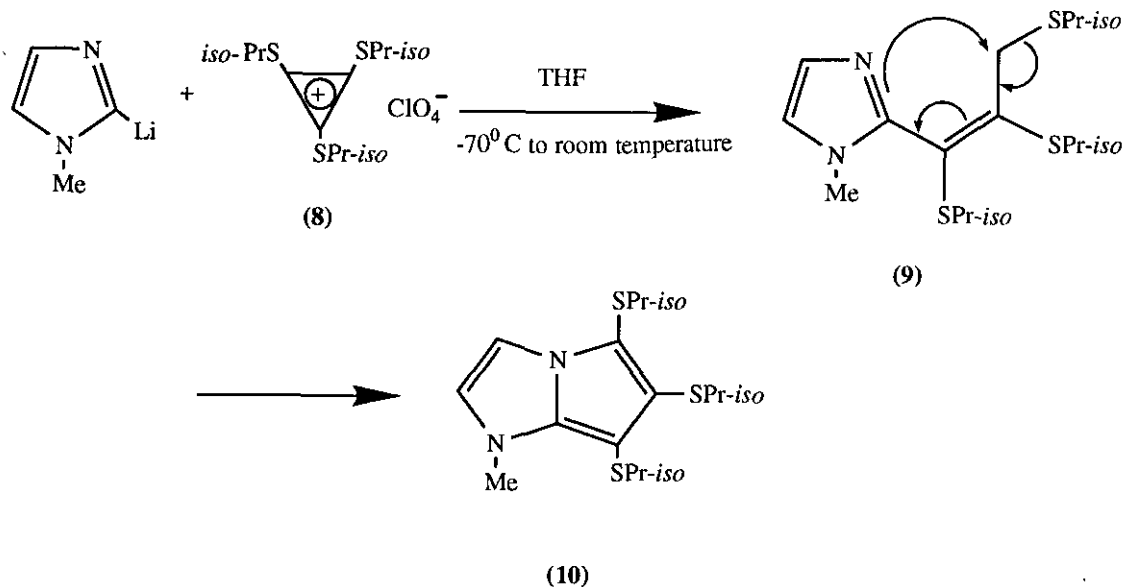
Lithiation of 1-methylimidazole and subsequent reactions of the imidazol-2-yl lithium derivative with electrophiles has been most studied (Table I) presumably because it is commercially available and able to withstand extreme metallation conditions.⁹⁰ Use of the *N*-methyl substituent as a protecting group has been reported,⁵² e.g. in the synthesis of compound (6) (Scheme 3). In this case the ease of demethylation, (6) → (7) (Scheme 3), is attributable to the presence of the cyano groups which stabilise the leaving imidazolium anions involved.



Scheme 3

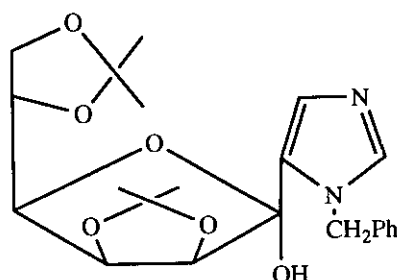
Demethylation, however, is usually very difficult. An attempt, e.g., to demethylate 4-bromo-1-methyl-2-nitroimidazole was unsuccessful.⁷¹

1-Methylimidazol-2-yllithium reacts with 1,2,3-*tris*(isopropylthio)cyclopropylm perchlorate (8) to give the pyrrolo[2,1-*b*]imidazole (10) in 98% yield.⁹¹ The reaction proceeds *via* formation of the intermediate vinyl carbene (9) (Scheme 4).

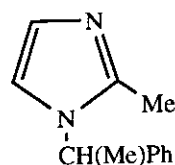


Scheme 4

N-Benzyl protecting groups may be removed by reductive cleavage techniques.^{18,31,55,86,92} The major disadvantage associated with the use of this protecting group is competitive α -(or lateral)metallation^{19,52,54,93,94} (see also ref. 18) (Section V). The 1-benzylimidazol-2-yl anion appears to be thermodynamically preferred to the N -C $_{\alpha}$ anion but it is not clear which of the two possible anions is kinetically preferred.⁵⁴ With the exception of benzyl halides and iodomethane most electrophiles appear to react at position-2; a steric argument has been advanced to account for this preference.⁵⁴ 1-Benzylimidazoles have been dialkylated in their benzyl groups⁹⁴ (see also Section V). The reported⁹⁵ synthesis of compound (11) through metallation of 1-benzylimidazole at position-5 has been shown to be faulty.¹⁹ Quenching the anion formed under the literature conditions with iodomethane gave compound (12) (however, see also ref. 54). Removal of the benzyl group from 1-benzyl- α -(4-chlorophenyl)- α -phenylimidazole-2-methanol with sodium in liquid ammonia results in loss of the chlorine atom.¹⁸



(11)



(12)

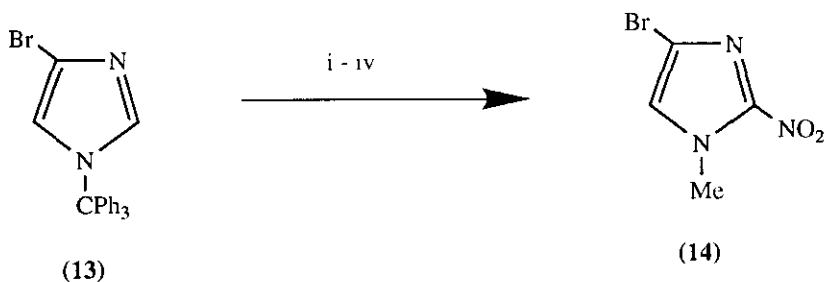
With butyllithium (THF/0 °C/1 hour) *bis*(imidazol-1-yl)methane yields both the 2-mono- and 2,2'-dimetallated derivative depending on the conditions of the reaction and the quenching reagent (Table II).⁹⁶ There is no evidence for lateral metallation in the methylene group. Use of LDA or an increase in the temperature produces results similar to those with butyllithium, which suggests that ring metallation is both kinetically and thermodynamically favoured.

The triphenylmethyl(trityl) group⁹⁷ has problems associated with solubility;¹⁹ (see also ref. 18). Reaction temperatures and solvents are thus restrictive. Deprotection, however, occurs readily by mild acid hydrolysis. A typical one-pot procedure is summarised in Scheme 5 for conversion of compound (13) into compound (14) (37% yield).⁷¹ Some of the moderate yields reported in Table I may be accounted for by steric hindrance towards metallation arising from the presence of a bulky *N*-1 protecting group (see Section II.B).

Table II
Ring Substitution of *Bis*(imidazol-1-yl)methane

Reagent	Substrate:BuLi:E ⁺	Monosubstitution (%) ^a	Disubstitution (%) ^a
MeI	1 : 1 : 1	53	31
MeI	1 : 2.1 : 2.1	0	100
Me ₂ S ₂	1 : 1 : 1	57	14
Me ₂ S ₂	1 : 1 : 1 ^b	58	12
Me ₂ S ₂	1 : 1 : 1 ^c	50	16
Me ₂ S ₂	1 : 2.4 : 2.4	12	75
Me ₃ SiCl	1 : 1 : 1	57	43
Me ₃ SiCl	1 : 2.1 : 2.1	38	62
(HCHO) _n	1 : 1 : 1	55	12
(HCHO) _n	1 : 2.1 : 2.1	36	64

^a By ¹H nmr spectroscopy. ^b With LDA. ^c At 60 °C.



Reagents: i) BuLi/THF/0°C; ii) PrNO₂; iii) H₃O⁺; iv) Me₂SO₄/K₂CO₃/Me₂CO.

Scheme 5

Alkoxymethyl and aryloxymethyl protecting groups are reported to be the most stable so far employed in imidazole metallation processes.⁵⁹ Deprotection, however, requires more severe conditions. Thus, 1-methoxymethylimidazoles have been reported⁹⁸ to be stable to prolonged boiling in 6M-hydrochloric acid. A mixture of hydrochloric and acetic acids has been found, however, to be effective in deprotection studies.¹⁸ Deprotection of 1,1'-*bis*(methoxymethyl)-4,4',5,5'-tetracyano-2,2'-bi-imidazole has been achieved by heating in a 1.2M-hydrochloric acid-THF mixture at 60 °C for 3 hours.⁵² A 2-(trimethylsilyl)ethoxymethyl (SEM) protecting group is cleaved similarly with 0.5M-ethanolic hydrochloric acid at 50 °C but 1.0M-

tetrabutylammonium fluoride in THF heated under reflux is equally effective.^{61,62} The latter system has been used for the simultaneous removal of a 5-trimethylsilyl group and an *N*-SEM group.¹⁶ Removal of an *N*-ethoxyethyl protecting group is possible with 0.1M-methanolic hydrogen chloride (at 55 °C/4 hours).²⁰ A tetrahydropyran-2-yl (THP) protecting group can be removed similarly with 0.1M-ethanolic hydrogen chloride.^{64,68} In addition to restrictive deprotection conditions, yields of isolated products are often moderate or low when these protecting groups are employed (Table I).

By contrast with alkoxymethyl protecting groups, dialkoxymethyl and trialkylsilyl protecting groups are very labile. Imidazoles carrying these protecting groups are deprotected by work-up procedures. Problems can arise too following chromatography on silica when the protecting group can be lost and the C-S bond of 2-phenylthio derivatives can be cleaved simultaneously.²²

An *N*-dialkylaminomethyl protecting group can be introduced under Mannich reaction conditions and removed by acidic work-up of reaction mixtures²¹ (but see ref. 99). The 2-lithiated derivatives of such protected imidazoles give poor yields on reaction with hindered electrophiles and with acidic substrates. In one reaction, when iodobutane was replaced with bromobutane as the electrophilic quenching reagent, further α -(or lateral)-deprotonation (Section V) of the initially introduced 2-butyl group occurred and the resulting anion captured another butyl group.²¹ Presumably reaction with iodobutane is faster and this side-reaction is avoided. With 2-arylethyl halides elimination occurs to produce the corresponding styrenes.⁹⁹

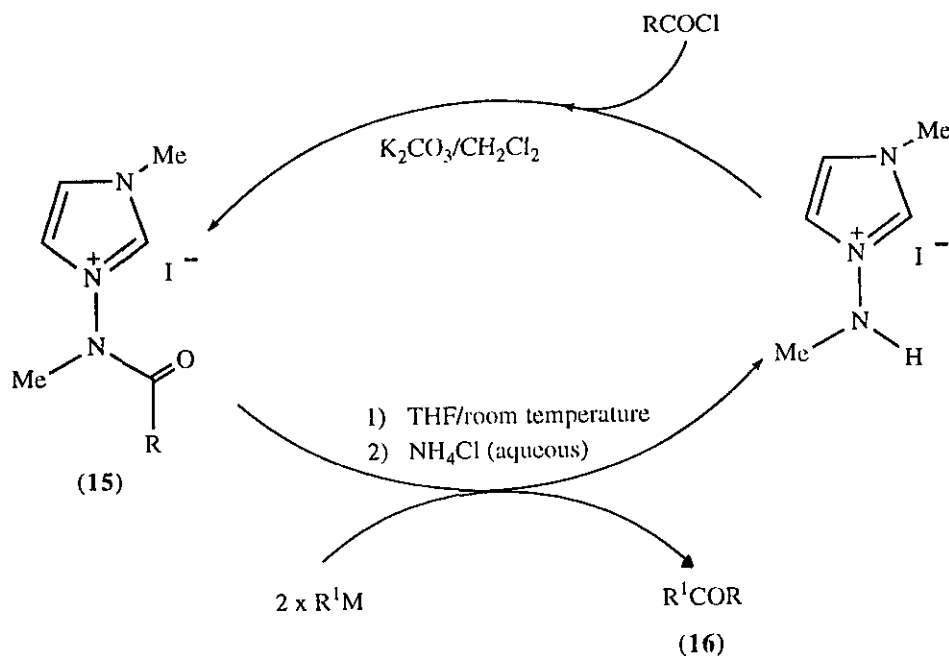
1-Aminopropylimidazole, protected as its diphenylmethylenide derivatives [i.e. $N-(CH_2)_3N=CPh_2$], can be metallated at position-2 and the resulting 2-lithiated derivative can be quenched with aroyl chlorides (71-90% yield).⁶⁹

Although there is evidence that 1-phenylsulphonylimidazole is metallated quantitatively in position-2 with *n*- or *tert*-butyllithium (THF/0° or -20 °C),¹⁰⁰ quenching the resulting anion with carbonyl compounds gives low yields (< 20%) of products.⁸ Similarly, whilst 1-tosylimidazole is metallated in position-2 with butyllithium reaction of the resulting anion with electrophiles results in product yields not exceeding 50%.^{8,18} Both these *N*-protecting groups appear to decrease the nucleophilicity of the 2-anions. The tosyl group is reported to be cleaved by phenylmagnesium bromide.¹⁸ High yields (up to 90%) of 2-substituted derivatives are obtained *via* metallation of *N,N*-dimethylimidazole-1-sulfonamide (Table I) but, again, there is evidence for decreased nucleophilicity of the 2-anion, e.g. quenching with *N,N*-dimethylformamide (DMF) fails to give the corresponding aldehyde.²⁰ Sulfonyl groups are cleaved by hydrolysis with either acid or base (which can be advantageous).

N-Protection with alkenyl (e.g. vinyl) groups is possible.¹⁸ These groups have been little exploited; they have the advantage that they can be cleaved by oxidation with potassium permanganate (alkaline conditions). With an *N*-vinyl group the vinyl protons are not removed. Whilst an *N*-allyl group is isomerised during the metallation step this is advantageous, for oxidative deprotection becomes feasible.

1-Methylimidazole can be quaternized at *N*-3 with 4-methoxybenzyl chloride, the resulting imidazolium salt is readily deprotonated at C-2 with sodium hydride (DMF), and addition of hexachloroethane allows chlorine to be introduced at this position.¹⁰¹ Other 2-substituents may be introduced similarly.¹⁰² 1,3-Dimethylimidazolium salts are deprotonated similarly at position-2 by butyllithium and the resulting anions have been quenched with deuterium oxide, bromomethane, chlorodiphenylphosphine, sulfur dioxide, sulfines, *N*-sulfinylamines, and thiirane (see also ref. 102).¹⁰³

The *N*-(*N*-acyl-*N*-methylamino)imidazolium salts (**15**; R = Me, -CH=CHPh, Ph, thien-2-yl) react with two mol.



Scheme 6

equiv. of an organometallic reagent R¹M (R¹ = Me, Et, Ph; M = MgBr or R¹ = Ph, PhC≡C⁻; M = Li) first by metallation in position-2, then by cleavage to give good yields (75-90%) of ketones (**16**), as shown in Scheme 6.¹⁰⁴ The cleaved imidazolium salt can be recycled. Organolithium reagents react faster than Grignard reagents.

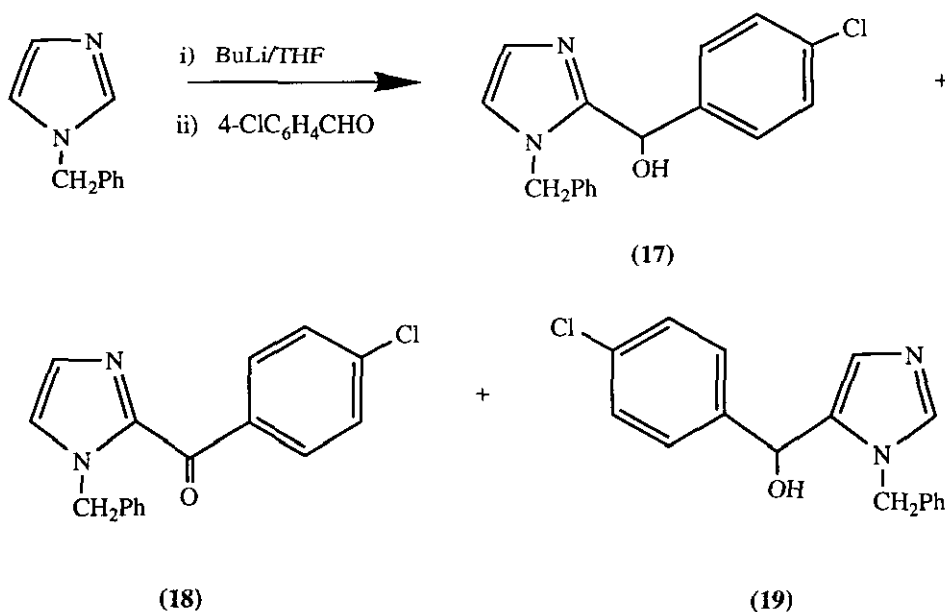
B Lithiation at position-4 (see also next Section)

Direct metallation at this position is only possible in the presence of a sterically demanding *N*-1 substituent or with activated imidazolium salts in which the adjacent position is blocked. Thus, with *tert*-butyllithium (also sterically demanding) in THF, even at -75°C , 2-fluoro-1-tritylimidazole is metallated at position-4.¹⁰⁵ In the case of 2-phenylthio-1-tritylimidazole, however, position-5 is hindered and position-4 is insufficiently reactive towards LDA in THF. Metallation of this substrate with *tert*-butyllithium in THF leads to a mixture of 4- and 5-substituted products in low yields.²²

The imidazolium salt formed by reacting 5-chloro-1-methyl-2-phenylimidazole with 4-methoxybenzyl chloride is readily deprotonated at position-4 (NaH/CH₂Cl₂, KNH₂/liquid NH₃, or BuLi) and the resulting anion can be quenched with various electrophilic reagents [MeI $\rightarrow$ Me (82%), Cl₃CCCl₃ $\rightarrow$ Cl (51%), CBr₄ $\rightarrow$ Br (63%), PhCHO $\rightarrow$ CH(OH)Ph (100%), MeCOCl $\rightarrow$ COMe (50%), MeNCS $\rightarrow$ NHCSMe (8%)].¹⁰¹ When halogen is introduced the 4-methoxybenzyl group is removed at the same time. Both this group and the chlorine atom are removed by nickel boride, thus providing an overall route to 4-substituted 1-methyl-2-phenylimidazoles.

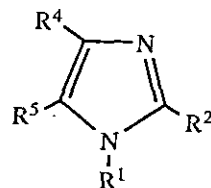
C Lithiation at position-5

Lithiation at this position is only possible when position-2 is blocked (Table III). The reported formation of compound (11) has been discussed earlier (Section II.A). Formation of compound (19) (Scheme 7) (13%

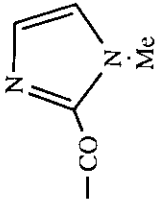
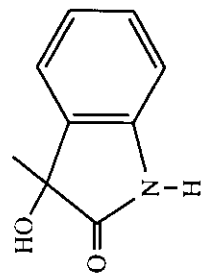


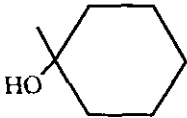
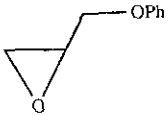
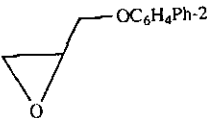
Scheme 7

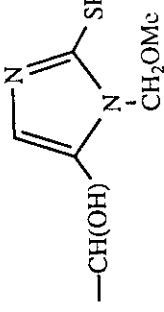
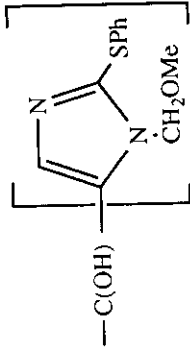
Table III
Imidazoles Synthesised from Imidazol-5-yllithium Compounds

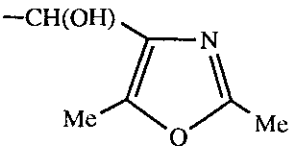
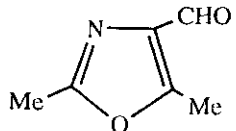
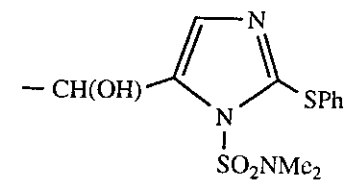


R ¹	R ²	R ⁴	R ⁵	Reagent	Yield (%)	Ref.
Me	Ph	H	CHO	DMF	23	106
Me	Ph	H	CO ₂ H	CO ₂	53	106
Me	Ph	H	COPh	PhCN	27	106
Me	Ph	H	CH(OH)Ph	PhCHO	36	106
Me	Ph	H		CuCl ₂	20	106
Me	CONMe ₂	H	Cl	ClSO ₂ NMe ₂	95	32
Me	CONMe ₂	H	Me	MeI	96	32
Me	CONMe ₂	H	C(OH)Ph ₂	Ph ₂ CO	91	32

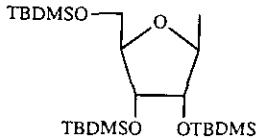
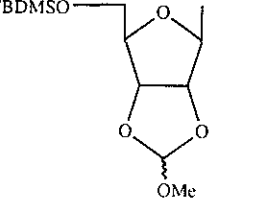
Me	CON(<i>Pr-iso</i>) ₂	H		19	32
Me	NMe ₂	H		45	107
Me	SH	H	CH(OH)Bu- <i>tert</i>	<i>tert</i> -BuCHO	108
Me	SH	H	CH(OH)C ₆ H ₁₁ -c	cyclohexylCHO	108
Me	SH	H	CH(OH)Ph	PhCHO	108
Me	SH	H	CH(OH)C ₆ H ₄ Me-2	2-MeC ₆ H ₄ CHO	108
Me	SH	H	CH(OH)C ₆ H ₄ Me-3	3-MeC ₆ H ₄ CHO	108
Me	SH	H	CH(OH)C ₆ H ₄ Me-4	4-MeC ₆ H ₄ CHO	108
Me	SH	H	CH(OH)C ₆ H ₄ Ph-4	4-PhC ₆ H ₄ CHO	108
Me	SH	H	CH(OH)C ₆ H ₄ O ^t Ph-2	2-PhOC ₆ H ₄ CHO	108
Me	SH	H	CH(OH)C ₆ H ₄ O ^t Ph-4	4-PhOC ₆ H ₄ CHO	108
Me	SH	H	C(OH)Ph ₂	Ph ₂ CO	108

Me	SH	H		cyclohexanone	45	108
Me	SH	H	CH ₂ CH(OH)CH ₂ OPh		17	108
Me	SH	H	CH ₂ CH(OH)CH ₂ OC ₆ H ₄ Ph-2		26	108
Me	SH	H	SPh	Ph ₂ S ₂	66	108
Me	SBu- <i>tert</i>	H	D	D ₂ O	64a	45
Me	SPh	H	CH(OH)Pr	PrCHO	50a	45
Me	SPh	H	CH(OH)Pr- <i>iso</i>	<i>iso</i> -PrCHO	56a	45
Me	SPh	H	CH(OH)Bu- <i>tert</i>	<i>tert</i> -BuCHO	63a	45
Me	SPh	H	CH(OH)Ph	PhCHO	74a	45
Me	SPh	H	CH(OH)C ₆ H ₄ OMe-4	4-MeOC ₆ H ₄ CHO	57a	45
Me	SPh	H	CH(OH)C ₆ H ₃ Cl ₂ -2,4	2,4-Cl ₂ C ₆ H ₃ CHO	57a	45
Me	SPh	H	C(OH)Me ₂	Me ₂ CO	39a	45
Me	SPh	H	C(OH)Et ₂	Et ₂ CO	54a	45

Me	SPh	H	C(OH)(Pr-iso) ₂	(iso-Pr) ₂ CO	69a	45
Me	SPh	H	C(OH)MePh	PhCOMe	70a	45
Me	SPh	H	C(OH)Ph ₂	Ph ₂ CO	91a	45
Me	NO ₂	Br	Bu	BuLi	18	71
CH ₂ OMe	SPh	H		(EtO) ₂ CO	97	22
CH ₂ OMe	SPh	H		HCO ₂ Et	90	22
CH ₂ OMe	Ph	H	CHO	DMF	-	14
CH ₂ OMe	SiMe ₂ Bu- <i>tert</i>	H	D	D ₂ O	100	32
CH ₂ OMe	SiMe ₂ Bu- <i>tert</i>	H	C(OH)Ph ₂	Ph ₂ CO	90	32
CH ₂ OEt	SPh	H	pyrid-2-yl	ZnCl ₂ /pyrid-2-ylBr/ Pd(PPh ₃) ₄	58	29

CH ₂ OE _t	SPh	H			> 98	109
CH ₂ OE _t	Ph	H	SiMe ₃	Me ₃ SiCl	52	16
CH ₂ O(CH ₂) ₂ SiMe ₃	SPh	H	CHO	DMF	90 ^b	63
CH ₂ O(CH ₂) ₂ SiMe ₃	SPh	H	OSiMe ₃	(Me ₃ SiO) ₂	79 ^b	63
CH ₂ O(CH ₂) ₂ SiMe ₃ ^c	Ph	H	I	I ₂	78	58
CH ₂ O(CH ₂) ₂ SiMe ₃	Ph	H	SiMe ₃	Me ₃ SiCl	54	16
CH ₂ O(CH ₂) ₂ SiMe ₃	SiMe ₃	H	CHO	DMF	83 ^{b,d}	63
CH ₂ O(CH ₂) ₂ SiMe ₃	SiMe ₃	H	SPh	Ph ₂ S ₂	83 ^{b,d}	63
CHMeOE _t	CH(OMe) ₂	H	CHO	DMF	78 (crude)	20
CHMeOE _t	Ph	H	Me	MeI	62	20
CHMeOE _t	Ph	H	CHO	DMF	61	20
CHMeOE _t	Ph	H	C(OH)Ph ₂	Ph ₂ CO	55	20
SO ₂ NMe ₂	SPh	H		HCO ₂ Et	84	22
SO ₂ NMe ₂	SiMe ₃	H	CH(OH)pyrid-4-yl	pyrid-4-ylCHO	—	80

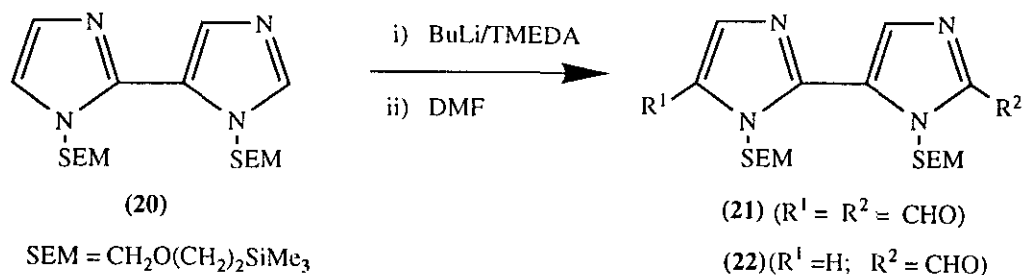
SO ₂ NMe ₂	SiEt ₃	H	D	MeOD	89 ^d	110
SO ₂ NMe ₂	SiEt ₃	H	Cl	ClSO ₂ NMe ₂	72 ^e	110
SO ₂ NMe ₂	SiEt ₃	H	Me	MeI	96 ^d	110
SO ₂ NMe ₂	SiEt ₃	H	CH ₂ Ph	PhCH ₂ Br	64 ^e	110
SO ₂ NMe ₂	SiEt ₃	H	CH ₂ CH=CH ₂	CH ₂ =CHCH ₂ I	85 ^d	110
SO ₂ NMe ₂	SiEt ₃	H	CHO	DMF	—	81
SO ₂ NMe ₂	SiEt ₃	H	CO ₂ H	CO ₂	74 ^{e,f}	110
SO ₂ NMe ₂	SiEt ₃	H	C(OH)Ph ₂	Ph ₂ CO	78 ^b	110
SO ₂ NMe ₂	SiEt ₃	H	SMe	Me ₂ S ₂	92 ^d	110
SO ₂ NMe ₂	SiEt ₃	H	SiMe ₃	Me ₃ SiCl	88 ^d	110
SO ₂ NMe ₂	SiMe ₂ Bu- <i>tert</i>	H	D	D ₂ O	100	32
SO ₂ NMe ₂	SiMe ₂ Bu- <i>tert</i>	H	Cl	ClSO ₂ NMe ₂	86	32
SO ₂ NMe ₂	SiMe ₂ Bu- <i>tert</i>	H	Me	MeI	—	32
SO ₂ NMe ₂	SiMe ₂ Bu- <i>tert</i>	H	(CH ₂) ₃ Cl	Cl(CH ₂) ₃ I	26 ^e	83
SO ₂ NMe ₂	SiMe ₂ Bu- <i>tert</i>	H	(CH ₂) ₄ Cl	Cl(CH ₂) ₄ I	35 ^e	83
SO ₂ NMe ₂	SiMe ₂ Bu- <i>tert</i>	H	(CH ₃) ₅ Cl	Cl(CH ₂) ₅ I	51 ^e	83
SO ₂ NMe ₂	SiMe ₂ Bu- <i>tert</i>	H	CH(OH)Ph	PhCHO	66 ^d	32
SO ₂ NMe ₂	SiMe ₂ Bu- <i>tert</i>	H	C(OH)Ph ₂	Ph ₂ CO	86	32
SO ₂ NMe ₂	SiMe ₂ Bu- <i>tert</i>	H	COC ₆ H ₃ Me ₂ -2,3	2,3-Me ₂ C ₆ H ₃ COCl	91	82

	Cl	CONH ₂	CHO	HCO ₂ Me	13 ^b	111
	Cl	CO ₂ Me	D	CD ₃ OD	93	112
	Cl	CO ₂ Me	I	I ₂	24	112
"	Cl	CO ₂ Me	Me	MeI	83	112-114
"	Cl	CO ₂ Me	CHO	HCO ₂ Et	—	112, 113
"	Cl	CO ₂ Me	CO ₂ Me	ClCO ₂ Me	84, 86	113, 114
"	Cl	CO ₂ Me	COPh	PhCOCl	86	112-114
"	Cl	CO ₂ Me	SPh	Ph ₂ S ₂	84	112-114
"	Cl	CO ₂ Me	SiMe ₃	Me ₃ SiCl	87	112-114
"	Cl	CONH ₂	Me	MeI	32	111
"	Cl	CONH ₂	CHO	HCO ₂ Me	—	111
"	Cl	CONEt ₂	CHO	HCO ₂ Me	63	111

^a With LiTMP/DME/THF at -78 °C. ^b The starting material was 1-SEM protected imidazole ("one-pot" reaction sequences). ^c 2,2'-Bis{5-iodo-1-[2-(trimethylsilyl)ethoxymethyl]imidazol-2-yl}biphenyl (72% yield) was prepared similarly from 2,2'-bis{1-[2-(trimethylsilyl)ethoxymethyl]imidazol-2-yl}biphenyl. ^d After 2-deprotection. ^e After 1- and 2-deprotection. ^f Isolated as the ethyl ester. ^g Overall yield starting from *N,N*-dimethylimidazole-1-sulfonamide. ^h With LDA (83% starting material recovered); use of LiTMP increased yield to 38%. ⁱ TBDMS = SiMe₂Bu-*tert*.

yield) has been reported following successive treatment of 1-benzylimidazole with 1 mol. equiv. each of butyllithium and 4-chlorobenzaldehyde in THF.⁵⁴ The other products isolated, **17** (9%) and **18** (13%), are derived from the 2-lithiated species.

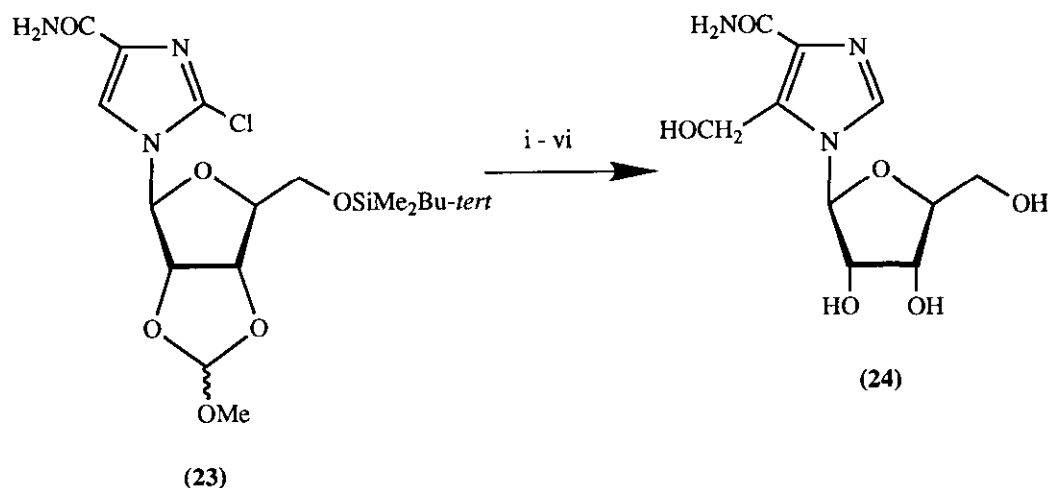
Choice of the metallating system seems to be determined by the structure of the imidazole to be metallated. The biimidazole (**20**) gave a mixture of compounds **21** (7% yield) and **22** (23%) (Scheme 8) following its



Scheme 8

successive treatment with butyllithium (in the presence of TMEDA) and DMF.⁶² 2-(2-Furyl)-1-methylimidazole is metallated (BuLi/Et₂O-hexane/-70 °C) exclusively in the furan ring.¹⁰⁶

Imidazole nucleosides carrying a Cl-atom at C-2 and an ester or amide functionality at C-4 have been deprotonated by LDA¹¹¹⁻¹¹⁴ as a means to the introduction of a substituent at C-5, e.g. the conversion **23** → **24** (Scheme 9) has been achieved in 19% overall yield¹¹¹ (see also ref. 112).



Reagents: i) LDA; ii) HCO₂Me; iii) NaBH₄; iv) H₂/10% Pd-C/MeOH;
v) 20% AcOH; vi) NH₃/MeOH.

Scheme 9

Attempts to deprotonate imidazoles protected at C-2 with trimethyl- or triethylsilyl groups have been less successful. With these substrates *sec*-butyllithium is the reagent of choice. These silyl groups are labile and are introduced immediately prior to metallation in the same pot; work-up invariably is accompanied by deprotection.^{19,63,81,110,115} Only with a *tert*-butyldimethylsilyl protecting group are the 2-protected compounds generally stable and isolable prior to metallation with butyllithium at position-5.^{32,83} The 2-substituent in 1-protected 2-triorganostannylimidazoles is similarly labile.⁴⁹

Recently, however, Winter and Rétey⁸¹ have claimed that 1-(*N,N*-dimethylsulfamoyl)-2-triethylsilylimidazole-4-carbaldehyde is produced in 87% yield when *N,N*-dimethylimidazole-1-sulfonamide is treated successively with butyllithium, chlorotriethylsilane (1 mol. equiv.), *sec*-butyllithium, and DMF, which suggests that *N,N*-dimethyl-2-triethylsilylimidazole-1-sulfonamide undergoes direct metallation at C-4 (see also Section III.A). This result, if correct, is out-of-line with the other results discussed in this Section.

N-Protected 2-phenylthioimidazoles are metallated also at position-5 (Table III).^{12,22,29,45,63,93,116,117} The preferred use of LDA was based on an observation⁹³ that *n*- and *tert*-butyllithium caused C-S bond cleavage. In later studies, however, use of butyllithium was reported to be successful.^{12,117} For the metallation of 1-methyl-2-phenylthioimidazole lithium 2,2,6,6-tetramethylpiperidide (LiTMP) has been used in a DME-THF mixture;⁴⁵ use of *n*- or *sec*-butyllithium gave complex mixtures whilst metallation with LDA was incomplete. When 1-methyl-2-phenylthioimidazol-5-ylithium is allowed to stand for 90 minutes in THF at 0 °C, the phenylthio group migrates to position-5 and 1-methyl-5-phenylthioimidazole and starting material (1:1) are the major products isolated²⁵ (see also Section IV.A). 1-Methylimidazole-2-thiol is metallated by two mol. equiv. of *tert*-butyllithium (THF/-78 °C) at position-5 and in the thiol group and the resulting dianion can be quenched with a wide range of electrophiles, to give the corresponding 5-substituted derivative.¹⁰⁸ Benzyl chloride, however, gave the *S*-benzylated product.

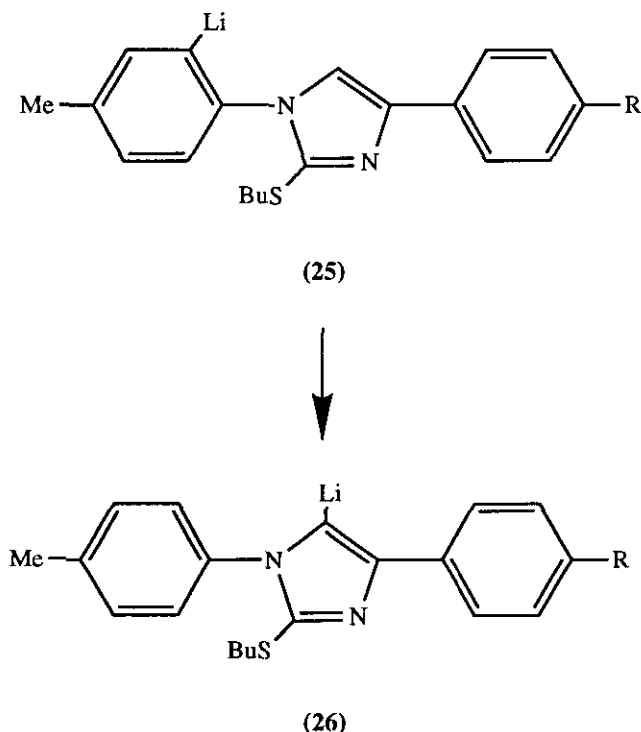
Though of limited application a carboxamide group is a useful 2-protecting group.³² Metallation is achieved with lithium amides.

A number of other *N*-protected 2-substituted imidazoles have been metallated at position-5 (Table III), recently 2-dimethylamino-1-methylimidazole with *sec*-butyllithium in THF.¹⁰⁷ 4-(4-Bromophenyl)- and 4-(2,4-dichlorophenyl)-1-(*N,N*-dimethylsulfamoyl)imidazole-2-carbonitrile apparently can be metallated at C-5 (BuLi/THF/-78 °C) without affecting the other functional groups and the resulting anions have been quenched with ethyl chloroacetate or iodomethane or tosyl cyanide, respectively.⁷⁵ 1,2-Dimethylimidazole is lithiated in

position-5 with butyllithium and LDA but, in addition, α -(or lateral)metallation is observed in the 2-methyl group (Section V)^{32,118} (see also ref. 119).

Various bases, including *tert*-butyllithium and potassium diisopropylamide (KDA), have failed to deprotonate *N*-protected 2-nitroimidazoles (*N*-protecting group = CPh₃, SO₂NMe₂, or SEM).⁷¹ With butyllithium alone, however, 4-bromo-1-methyl-2-nitroimidazole gives a low yield (18%) of its 5-butyl derivative.⁷¹ In this reaction the reagent is behaving as a nucleophile.

The transmetallation reactions **25** $\rightarrow$ **26** (R = H, Me) (Scheme 10) have been proposed to account for the formation of imidazole-5-carboxylic acids following successive treatment of 2-arylimidazo[2,1-*b*]benzothiazoles (C-S bond cleavage) with butyllithium (THF/-70 °C) and carbon dioxide.¹²⁰



Scheme 10

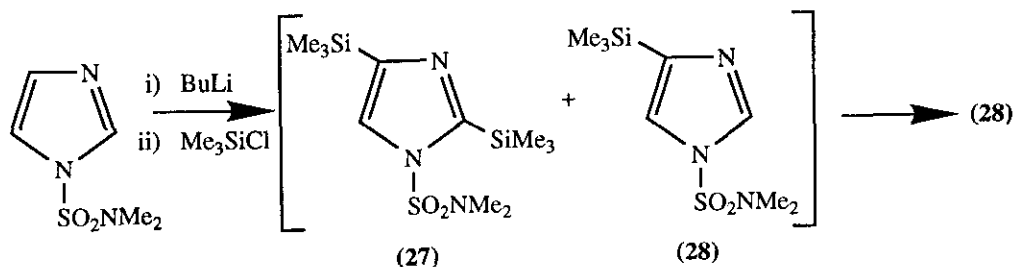
4-Chloro-1,3-dimethyl-2-phenylthioimidazolium salts are deprotonated with sodium hydride in DMF at position-5.¹⁰² Attempts to methylthiolate (with MeSSO₃Na/DMF) the resulting anion results in the formation of a 4-

chloro-1,3-dimethyl-2-methylthio-5-phenylthioimidazolium salt *via* transfer of the phenylthio group from position-2 to position-5.

III POLYLITHIATED DERIVATIVES

A 2,4-Dilithiation

Recently Effenberger *et al.*¹²¹ have claimed that treatment of *N,N*-dimethylimidazole-1-sulfonamide with two mol. equiv. of butyllithium in DME followed by quenching with chlorotrimethylsilane (TMS) and a work-up which results in loss of the 2-trimethylsilyl group from the initial product (27) yields *N,N*-dimethyl-4-trimethylsilylimidazole-1-sulfonamide (28) (Scheme 11), whilst similar treatment of the same substrate with LDA in THF gives *N,N*-dimethyl-5-trimethylsilylimidazole-1-sulfonamide. It is well-known that imidazol-4-yl sp^2



Scheme 11

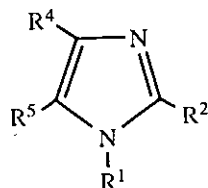
anions are less stable than their 5-counterparts. This has been attributed to the "adjacent lone pair effect".¹²²⁻¹²⁴ Therefore, Effenberger's results¹²¹ seem surprising and merit further investigation (see also Sections II.B and II.C).

B 2,5-Dilithiation

N-Protected imidazoles are *dilithiated* in positions-2 and -5 for the reasons given in Section III.A.^{19,49,90,115} The resulting 2,5-dilithiated species have been quenched with a variety of electrophilic reagents to give 1,2,5-trisubstituted imidazoles; in some cases mixtures of 1,2-di- and 1,2,5-trisubstituted products are isolated (Table IV). Yields of trisubstituted products are related to the ability of the initially generated 2-anion to undergo further

Table IV

Synthesis of 1,2,5-Trisubstituted Imidazoles by 2,5-Dilithiation of 1-Substituted Imidazoles

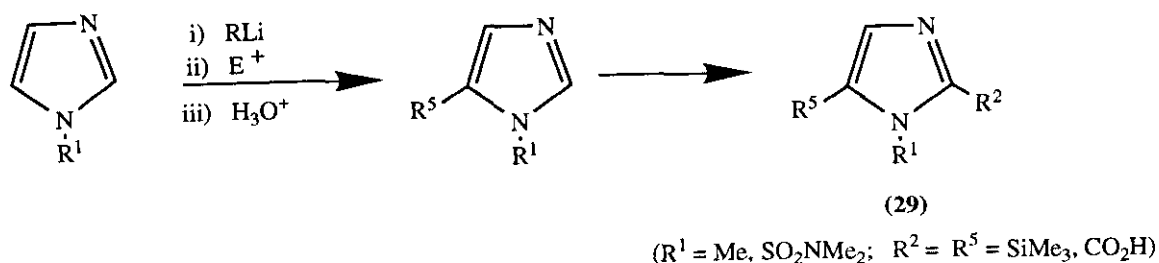


R ¹	R ²	R ⁵	Reagent	Yield (%)	Ref.
Me	CO ₂ H	CO ₂ H	CO ₂	—	22
Me	SMe	SMe	Me ₂ S ₂	34	44
Me	SiMe ₃	SiMe ₃	Me ₃ SiCl	58 ^a , 68	22, 115
Me	SnBu ₃	SnBu ₃	Bu ₃ SnCl	91 ^b	49
CH ₂ OBu- <i>tert</i>	D	D	D ₂ O	50	59
CH ₂ O(CH ₂) ₂ OMe	D	D	D ₂ O	40	59
SO ₂ NMe ₂	SiMe ₃	SiMe ₃	Me ₃ SiCl	85 ^c	121

^a After 2-desilylation. ^b After 2-destannylation ^c After 1-deprotection.

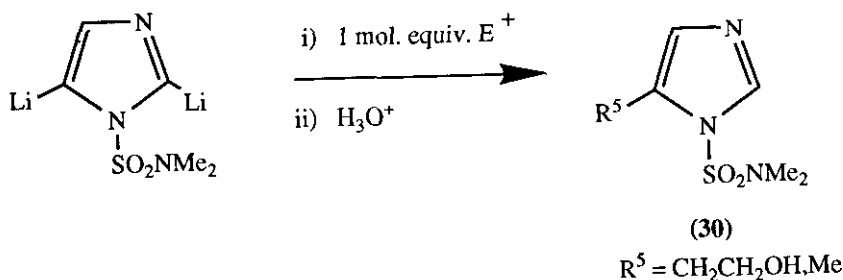
deprotonation, to yield the 2,5-dianion.⁹⁰ Whereas a large excess of reagent is required to quantitatively dilithiate 1-methyl- and 1-methoxymethylimidazoles, *N,N*-dimethylimidazole-1-sulfonamide is 2,5-dilithiated in quantitative yield under milder conditions.¹⁹

Some of the 1,2,5-trisubstituted imidazoles initially generated by quenching are prone to lose their labile 2-substituents. This is observed, e.g., with compounds carrying trimethylsilyl, tributylstannyl, or carboxyl groups at position-2.^{22,49,90,121} [Scheme 12 for generation of compounds (29)].



Scheme 12

Another advantage of the sulfonamide group as an *N*-protecting group in dilithiation studies is that the negligible excess of lithiating reagent over substrate required permits reaction of the 2,5-dilithiated intermediate with one mol. equiv. of an electrophile, which yields a 1,5-disubstituted product (30) (Scheme 13).¹⁹ Dimethyl sulfate is



Scheme 13

preferred to iodomethane for introduction of a 5-methyl group. Position-5 in the 2,5-dilithiated intermediate is more reactive than position-2. Hydrolysis on work-up removes lithium at position-2 but presumably a different substituent could be introduced at this position if a further mol. equiv. of the same or a different electrophile was added.

C Others

When treated with two mol. equiv. of butyllithium (THF/-78 °C) 4-(2,4-dichlorophenyl)-*N,N*-dimethylimidazole-1-sulfonamide is metallated both at C-2 and between the Cl-atoms in the 4-aryl ring; the corresponding dialdehyde is isolated following quenching with DMF.⁷⁵

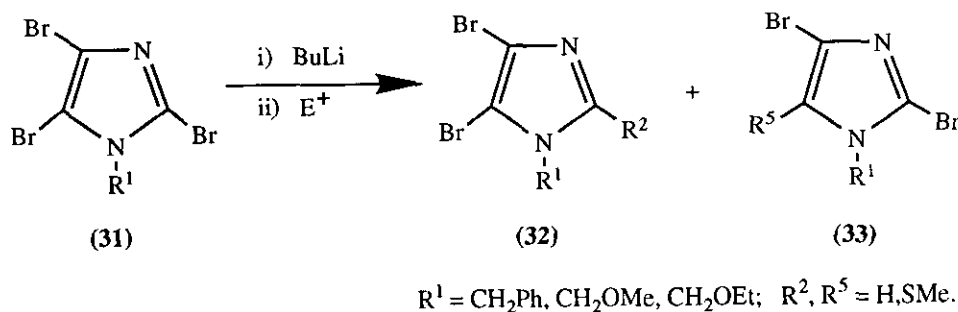
Several polyolithiated imidazoles have been synthesised *via* Br $\rightarrow$ Li exchange reactions (see Section IV).

IV HALOGEN $\rightarrow$ LITHIUM EXCHANGE REACTIONS

Halogenated imidazoles undergo halogen $\rightarrow$ metal exchange reactions with organolithium reagents and the derived imidazolylithium derivatives have been used for the introduction of a variety of substituents. These reactions have the advantage that they can be carried out at low temperatures, even as low as -100 °C, often in the presence of other substituents normally reactive towards the reagent at higher temperatures. The order of reactivity is 2-X > 5-X > 4-X ("ALP effect" applicable; see Section III.B) (X = halogen, usually Br but occasionally I and, rarely, Cl).

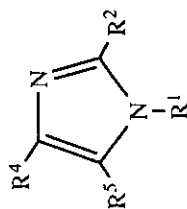
A *N*-Protected imidazoles

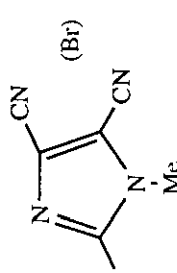
It is possible to exchange bromine (and iodine) atoms for lithium at any position in an *N*-protected bromo(or iodo)imidazole. With *N*-protected 2,4,5-tribromoimidazoles the bromine atoms can be replaced selectively in the order 2 $\rightarrow$ 5 $\rightarrow$ 4 in good to excellent yields,^{8,125-128} thus providing a useful route to polysubstituted imidazoles (Table V). For selective exchange at position-2 in the presence of halogens at other positions yields are dependent on the metallating reagent and its rate of addition to the substrate. Careful temperature control is important also. In THF or ether at -78 °C *N*-protected 2,4,5-tribromoimidazoles (**31**) seem to react with butyllithium to give mixtures of the 2- (**32**; R² = Li) and 5-lithiated derivatives (**33**; R⁵ = Li) (Scheme 14),¹²⁵⁻¹²⁶ although a recent

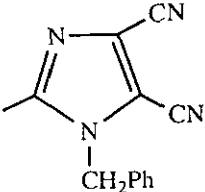


Scheme 14

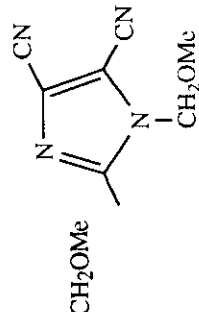
Table V

1-Protected Imidazoles Synthesised via Halogen $\rightarrow$ Lithium Exchange Reactions^a

R ¹	R ²	R ⁴	R ⁵	Reagent	Yield (%)	Ref.
Me	SPh (Br)	H	Br	PhSO ₂ Ph	80	25
Me	SiMe ₃ (Br)	H	Br	Me ₃ SiCl	—	25
Me	SiMe ₂ Bu- <i>tert</i> (Br)	H	Br	<i>tert</i> -BuMe ₂ SiCl	—	25
Me	SMe (Br)	Br	Br	Me ₂ S ₂	93	128
Me	H (Br)	CN	CN	H ₂ O	48	52, 15
Me	Me (Br)	CN	CN	MeI	—	15
Me	CO ₂ H (Br)	CN	CN	CO ₂	42	15
Me		CN	CN	CuCl ₂ /O ₂ /H ₃ O ⁺	58	52
Me	H	CHO (I)	CH(OEt) ₂	DMF	47 ^b	129

Me	H	Br	H (Br)	H ₂ O	80	24
Me	H	Br	CO ₂ Me (Br)	(MeO) ₂ CO	50	130
Me	SPh	H	Bu (Br)	BuBr ^c	65	25
Me	H	I	H (I)	H ₂ O	85	24
Me	H (Br)	Br	H (Br)	H ₂ O	—	24
Me	CHO (Br)	H	CHO (Br)	DMF	48 ^d	25
Me	SMe (Br)	Br	CHO (Br)	Me ₂ S ₂ , DMF	85 ^e	128
Me	SiMe ₃ (Br)	H	SiMe ₃ (Br)	Me ₃ SiCl	88 ^d	25
Me	SMe (Br)	CHO (Br)	CHO (Br)	Me ₂ S ₂ /DMF/DMF	51 ^e	128
Me	SMe (Br)	SnBu ₃ (Br)	H (Br)	Me ₂ S ₂ / <i>iso</i> -PrOH/Bu ₃ SnCl	40 ^e	128
CH ₂ Ph	SMe (Br)	Br	Br	Me ₂ S ₂	72	125, 126
CH ₂ Ph	SPh (Br)	Br	Br	Ph ₂ S ₂	97	128
CH ₂ Ph	 (Br)	CN	CN	CuCl ₂ /O ₂ /H ₃ O ⁺	60	52
CH ₂ Ph	SMe (Br)	Br	CHO (Br)	Me ₂ S ₂ /DMF	60 ^e	126
CH ₂ Ph	H	Br	CHO (Br)	DMF	53	125
CH ₂ Ph	H	Br	CO ₂ H (Br)	CO ₂	67	125

CH ₂ Ph	H	Br	CO ₂ Me (Br)	ClCO ₂ Me	61	125
CH ₂ Ph	H	Br	SH (Br)	S ₈	68	125
CH ₂ Ph	SCH ₂ Ph	Br	CHO (Br)	DMF	54	125
CH ₂ Ph	SPh	Br	CHO (Br)	DMF	52	125
CH ₂ Ph	Ph	Br	CHO (Br)	DMF	82	131
CH ₂ Ph	H (Br)	Br	H (Br)	H ₂ O	71 $\frac{1}{2}$	126
CH ₂ Ph	SMe (Br)	Br	SMe (Br)	Me ₂ S ₂	72 $\frac{1}{2}$	126
CH ₂ Ph	SMe (Br)	SMe (Br)	SMe (Br)	Me ₂ S ₂	67 $\frac{1}{2}$	126
CH ₂ Ph	SMe (Br)	CH(OH)Ph (Br)	H (Br)	Me ₂ S ₂ / <i>iso</i> -PrOH/PhCHO	55 $\frac{1}{2}$	128
CH ₂ Ph	SMe (Br)	CH(OH)C ₆ H ₁₃ (Br)	H (Br)	Me ₂ S ₂ / <i>iso</i> -PrOH/C ₆ H ₁₃ CHO	66 $\frac{1}{2}$	128
CH ₂ Ph	SMe (Br)	C(OH)Me ₂ (Br)	H (Br)	Me ₂ S ₂ / <i>iso</i> -PrOH/Me ₂ CO	71 $\frac{1}{2}$	128
CH ₂ Ph	SMe (Br)	CHO (Br)	SiMe ₃ (Br)	Me ₂ S ₂ /Me ₃ SiCl/DMF	59 $\frac{1}{2}$	128
CH ₂ Ph	SMe (Br)	CH(OH)C ₅ H ₁₁ (Br)	SiMe ₃ (Br)	Me ₂ S ₂ /Me ₃ SiCl/C ₅ H ₁₁ CHO	61 $\frac{1}{2}$	128
CH ₂ Ph	SPh (Br)	Cl (Br)	H (Br)	Ph ₂ S ₂ / <i>iso</i> -PrOH/Cl ₃ CCCl ₃	44 $\frac{1}{2}$	128
CH ₂ Ph	SPh (Br)	CHO (Br)	H (Br)	Ph ₂ S ₂ / <i>iso</i> -PrOH/DMF	64 $\frac{1}{2}$	128
CHBuPh	SMe (Br)	SMe (Br)	SMe (Br)	Me ₂ S ₂ /BuBr $\frac{1}{2}$	33 $\frac{1}{2}$	126
CHBuPh	SMe (Br)	CHO (Br)	SMe (Br)	Me ₂ S ₂ /DMF/BuBr $\frac{1}{2}$	46 $\frac{1}{2}$	126
CH ₂ C ₆ H ₄ OMe-4	H	Br	CHO (Br)	DMF	50	125
CH ₂ C ₆ H ₃ (OMe) ₂ -3,4	H	Br	CHO (Br)	DMF	55	125

	CN	CuCl ₂ /O ₂ /H ₃ O ⁺	27	52
CH ₂ OMe	CH ₂ OMe	CH ₂ OMe	Br	125
CH ₂ OMe	CH ₂ OMe	CH ₂ OMe	Br	125
CH ₂ OMe	SPh	CH ₂ OMe	Br	125
CH ₂ OMe	SPh	CH ₂ OMe	Br	125
CH ₂ OMe	SiMe ₃	CH ₂ OMe	Cl	57
CH ₂ OCH ₂ Ph	H (l)	CH ₂ OMe	I	60
CH ₂ OCH ₂ Ph	SPh (l)	CH ₂ OMe	I	127
CH ₂ OCH ₂ Ph	H (l)	CH ₂ OMe	H (l)	60
CH ₂ OCH ₂ Ph	CO ₂ Me (l)	CH ₂ OMe	CO ₂ Me (l)	127
CH ₂ OCH ₂ Ph	H	CH ₂ OMe	I	60
CH ₂ OCH ₂ Ph	H	CH ₂ OMe	I	60
CH ₂ OCH ₂ Ph	Bu	CH ₂ OMe	I	132

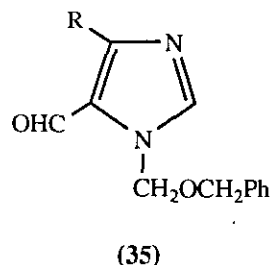
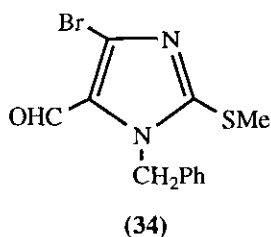
CH ₂ OCH ₂ Ph	SPh	I	CHO (I)	DMF	99	127
CPh ₃	H	CHO (I)	H	DMF	83	124

^a Position of halogen → lithium exchange in parentheses; butyllithium used in all cases except for ref. 126 in which methylolithium was used to introduce substituents into position-2 (first) of 1-benzyl-2,4,5-tribromimidazole. ^b After deprotection with H₃O⁺ at position-5. ^c Generated by the initial Br → Li exchange reaction. ^d 2-Substituent lost on work-up. ^e "One pot" reactions starting with 1-substituted 2,4,5-tribromimidazole. ^f 2-Py = pyrid-2-yl.

report¹²⁸ claims exclusive bromine $\rightarrow$ lithium exchange at position-2 with butyllithium (THF/-78 °C). The electrophilic quenching reagents were added just 5 minutes following addition of the butyllithium, which might be significant.

Selective exchange of the 2-bromine atom in compound (**31**; $R^1 = \text{CH}_2\text{Ph}$) is possible, however, with methyl-, phenyl-, or *sec*-butyllithium, to give the 2-lithiated derivative (**32**; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Li}$).^{125,126} With methyl-lithium compound (**31**; $R^1 = \text{CH}_2\text{OMe}$) yields lithium derivative (**32**; $R^1 = \text{CH}_2\text{OMe}$, $R^2 = \text{Li}$) which has been converted to the 2-methylimidazole (**32**; $R^1 = \text{CH}_2\text{OMe}$, $R^2 = \text{Me}$) with bromomethane.¹²⁵ To avoid coupling of imidazolyl-lithium derivatives with the bromo(or iodo)alkanes released by the initial halogen $\rightarrow$ metal exchange reaction it is preferable to quench them without too much delay.

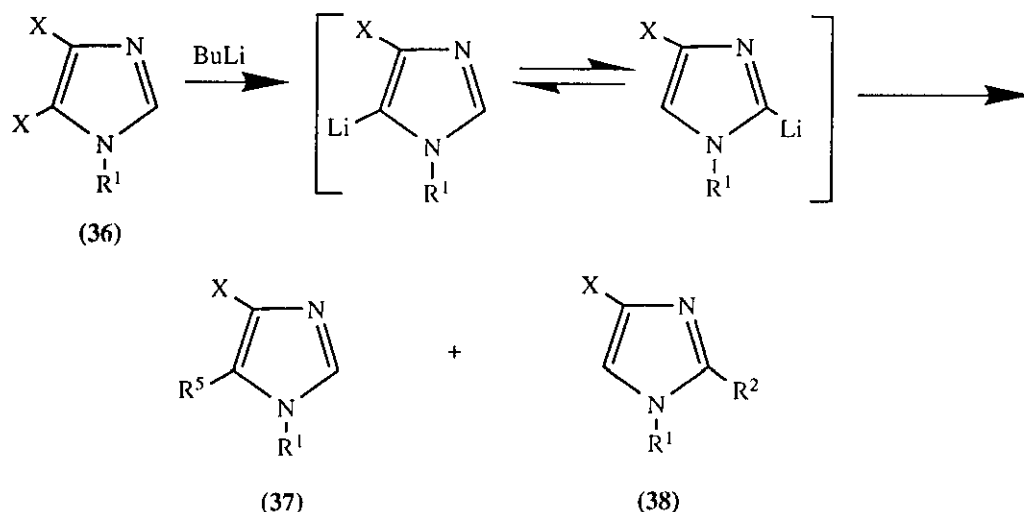
When 5-bromo-2-*tert*-butyldimethylsilyl-1-methylimidazole is treated with butyllithium (THF/-70 °C) and the reaction mixture quenched (with aqueous NH_4Cl) the product is 5-*tert*-butyldimethylsilyl-1-methylimidazole (55% yield); the 2-silyl group migrates to position-5.²⁵ When 1-methyl-2-trimethylsilylimidazol-5-yl-lithium is prepared similarly and quenched with DMF prior to work-up, the product is a mixture (50% yield) of 1-methylimidazole-5-carbaldehyde and 5-trimethylsilyl-1-methylimidazole-2-carbaldehyde (40:60).²⁵ 5-Butyl-1-methyl-2-phenylthioimidazole is formed in 65% yield when 5-bromo-1-methyl-2-phenylthioimidazole is treated with butyllithium in THF at -70 °C, and the resulting lithiated imidazole is allowed to warm up to 0 °C.²⁵ The result of bromine $\rightarrow$ lithium exchange at position-5 is dependent on the nature of the substituent at position-2 (Table V). In a one-pot procedure exchange at position-2 in 1-benzyl-2,4,5-tribromoimidazole (**31**; $R^1 = \text{CH}_2\text{Ph}$) with one mol. equiv. methyl-lithium, quenching with one mol. equiv. of dimethyl disulfide, exchange at position-5 with one mol. equiv. of butyllithium, and quenching with DMF gave compound (**34**) (60% overall yield).¹²⁶ Compound (**35**; $R = \text{I}$) (62% yield) was obtained similarly from 1-benzyloxymethyl-2,4,5-



triiodoimidazole when the 2-protecting group and metallating agent were the labile trimethylsilyl group and butyllithium, respectively.¹²⁷ A one-pot exchange procedure gave **35** ($R = \text{Me}$) (29%) and **35** ($R = \text{CO}_2\text{Me}$)

(25%) after sequential work-up of the lithiated intermediate (generated with BuLi) with chlorotrimethylsilane, 1-formyl-1,2,2-trimethylhydrazine, and iodomethane ($R = \text{Me}$) or chlorotrimethylsilane, 1-formyl-1,2,2-trimethylhydrazine, and dimethylpyrocarbonate ($R = \text{CO}_2\text{Me}$), respectively.¹²⁷ The different atoms or functional groups can be introduced into *N*-protected 2,4,5-trihaloimidazoles *via* these halogen $\rightarrow$ lithium exchange techniques in the order position-2 $\rightarrow$ -5 $\rightarrow$ -4.^{8,125-128,132} Thus, e.g. starting with 1-benzyloxymethyl-2,4,5-triiodimidazole the following groups can be introduced in the following order: 2-SPh with diphenyl disulfide (94% yield), 5-CHO with DMF (99%), 4-CO₂Me with methyl chloroformate [80% after protection of the formyl group (58% yield) as its ethylene acetal].¹²⁷ Recently Lipshutz and Hagen¹²⁸ have used this methodology to good effect to synthesise 1-methyl-2-methylthioimidazole-4,5-dicarbaldehyde, a starting material for a preparation of the antitumour agent carmethizole, in 51% yield in a "one-pot" reaction sequence. Starting with 1-benzyl(or methyl)-2,4,5-tribromoimidazole a number of *N*-protected 2,4-di- or 2,4,5-trisubstituted imidazoles were prepared similarly (40-71% yields) in "one-pot" reaction sequences, e.g. (1-benzyl-2-methylthioimidazol-4-yl)dimethylmethanol (71%) (H was introduced at position-5 using 2-propan-ol). 1-Benzyloxymethyl-2-butyl-4,5-diiodimidazole may be converted similarly into 1-benzyloxymethyl-2-butyl-4-iodimidazole-2-carbaldehyde (66% yield; 19% of product arising from hydrolysis of imidazol-5-yl lithium compound isolated also), a starting material for the synthesis of Angiotensin II inhibitors related to Losartan (DuP 753).¹³²

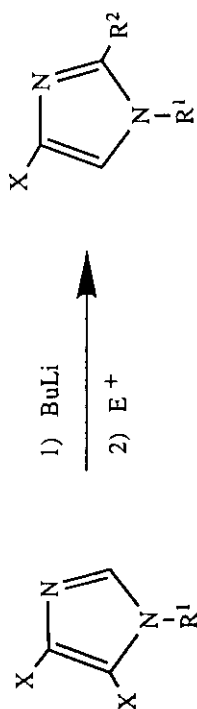
Complications arise when *N*-protected 4,5-dihaloimidazoles (**36**; $X = \text{Br}$ or I) are allowed to react with organolithium reagents. Exchange initially occurs at position-5 but transmetalation with position-2 can occur, even at -78°C , resulting in the formation of mixtures of products, (**37**) and (**38**) (Scheme 15) [cf.



Scheme 15

Table VI

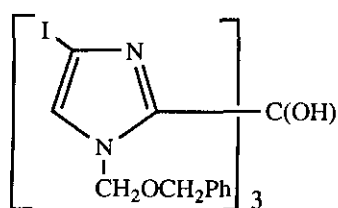
Imidazoles Synthesised *via* Halogen $\rightarrow$ Metal Exchange Followed by Transmetalation of a 5-Lithiated
to a 2-Lithiated Intermediate



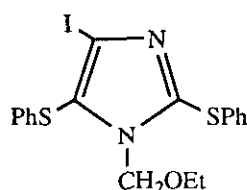
R ¹	X	R ²	Reagent	Yield (%)	Ref.
Me	Br	Br	Br ₂	87	24
Me	I	I	I ₂	53	24
Me	Br	CHO	DMF	52	134
CH ₂ OCH ₂ Ph	I	CHO	DMF	68	60
CH ₂ OCH ₂ Ph	I	$\left[\begin{array}{c} \text{I} \\ \text{N} \diagup \text{C}(\text{OH}) \diagdown \\ \text{N} \end{array} \right] \left[\begin{array}{c} \text{CH}_2\text{OCH}_2\text{Ph} \end{array} \right]_2$	1/3(EtO) ₂ CO	59	60

the behaviour of similar Grignard compounds (Section VI)].

Compound (39) was isolated in 59% yield when the lithium derivative (36; X = I, R¹ = CH₂OCH₂Ph) was allowed to react with 0.33 mol. equiv. of diethyl carbonate.⁶⁰ 5-Bromo-1-methylimidazole is reported to give its 5-lithiated derivative with butyllithium;¹³³ quenching with acetaldehyde yields the corresponding carbinol (no rearrangement). In the reaction of 1-ethoxymethyl-4,5-diiodoimidazole (36; X = I, R¹ = CH₂OEt) with one mol. equiv. of butyllithium followed by quenching with diphenyl disulfide compound (38; X = I, R¹ = CH₂OEt, R² = SPh) was obtained together with imidazole (40) (ratio 4.6:1).¹³ The formation of compound (40) is indicative



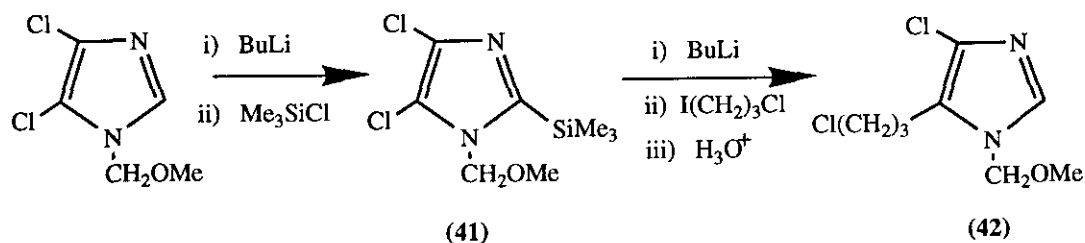
(39)



(40)

of competing metallation at position-2 and iodine → lithium exchange at position-5. Transmetallation from position-5 to position-2 is common when quenching is carried out with weak electrophiles.

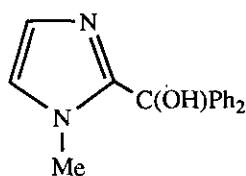
4,5-Dichloro-1-methoxymethylimidazole undergoes metallation at position-2 with butyllithium (THF/-70 °C).⁵⁷ However, initial protection of position-2 by a silyl group (41) followed by addition of butyllithium apparently results in exchange of chlorine at position-5; quenching the 5-lithiated intermediate with 1-chloro-3-iodopropane gives imidazole (42) (Scheme 16). Other examples of 2-lithiation of 5-chloroimidazoles are given in Table I.



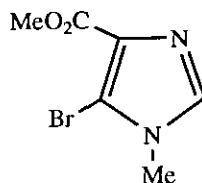
Scheme 16

With lithium naphthalenide, however, 5-chloro-1-methylimidazole gives compound (43) (83% yield) on quenching the lithiated derivative with benzophenone, presumably due to transmetallation of the initially generated 5-lithiated compound (*cf.* Scheme 15).⁸⁵

Rapoport's group isolated products different from those expected from Scheme 15 when they allowed 4,5-dibromo-1-methylimidazole to react with butyllithium ($\text{Et}_2\text{O}/-78^\circ\text{C}$) and quenched the reaction mixture with dimethyl carbonate, which gave the expected 5-carboxylate (**37**; $\text{X} = \text{Br}$, $\text{R}^1 = \text{Me}$, $\text{R}^5 = \text{CO}_2\text{Me}$) (50% yield) together with compound (**44**) (10%).¹³⁰ This result suggests that both the bromine atoms undergo exchange in ether, with the lower yield of compound (**44**) reflecting the expected lower reactivity at position-4.

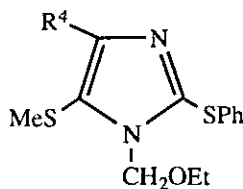


(43)

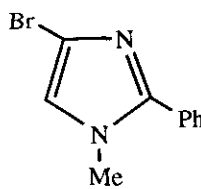


(44)

Exchange of bromine at position-4 is feasible when both positions-2 and -5 are blocked.¹²⁶ Starting with 1-benzyl-2,4,5-tribromoimidazole exchange of the bromine atoms at positions-2 and -5 with butyllithium followed by addition of dimethyl disulfide yields 1-benzyl-4-bromo-2,5-bis(methylthio)imidazole (72% yield). The remaining bromine atom can be exchanged by addition of another mol. equiv. of butyllithium and the resulting 4-lithiated species can be quenched with various electrophiles. Similarly 1-benzyl-2,4,5-tribromoimidazole can be converted in a "one-pot" sequence into 1-benzyl-2,4,5-tris(methylthio)imidazole (67%).¹²⁶ Compound (**45**; $\text{R}^4 = \text{Br}$) yields a 4-lithiated derivative with butyllithium ($\text{Et}_2\text{O}/-70^\circ\text{C}$) which can be quenched with carbon dioxide, dimethyl disulfide, and DMF to give the expected products (**45**; $\text{R}^4 = \text{CO}_2\text{H}$, SMe , or CHO , respectively) in high yields.^{12,117}



(45)



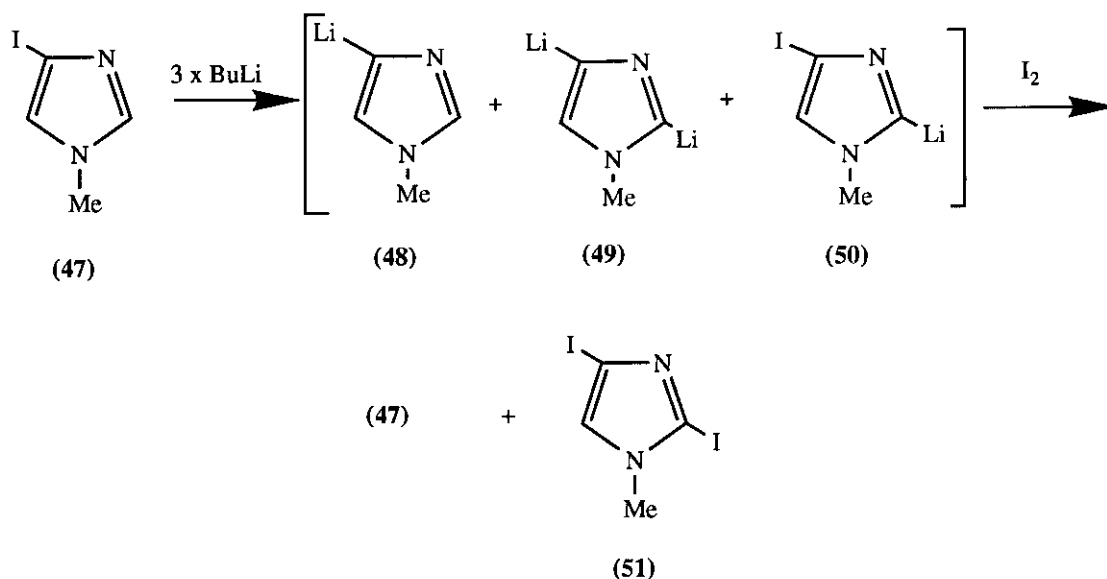
(46)

Exchange of bromine at position-4 with position-5 unprotected ($\text{BuLi}/\text{THF}/-78^\circ\text{C}$) has been claimed¹¹⁶ for compound (**46**). With diethyl carbonate the resulting 4-lithiated derivative gave ethyl 1-methyl-2-phenylimidazole-4-carboxylate. Attempts to exchange the bromine atoms in 4- and 5-bromo-1-methylimidazole for

lithium with butyllithium have been reported as unsuccessful.^{13,22,93} 4-Bromo-1-methylimidazole is metallated instead at position-2 (Table I).¹³³

Exchange of iodine at position-4 with butyllithium is known to occur in imidazoles unprotected at positions-2 and -5. 4-Iodo-1-triphenylmethylimidazole, e.g., readily gives its 4-lithiated derivative which can be quenched after 2 seconds with DMF, to give the corresponding 4-carbaldehyde (83% yield).¹²⁴ A two-three mol. equiv. excess of butyllithium is required to react also with the iodobutane generated in the reaction. Under these conditions 1-triphenylmethylimidazole-2-carbaldehyde (11%) and 1-triphenylmethylimidazole-4,5-dicarbaldehyde are present also in the crude product. When a stoichiometric amount of butyllithium is employed, the yield of 1-triphenylmethylimidazole-4-carbaldehyde is reduced to 50% and 1-triphenylmethylimidazole (19%), starting material (8%), 1-triphenylmethylimidazole-2-carbaldehyde (7%), and 4-iodo-1-triphenylmethylimidazole-2-carbaldehyde (16%) were detected also in the crude product.¹²⁴

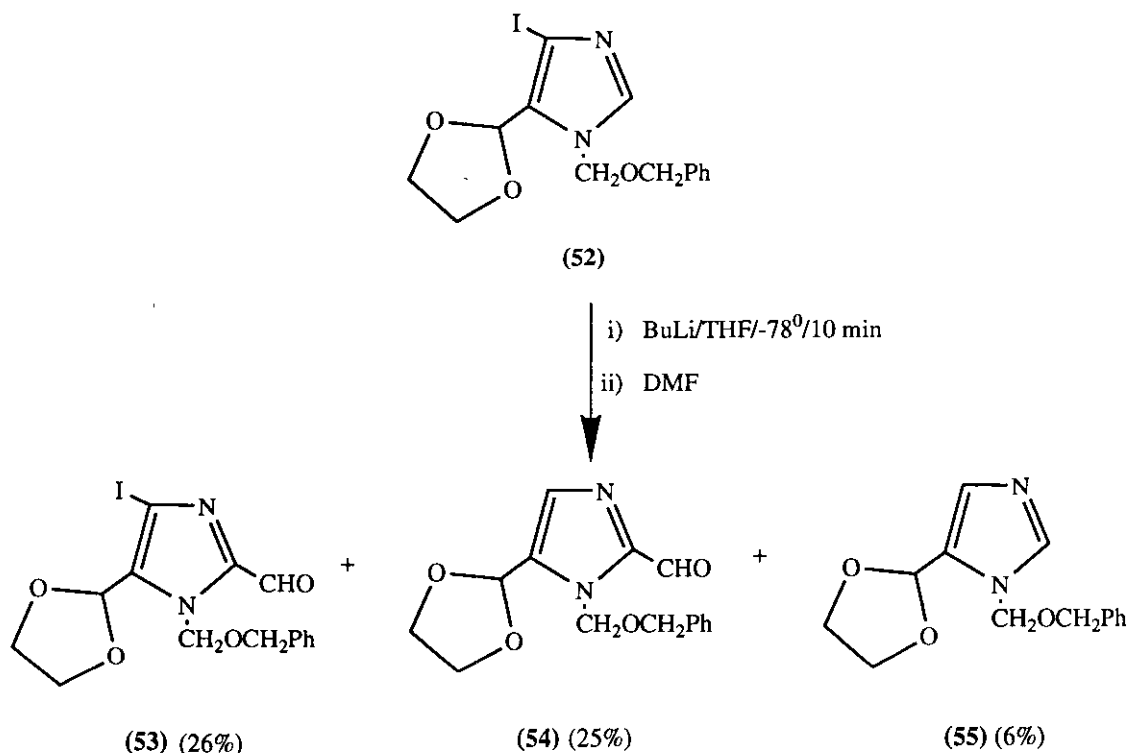
A similar study with 4-iodo-1-methylimidazole (**47**) gave 2,4-diiodo-1-methylimidazole (**51**) (Scheme 17) in a maximum yield of 40% when the reaction was quenched with iodine.¹³⁵ Starting material was recovered even



Scheme 17

though three mol. equiv. of butyllithium was used. The lithiated derivatives (48)-(50) were believed to be present in the reaction mixture prior to quenching, suggesting that metallation in position-2 is significant in this case.

An intermediate similar to **50** has been trapped by Groziak's group,⁶⁰ who reported isolation of aldehyde (**53**) (26% yield) (Scheme 18) from treatment of the 4-iodoimidazole (**52**) with butyllithium (THF/-78 °C) followed

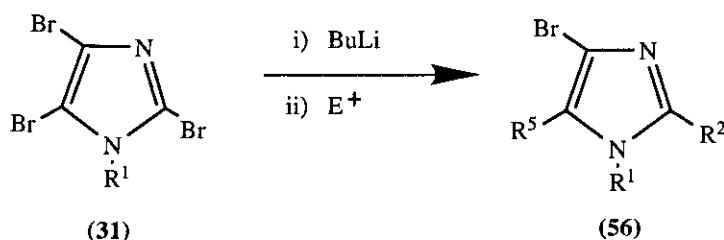


Scheme 18

by addition of DMF. Simultaneous formation of compound (**54**) is evidence of transmetallation to position-2. When the 2-lithiated derivative of compound (**52**) was quenched after 15 minutes with aqueous ammonium chloride, imidazole (**55**) was obtained (76%). The 2-deuteriated derivative of **55** was obtained with deuterium oxide as the quenching reagent, indicating transmetallation of the 4-lithiated intermediate to the 2-lithiated derivative. Similar results were obtained at -100 °C after 15 min.

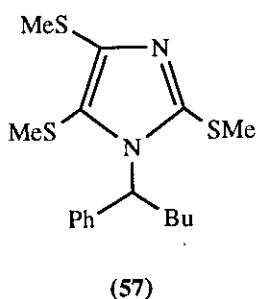
However, when 5-diethoxymethyl-4-iodo-1-methylimidazole is treated successively with butyllithium ($\text{Et}_2\text{O}/-30^\circ\text{C}$), DMF, and acid, it yields a moderate yield (47%) of 1-methylimidazole-4,5-dicarbaldehyde *via* an intermediate 4-lithiated compound.¹²⁹

As hinted above *N*-protected 2,4,5-tribromoimidazoles (**31**) yield their 2,5-dilithiated derivatives (**56**; $\text{R}^2 = \text{R}^5 = \text{Li}$) with two mol. equiv. of an organolithium reagent (Scheme 19). 4-Bromo-1-methylimidazole is obtained when the 2,5-dilithiated derivative (**56**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{R}^5 = \text{Li}$) of 2,4,5-tribromo-1-methylimidazole



Scheme 19

(**31**; $\text{R}^1 = \text{Me}$) is quenched with water.²⁴ 1-Benzyl-2,4,5-tribromoimidazole (**31**; $\text{R}^1 = \text{CH}_2\text{Ph}$) (Scheme 19) similarly yields compound (**56**; $\text{R}^1 = \text{CH}_2\text{Ph}$; $\text{R}^2 = \text{R}^5 = \text{H}$) (71% yield).¹²⁶ When the quenching reagent is dimethyl disulfide, compound (**56**; $\text{R}^1 = \text{CH}_2\text{Ph}$, $\text{R}^2 = \text{R}^5 = \text{SMe}$) (72%) is the product. Attempts to prepare the 2,4,5-trilithiated derivative of compound (**31**; $\text{R}^1 = \text{CH}_2\text{Ph}$) with five mol. equiv. of butyllithium resulted in α -(or lateral)metallation in addition to bromine $\rightarrow$ lithium exchange and, after quenching with dimethyl disulfide,



afforded compound (**57**) (33% yield).¹²⁶ The butyl group is introduced by capture of the bromobutane generated by the initial bromine $\rightarrow$ lithium exchange reactions.

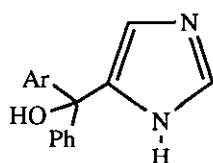
With two mol. equiv. of butyllithium ($\text{THF}/-70^\circ\text{C}$) 2,5-dibromo-1-methylimidazole gives the corresponding 2,5-dilithiated imidazole which can be quenched with 2 mol. equiv. of DMF or chlorotrimethylsilane, to give 1-

methylimidazole-5-carbaldehyde (48% yield; the major product is 1-methylimidazole) or 1-methyl-5-trimethylsilylimidazole (88%), respectively. The 2-substituent is lost on work-up (with aqueous NH_4Cl).²⁵

B N-Unprotected imidazoles

Metallation of mono- or polyhalogenated imidazoles *unsubstituted* on the ring N-atom occurs initially to give the N-lithiated species^{12,13,22,125} then, with an excess of the organolithium reagent, halogen $\rightarrow$ metal exchange is observed. With five mol. equiv. of butyllithium in THF 4(5)-bromimidazole, e.g., yields a 1,4(5)-dilithiated derivative which affords imidazole or 4(5)-deuterioimidazole following addition of methanol or deuteriomethanol, respectively.¹³⁶ With lithium naphthalenide followed by quenching with benzophenone the same substrate affords carbinol (**58**; Ar = Ph) in yields of up to 64%.^{22,125,137}

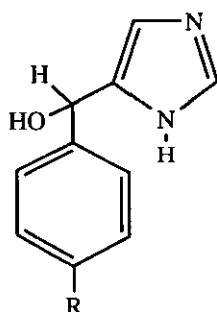
The yields of products derived from 4(5)-bromimidazole are dependent on the base used, the time taken to generate the dilithiated species, and the quantity of electrophilic quenching reagent added.²² Compounds (**58**)-(**61**) have all been prepared in this manner (22-64% yields) (*tert*-BuLi/THF/-78 °C).²² The generation of compounds (**59**; R = H, Me, OMe, or Cl) is followed by their spontaneous aerial oxidation to the corresponding ketones (37-61% yield).²² In a similar study the ketones derived by oxidation of carbinols [**59**; R = H (55%),



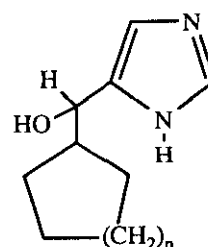
(58)

Ar = Ph (64%)

Ar = imidazol-4-yl (22%)



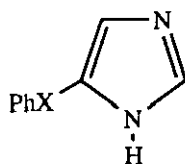
(59)



(60)

n = 1 (29%)

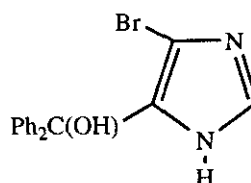
n = 2 (48%)



(61)

X = S (62.5%)

X = CONH (33%)



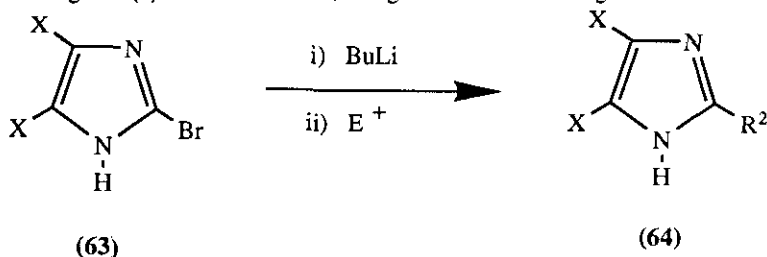
(62)

2-OMe (52%), 4-OMe (48%), 3,4-(OMe)₂ (63%)] were obtained by treatment of 4(5)-bromoimidazole with lithium naphthalenide followed by addition of the appropriate aldehyde.¹³⁸ Yields of ketones were much lower (17% and 24%, respectively, when R = H or 4-OMe) when the quenching electrophile was the corresponding benzonitrile.¹³⁸

When 4,5-dibromoimidazole is allowed to react with two mol. equiv. of butyllithium and the resulting 1,5-dilithiated derivative is quenched with benzophenone, a disappointing yield (only 17%) of carbinol (**62**) is obtained.¹²⁵

Various polysubstituted imidazoles are available through treatment of polyhalogenated imidazoles *unprotected* on the ring *N*-atom with organolithium reagents followed by addition of suitable electrophiles (Scheme 20) (Table VII).¹³⁹

With four mol. equiv. of butyllithium followed by addition of methanol 2,4,5-tribromoimidazole (**63**; X = Br) has been reported to give 4(5)-bromoimidazole,¹³⁶ again evidence of the greater resistance of the bromine atom



Scheme 20

next to the pyridine-like *N*-atom to undergo bromine → lithium exchange compared with the other two bromine atoms ("ALP effect");¹²²⁻¹²⁴ 4,5-dibromoimidazole (**64**; X = Br, R² = H) and 4(5)-bromo-5(4)-butylimidazole were obtained also.

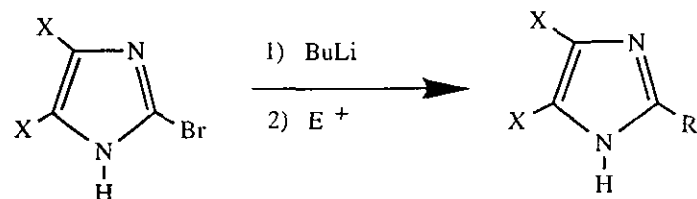
The yields of products obtained by bromine → lithium exchange of *N*-unsubstituted bromoimidazoles are lower than those obtained from the corresponding *N*-protected compounds. Thus, the synthetic utility of these procedures is limited currently although further work should be encouraged since protection and deprotection of imidazoles is wasteful of materials and time.

V LATERAL METALLATION

Some substituents on the imidazole ring, particularly 2-alkyl groups, are prone to α -(or lateral)metallation (Table VIII). Tertov's group reported¹⁴⁰ that 1,2-dimethylimidazole is metallated by butyllithium (at -10 °C) exclusively

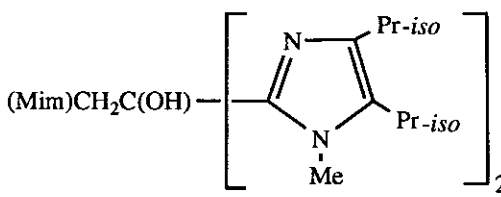
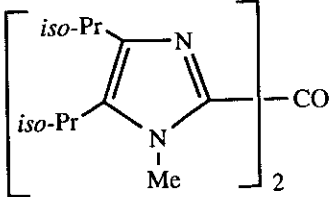
Table VII

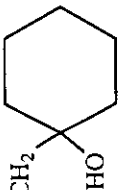
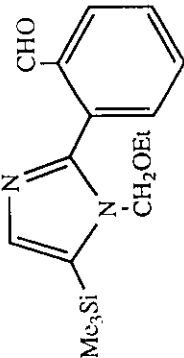
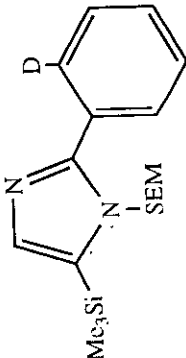
Exchange at Position-2 of 2,4,5-Trihalogenated Imidazoles with Butyllithium

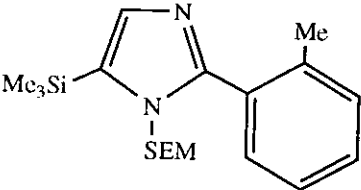
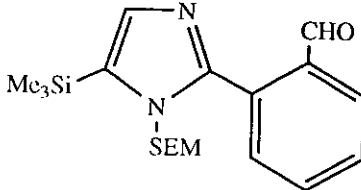
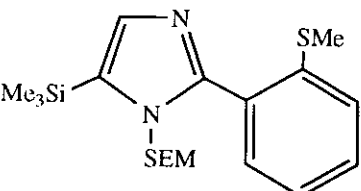
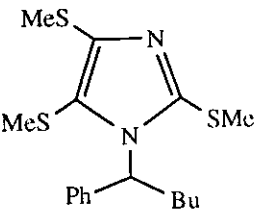


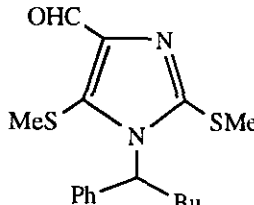
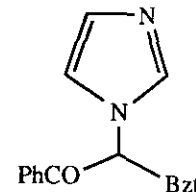
X	R	Reagent	Yield (%)	Ref.
Cl	CHO	DMF	52	125
Cl	CO ₂ H	CO ₂	48	125
Cl	CH(OH)C ₆ H ₃ (OMe) _{2-2,3}	2,3-(MeO) ₂ C ₆ H ₃ CHO	44	139
Cl	CH(OH)C ₆ H ₃ (OMe) _{2-2,5}	2,5-(MeO) ₂ C ₆ H ₃ CHO	-	139
Cl	CH(OH)C ₆ H ₃ (OMe) _{2-3,4}	3,4-(MeO) ₂ C ₆ H ₃ CHO	-	139
Cl	SBu	Sg, BuI	42	125
Br	H	H ₃ O ⁺	40	125
Br	CHO	DMF	43	125
Br	CO ₂ H	CO ₂	57	125
Br	SBu	Sg, BuI	40	125

Table VIII
Imidazoles Synthesised *via* Lateral Metallation^a

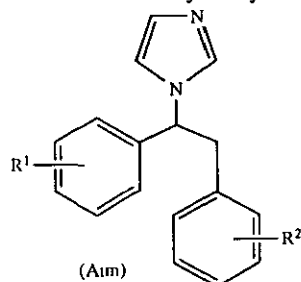
Substituent ^b	Product ^c	Reagent ^c	Yield (%)	Ref.
2-Me	(Mim)CH ₂ D	D ₂ O	84 ^d	32
2-Me	(Dam)CH ₂ Ar ^e	ArCH ₂ Cl ^e	50-63	99
2-Me	(Mim)CH ₂ CH(OH)C ₆ H ₄ Me-4	4-MeC ₆ H ₄ CHO	82, 70 ^f	118
2-Me	(Mim)CH ₂ CH(OH)(2-py)	2-PyCHO	67	118
2-Me	(Mim)CH ₂ C(OH)Ph ₂	Ph ₂ CO	54	118
2-Me	(Mim)CH ₂ C(OH)(Mim) ₂	(Mim) ₂ CO	43	37
2-Me	(Mim)CH ₂ C(OH)- 		63	141
2-Me	(Mim)C(SMe) ₃	Me ₂ S ₂	41	118
2-Me	(Mim)CH ₂ SiMe ₃	Me ₃ SiCl	63	142
2-Me	(Eom)CH ₂ CO ₂ Et	(EtO) ₂ CO	23	116
2-Me	(Eom)CH ₂ C(OH)(Eom) ₂	(Eom) ₂ CO	33.5	116
2-Me	[(Eom)CH ₂] ₃ P	1/3PCl ₃	46 ^g	143

2-Bu	(Dam)CHPrBu	BuBr	27	21
2-CMe=CH ₂	(Mim)C(=CH ₂)(CH ₂) ₂ OH	HCHO	41	40
2-CMe=CH ₂	(Mim)C(=CH ₂)CH ₂ CH(OH)-C ₆ H ₃ (OCH ₂ O)-3,4	3,4-(OCH ₂ O)C ₆ H ₃ CHO	32	40
2-CMe=CH ₂	(Mim)C(=CH ₂)CH ₂ 	cyclohexanone	47	40
2-CMe=CH ₂	(Mim)C(=CH ₂)CH ₂ C(OH)CMePh	PhCOMe	43	40
2-CMe=CH ₂	(Mim)C(=CH ₂)CH ₂ C(OH)Ph ₂	Ph ₂ CO	30	40
2-SMe	(Mom)CH ₂ Li	no derivatives mentioned		93
2-SCH ₂ R ^h	(Mim)SCH ₂ CH ₂ SnBu ₃	Bu ₃ SnCH ₂ I	31	144
2-SOCH ₂ CHMeEt	(Mim)SOCH[CH(OH)Ph]CHMeEt ^d	PhCHO	—	145
2-Ph		DMF	73	16
2-Ph		MeOD	38 ^d	16

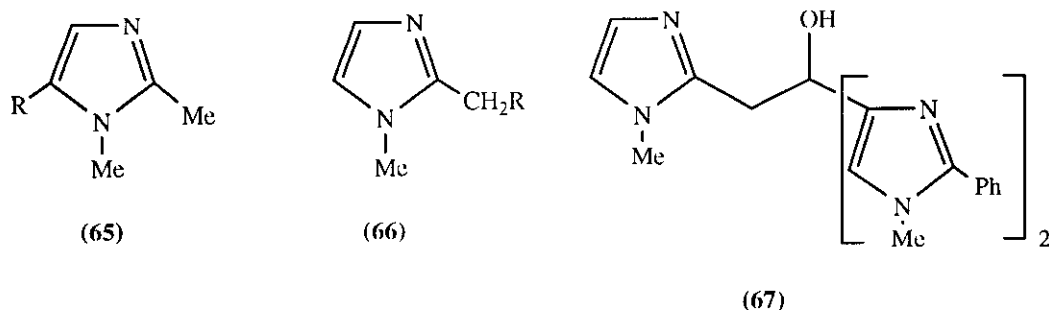
2-Ph		MeI	56i	16
2-Ph		DMF	52, 41j	16
2-Ph		Me ₂ S ₂	52i	16
1-CH ₂ Ph	Aim (R ¹ = R ² = H)	PhCH ₂ Br	12k	54
1-CH ₂ Ph	Aim (R ¹ = R ² = H)	PhCH ₂ Cl	61, –	94, 54
1-CH ₂ Ph	Aim (R ¹ = R ² = Cl)	4-ClC ₆ H ₄ CH ₂ Cl	29, 7k	94, 54
1-CH ₂ Ph	Aim (R ¹ = H, R ² = 4-Me)	4-MeC ₆ H ₄ CH ₂ Cl	61	94
1-CH ₂ Ph		BuBr	33	126

1-CH ₂ Ph		BuBr	46	126
1-CH ₂ C ₆ H ₄ Cl-4	Aim (R ¹ = 4-Cl, R ² = H)	PhCH ₂ Cl	48	94 ^l
1-CH ₂ C ₆ H ₄ Me-4	Aim (R ¹ = 4-Me, R ² = H)	PhCH ₂ Cl	41	94
1-CH ₂ C ₆ H ₃ Cl ₂ -2,4	Aim (R ¹ = R ² = 2,4-Cl ₂)	2,4-Cl ₂ C ₆ H ₃ CH ₂ Cl	45	94
1-CH ₂ C ₆ H ₃ Cl ₂ -2,4	Aim (R ¹ = 2,4-Cl ₂ , R ² = 4-Ph)	4-PhC ₆ H ₄ CH ₂ Cl	38	94
1-CH ₂ C ₆ H ₄ Ph-4	Aim (R ¹ = Ph, R ² = H)	PhCH ₂ Cl	64	94
1-CH ₂ Bzt ^g		PhCO ₂ Et	53	56

^a With BuLi unless stated otherwise. ^b Substituent laterally metallated. ^c **ABBREVIATIONS USED:** Mim = 1-methylimidazol-2-yl; Mom = 1-methoxymethylimidazol-2-yl; Eom = 1-ethoxymethylimidazol-2-yl; Dam = 1-dimethylaminomethylimidazol-2-yl; Aim = (see formula) ; 2-Py = pyrid-2-yl; Bzt = benzotriazol-1-yl; TMS = Me₃Si; SEM = Me₃SiCH₂CH₂OCH₂. ^d With LDA. ^e Ar = Ph, C₆H₄Br-2(or 4), C₆H₄Cl-4, C₆H₄OMe-4, C₆H₃F₂-2,4, C₆H₃Cl₂-2,4, or C₆H₃(OMe)₂-3,4. ^f With *tert*-BuOLi/KDA. ^g Yield after deprotection during which simultaneous oxidation at phosphorus occurs. ^h R = CH₂=CMe(CH₂)₂CH=CMe₂ (product reacts further). ⁱ As a mixture of diastereomers. ^j Yields of products after removal of 1-SEM^c and 5-TMS^c protecting groups ("one-pot" reactions starting with 2-phenylimidazole). ^k Reaction carried out at ambient temperature. ^l 1-(4-Chlorobenzyl)-imidazole is metallated by butyllithium both at position-2 and in its N-C_α methylene group. The resulting anion has been quenched with 4-chloro- and 4-methoxybenzophenone.¹⁸

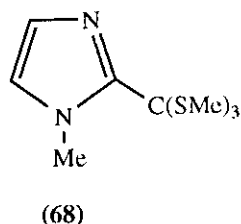


at position-5 to give, after addition of suitable quenching reagents, compounds [65; R = Br (26%), I (45%), CHO (20%), CH(OH)Ph (59.5%), C(OH)Ph₂ (73%)]. By contrast, others have reported the isolation of a mixture of compounds [65; R = CH(OH)Ph] and [66; R = CH(OH)Ph] following successive treatment of this substrate with butyllithium (at 0 °C)^{140,146} or phenyllithium¹⁴⁷ and benzaldehyde. To further complicate the picture, exclusive α -(or lateral)metallation is suggested by the isolation of compounds [66; R = CH(OH)pyrid-2-yl] (66% yield) (BuLi/-15 °C, then pyrid-2-ylCHO) and (67) (19%) (BuLi also).¹¹⁶ We have carried out a detailed investigation of the metallation of 1,2-dimethylimidazole with butyllithium and other reagents.¹¹⁸ The results show that products arising from exclusive lateral metallation [66; R = CH(OH)C₆H₄Me-4 (82% yield) or



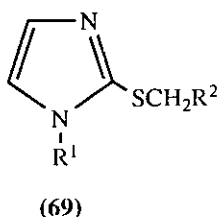
CH(OH)pyrid-2-yl (67%)] or exclusive metallation at position-5 [65; R = D (50% deuterium incorporation), SiMe₃ (72%), SnMe₃ (58%), SnBu₃ (difficult to purify)] may be obtained or mixtures of both types of product, (65) and (66) [R = SMe, C(OH)Ph₂], may be formed depending on the metallating agent, reaction conditions, and the quenching reagent. The product claimed to be compound [65; R = C(OH)Ph₂] by Tertov's group¹⁴⁰ was shown to be its isomer [66; R = C(OH)Ph₂].¹¹⁸ The conditions best suited to lateral metallation in the 2-methyl group include the use of butyllithium in ether in the presence of TMEDA or in ether *but at -110 °C*, butyllithium in THF, or LDA in ether.¹¹⁸ The results of this investigation suggest that the laterally metallated product is more stable than the 5-lithiated product. The 5-lithiated product can be obtained by treatment of 1,2-dimethyl-5-trimethylstannylimidazole with butyllithium in THF at -110 °C; with dimethyl disulfide or benzophenone added at this temperature the 5-substituted compounds [65; R = SMe (100%), C(OH)Ph₂ (94%)] are formed exclusively. However, if the reaction mixture is allowed to warm up (e.g. to -20 °C), the initially formed 5-lithiated compound equilibrates with the more stable laterally metallated species and, following addition of benzophenone, a mixture

of carbinols (**65**) and (**66**) [$R = C(OH)Ph_2$] is formed instead.¹¹⁸ Repeated lateral metallation of 1,2-dimethylimidazole in its 2-methyl group (Et_2O /ambient temperature) and quenching with dimethyl disulfide leads to compound (**68**) (41% yield).¹¹⁸

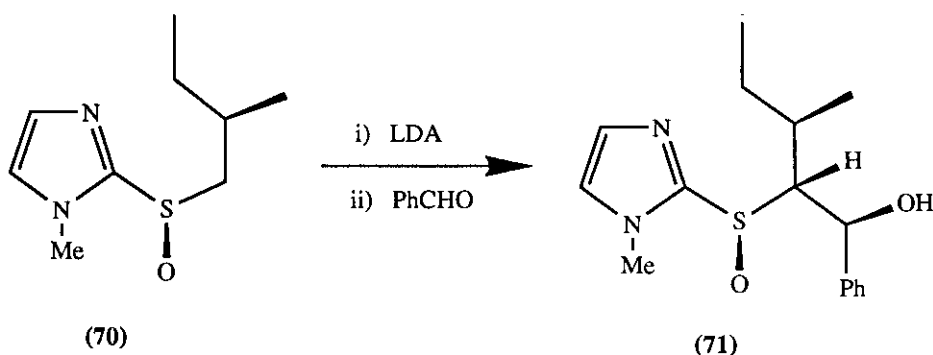


1-Dimethylaminomethyl-2-methylimidazole is laterally metallated with butyllithium (THF/-78 °C) in its 2-methyl group and the resulting anion can be quenched with benzyl chloride and a number of its derivatives (Table VIII) to give the corresponding 2-arylethyl derivative.⁹⁹

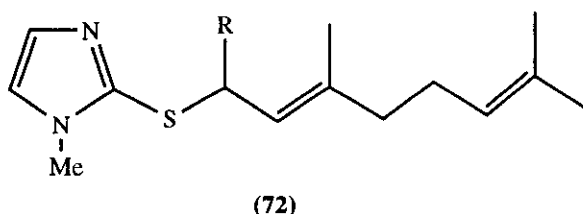
A 2-(1-propen-2-yl)-substituent has been reported⁴⁰ to undergo lateral metallation with butyllithium in THF at -78 °C in the presence of HMPA and triethylaluminium and the resulting anion has been trapped with various carbonyl compounds.



Lateral metallation has been reported for the 2-methylthio group in compound (**69**; $R^1 = CH_2OMe$, $R^2 = H$).⁹³ Similar metallation of compound (**70**) (Scheme 21) with LDA gives a lithium derivative whose lithium atom is chelated with the ring N-atom; reaction with benzaldehyde is stereocontrolled as a consequence and a 5:1 mixture of the diastereoisomers of compound (**71**) is obtained.¹⁴⁵ Compound (**72**; $R = H$) reacts with butyllithium (THF/-78 °C) to give, after quenching the resulting anion with tributylstannylmethyl iodide, what is believed to be compound (**72**; $R = CH_2SnBu_3$).¹⁴⁴ The initially generated anion reacts further with this compound as it forms to give compound (**72**; $R = SnBu_3$) (31% yield) and the lithium salt of 1-methylimidazole-2-thiol, which is captured by the added tributylstannylmethyl iodide to produce compound (**69**; $R^1 = Me$, $R^2 = SnBu_3$) (43% yield). Starting material (**72**; $R = H$) (14%) is recovered whilst the major product is the eliminated 4,8-dimethylnona-1,3,7-triene (45%).



Scheme 21

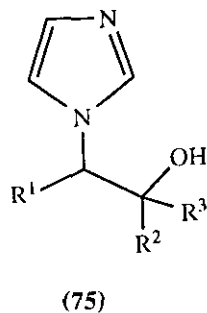
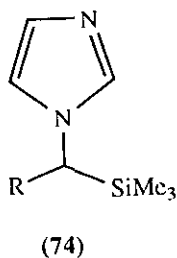
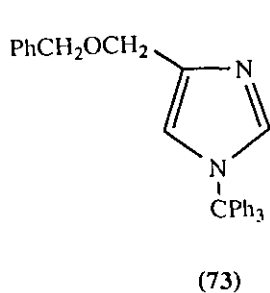


The 2-phenyl groups in 1-ethoxymethyl- and 1-trimethylsilylethoxymethyl-2-phenyl-5-trimethylsilylimidazole are *ortho*-lithiated by butyllithium (THF/-78 °C) and the resulting anions can be quenched with various electrophiles (MeOD, MeI, Me₂S₂, DMF) (Table VIII).¹⁶ Starting with 2-phenylimidazole the 1- and 5-protecting groups can be introduced, the substituent introduced into the phenyl ring, and both protecting groups removed all in one pot (38-41% overall yields). 1-Ethoxymethyl-2-phenylimidazole is dilithiated with an excess of butyllithium (THF/-20 °C) in position-5 and in the *ortho*-position of the phenyl ring; quenching with an excess of DMF yields the corresponding dialdehyde in good yield but addition of one mol. equiv. of DMF also yields the dialdehyde together with starting material.¹⁶ A monoaldehyde is not available *via* this route.

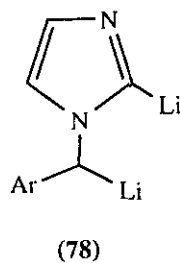
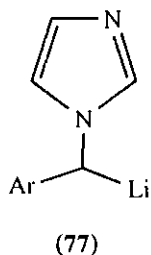
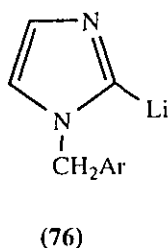
The C-4 methylene group in 4-benzyloxymethyl-1-triphenylmethylimidazole (73) is laterally metallated.⁷⁰ Noteworthy are the fluoride ion desilylation reactions of compounds (74; R = H)¹⁴⁸ and (74; R = SMe)¹⁴⁹ which give stabilised N-C_α anions that react with various reagents, e.g. aldehydes and ketones to give compounds (75; R¹ = H, SMe; R² = Ph, C₆H₄Cl-4; R³ = H, Me, Ph) (22-89% yields).

Lateral metallation of an *N*-benzyl group has been mentioned in Section II.A in connection with the isolation of compound (12) and in Section IV.A in connection with the formation of compound (57). The *N*-benzyl

protecting group possesses this disadvantage as an *N*-protecting group and its lateral metallation is probably responsible for non-quantitative 2-metallation of such protected compounds and the low to moderate yields of



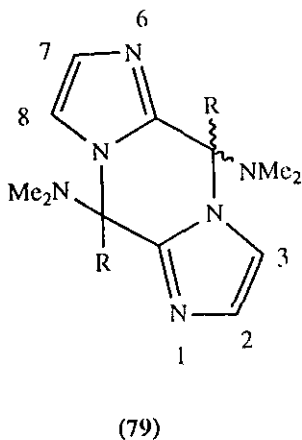
products given in Table VIII. It has been suggested⁵⁴ that the 2-lithiated derivatives (76) are more favoured both kinetically and thermodynamically than their laterally metallated isomers (77) but the mechanism of equilibration,



(76) (77), is unknown. The dilithiated derivatives (78) are readily generated in the presence of a slight excess of butyllithium¹⁹ (but see also ref. 94).

ortho-Lithiation of 1-phenylimidazole has been mentioned in Section II.A.

Dilithiation (three mol. equiv. *tert*-BuLi/THF/-65 °C) of the diimidazopyrazine (79; R = H) is 85% complete after

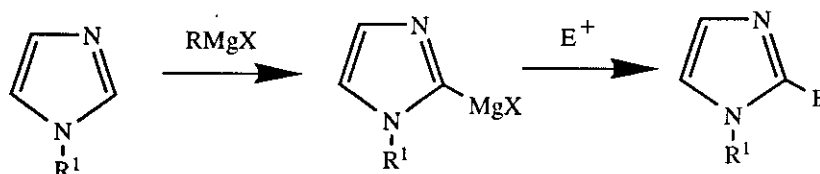


30 minutes with no further change, as shown by a deuterium oxide quench.¹⁵⁰ Compounds {(79): R = Me (MeI/54% yield); R = Pr (PrBr/53%) (PrI/72%); R = *iso*-Pr (*iso*-PrI/49%); R = (CH₂)₄Me [Me(CH₂)₄Br/71%] [Me(CH₂)₄I/74%]; and R = CH₂Ph (PhCH₂Br/23%) (PhCH₂I/25%)} are obtained following addition of the appropriate alkyl halide and these are hydrolysed in hot aqueous sodium hydrogencarbonate solution to give the corresponding 2-alkanoyl(COR)imidazole.¹⁵⁰

With sodium hydride in DMF, lateral metallation of the 2-methyl group occurs in 1,2,3-trimethylimidazolium iodide. In the presence of iodomethane the 2-ethyl derivative is formed, then the 2-isopropyl derivative.¹⁰² Steric factors apparently prevent further alkylation of the latter product.

VI OTHER ORGANOMETALLIC DERIVATIVES

N-Protected imidazoles are metallated in position-2 in hot THF with ethylmagnesium bromide^{36,151-153} or chloride (Scheme 22).¹⁵⁴



Scheme 22

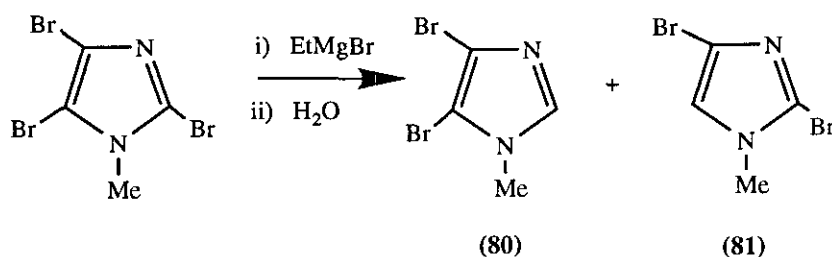
4- And 5-chloro-1-methylimidazoles fail to react with magnesium¹⁵⁵ unless the entrainment technique is used,¹⁵² e.g. with dibromoethane in hot THF. Use of bromoethane results in competition between formation of the Grignard compound at position-4 or -5 and metallation in position-2.¹⁵² In ether or cold THF the magnesium bromide or ethylmagnesium bromide formed initially gives insoluble co-ordination complexes with the imidazole which screen the surface of the magnesium, thus inhibiting the reaction.¹⁵² For the formation of 4- and 5-trimethylsilylimidazoles it is preferable to bring together the chloro(or bromo)imidazole, magnesium, and chlorotrimethylsilane in a "one pot" procedure.¹²¹

There is evidence that the formation of 1-methylimidazol-4(or 5)-ylmagnesium bromides is accompanied by a transmetallation process with position-2 of the starting material. Following quenching with a suitable electrophile a mixture of 4(or 5)-substituted 1-methylimidazole and the corresponding 2-substituted 4(or 5)-chloro-1-methylimidazole is obtained.¹⁵² However, treatment of *N*-protected 4-iodoimidazoles with ethylmagnesium

bromide in dichloromethane^{156,157} or ether^{129,134} generates the corresponding Grignard derivative which can be quenched with various electrophilic reagents (Table IX). There was no evidence in these reactions for rearrangement of the initially generated imidazol-4-yl anion.

A note has appeared¹⁵⁶ which proposes that the reactivity of *N*-protected imidazol-4-ylmagnesium salts can be modified by addition of other metal salts (e.g. ZnCl_2 , CuCN).

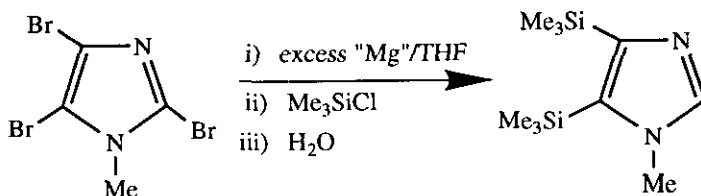
N-Protected 2,4,5-tribromoimidazoles also react with ethylmagnesium bromide in ether, THF, or benzene at position-2;^{22,125,130} hydrolysis of the resulting Grignard compound usually leads to the corresponding *N*-protected 4,5-dibromoimidazole. However, choice of solvent can be important.



Scheme 23

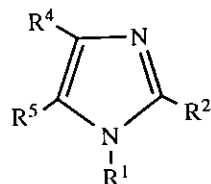
Thus, whilst 2,4,5-tribromo-1-methylimidazole reacts with ethylmagnesium bromide in ether at ambient temperature to give, after hydrolysis, exclusively 4,5-dibromo-1-methylimidazole (**80**) (Scheme 23) (80% yield), in THF the same procedure yields a 1:1 mixture of compound (**80**) and its isomer (**81**).¹³⁰

4,5-Dibromo-1-methylimidazole (**80**) reacts with 2.5 mol. equivs. of "activated magnesium" in HMPA to give, after addition of chlorotrimethylsilane, 4-bromo-1-methyl-5-trimethylsilylimidazole (77% yield).¹²¹ A 4,5-*bis*(silylated) derivative has been prepared similarly (Scheme 24).



Scheme 24

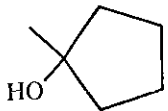
Table IX
Imidazoles Prepared *via* Grignard Intermediates^{a,b}



R ¹	R ²	R ⁴	R ⁵	Solvent	Reagent	Yield (%)	Ref.
H	H (Br)	Br	Br	THF	H ₃ O ⁺	67	125
Me	COPh (H)	H	H	—	PhCN	60	36
Me	CO(4-Py) ^c (H)	H	H	—	4-PyCN ^c	30	36
Me	CH(OH)Ph (H)	H	H	THF	PhCHO	85	151
Me	CH(OH)C ₆ H ₄ Cl-2 (H)	H	H	THF	2-ClC ₆ H ₄ CHO	—	153
Me	CH(OH)C ₆ H ₄ Me-2 (H)	H	H	THF	2-MeC ₆ H ₄ CHO	—	153
Me ^d	CH(OH)C ₆ H ₃ NO ₂ Cl-2,5 (H)	H	H	THF	2,5-(O ₂ N)ClC ₆ H ₃ CHO	43	154
Me	CH(OEt) ₂ (Br)	H	H	Et ₂ O/C ₆ H ₆	HC(OEt) ₃	56	134
Me	CH(OEt) ₂ (I)	H	H	Et ₂ O/C ₆ H ₆	HC(OEt) ₃	65	134
Me	CH(OH)Ph (H)	Cl	H	THF	PhCHO	77, 9.5	151, 152
Me	CH(OH)Ph (H)	H	Cl	THF	PhCHO	87, 7.5	151, 152

Me	C(OH)Ph ₂ (H)	H	Cl	THF	Ph ₂ CO	82	151
Me	H (Br)	Br	Br	C ₆ H ₆	H ₂ O	48	22
Me	H (Br)	Br	Br	Et ₂ O	H ₂ O	80	130
Me	H	CH(OH)Ph (Cl)	H	THF	PhCHO	26.5	152
Me	H	C(OH)Ph ₂ (Cl)	H	THF	Ph ₂ CO	10	152
Me ⁸	H	SiMe ₃ (Cl)	H	THF	Me ₃ SiCl	58	121
Me	H	CH(OEt) ₂ (Br)	H	Et ₂ O/C ₆ H ₆	HC(OEt) ₃	48	134
Me ⁸	Br	SiMe ₃ (Br)	SiMe ₃ (Br)	THF	MeSiCl	63	121
Me	H	CH(OEt) ₂ (I)	H	Et ₂ O/C ₆ H ₆	HC(OEt) ₃	57	134
Me	H	CH(OEt) ₂ (I)	CH(OEt) ₂	CH ₂ Cl ₂	HC(OEt) ₃	58	129
Me	H	H	CH(OH)Ph (Cl)	THF	PhCHO	41	152
Me	H	H	C(OH)Ph ₂ (Cl)	THF	Ph ₂ CO	17	152
Me ⁸	H	H	SiMe ₃ (Cl)	THF	Me ₃ SiCl	81	121
Me	H	Br	H (Br)	–	H ₂ O	–	121
Me	H	H	CH(OEt) ₂ (Br)	Et ₂ O/C ₆ H ₆	HC(OEt) ₃	60	134
Me ⁸	H	Br	SiMe ₃ (Br)	HMPT	Me ₃ SiCl	77	121
Me	H	H	CH(OEt) ₂ (I)	Et ₂ O/C ₆ H ₆	HC(OEt) ₃	87	134
Me	H	I	CH(OEt) ₂ (I)	Et ₂ O	HC(OEt) ₃	68	129
CH ₂ Ph	H (Br)	Br	Br	Et ₂ O	aq. NH ₄ Cl	80	125
CH ₂ C ₆ H ₄ OMe-4	H (Br)	Br	Br	THF	aq. NH ₄ Cl	73	125
CH ₂ C ₆ H ₄ OMe-4	C(OH)Ph ₂ (Br)	Br	Br	Et ₂ O	Ph ₂ CO	83	125

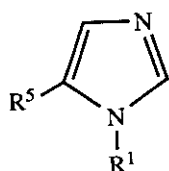
CH ₂ C ₆ H ₃ (OMe) ₂ -3,4	H (Br)	Br	Br	THF	aq. NH ₄ Cl	72	125
CH ₂ OMe	H (Br)	Br	Br	Et ₂ O	aq. NH ₄ Cl	73	125
CH ₂ OMe	SCH ₂ Ph	Br	H (Br)	Et ₂ O	aq. NH ₄ Cl	81	125
CH ₂ OEt	H (Br)	Br	Br	Et ₂ O	aq. NH ₄ Cl	80	125
CPh ₃	H	CH ₂ CH=CH ₂	H	THF	CH ₂ =CHCH ₂ Br	91 ^f	158
CPh ₃	H	2-Py	H	CH ₂ Cl ₂	2-PyBr	66 ^g	158
CPh ₃	H	COPh	H	CH ₂ Cl ₂	PhCN	54	158
CPh ₃	H	CONHPh	H	CH ₂ Cl ₂	PhNCO	82	158
CPh ₃	H	CH(OH)Me (I)	H	THF	MeCHO	66	156
CPh ₃	H	CH(OH)Me (I)	H	CH ₂ Cl ₂	MeCHO	83	156
CPh ₃	H	CH(OH)(CH ₂) ₃ CO ₂ Me (I)	H	CH ₂ Cl ₂	MeO ₂ C(CH ₂) ₃ CHO	63	156
CPh ₃	H	CH(OH)CH=CH ₂ (I)	H	CH ₂ Cl ₂	CH ₂ =CHCHO	60	156
CPh ₃	H	CH(OH)CF=C(SMe) ₂ (I)	H	CH ₂ Cl ₂	(MeS) ₂ C=CFCHO	72	157
CPh ₃	H	CH(OH)Ph (I)	H	CH ₂ Cl ₂	PhCHO	79	156
CPh ₃	H	C(OH)(C ₆ H ₄ Cl-4) ₂ (I)	H	THF	(4-ClC ₆ H ₄) ₂ CO	53	156
CPh ₃	H	C(OH)(C ₆ H ₄ Cl-4) ₂ (I)	H	CH ₂ Cl ₂	(4-ClC ₆ H ₄) ₂ CO	69	156
CPh ₃	H	SiMe ₃	H	CH ₂ Cl ₂	Me ₃ SiOSO ₂ CF ₃	58	158
CPh ₃	H	SePh	H	CH ₂ Cl ₂	PhSeCl	86	158
CPh ₃	H	tetrahydropyran-2-yl	H	CH ₂ Cl ₂	phenyl tetrahydro- pyran-2-yl sulfone	53	158

CPh ₃	H	<i>N</i> -formylpiperidin-2-yl	H	CH ₂ Cl ₂	<i>N</i> -formylpiperidin-2-yl phenyl sulfone	65	158
Ph	COPh (H)	H	H	—	PhCN	85	36
Ph	CO(4-Py) [§] (H)	H	H	—	4-PyCN [§]	50-60	36
SEM [§]	H	CH(OH)Ph (I)	H	CH ₂ Cl ₂	PhCHO	66	156
SO ₂ NMe ₂	H	CH(OH)Me (I)	H	CH ₂ Cl ₂	MeCHO	80	156
SO ₂ NMe ₂	H	CH(OH)(CH ₂) ₂ CH=CMe ₂ (I)	H	CH ₂ Cl ₂	Me ₂ C=CH(CH ₂) ₂ CHO	83	156
SO ₂ NMe ₂	H	 (I)	H	CH ₂ Cl ₂	cyclopentanone	77	156
SO ₂ NMe ₂	H	CH ₂ CH(OH)Ph ^h	H	CH ₂ Cl ₂	2-phenyloxirane	26 ^h	158
SO ₂ NMe ₂	H	CH(OH)Ph (I)	H	CH ₂ Cl ₂	PhCHO	83	156
SO ₂ NMe ₂	H	C(OH)Ph ₂ (I)	H	CH ₂ Cl ₂	Ph ₂ CO	82	156
SO ₂ NMe ₂	H	CH(OEt) ₂	H	CH ₂ Cl ₂	PhOCH(OEt) ₂	97	158

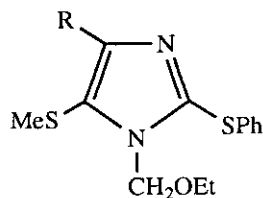
^a With EtMgBr unless stated otherwise. ^b (H) or (Br) means metallation or halogen → metal exchange at the position indicated. [§] **ABBREVIATIONS USED:** 4-Py = pyrid-4-yl; SEM = Me₃SiCH₂CH₂OCH₃. ^d With EtMgCl. [§] With Mg. ^f Grignard reagent converted to cuprate through addition of CuCN.2LiCl. [§] Grignard reagent converted to zincate through addition of ZnBr₂; coupling with pyrid-2-ylBr required a catalytic quantity of Pd(PPh₃)₄. ^h Isomer with 4-substituent = CHPhCH₂OH (41% yield) formed also.

Apart from this paper, however, there have been no other reports to date of polymetallation of imidazoles *via* the use of or formation of Grignard reagents. Table IX lists the imidazoles that have been prepared from Grignard reagents.

Imidazoles (**82**; $R^1 = \text{Me, CH}_2\text{Ph, Ph}$; $R^5 = \text{H, Cl}$) are metallated by phenylsodium in toluene in position-2^{119,159} and the resulting sodio derivatives can be quenched with various electrophiles. Similar results are obtained with sodium naphthalenide.¹³⁴ A report¹⁴⁰ (see also ref. 119) that 1,2-dimethylimidazole is metallated exclusively in position-5 with phenylsodium has been shown to be incorrect; lateral metallation occurs instead in the 2-methyl group (Section V).¹¹⁸



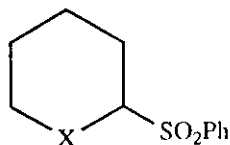
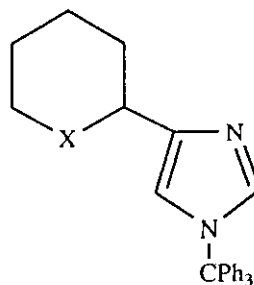
(82)



(83)

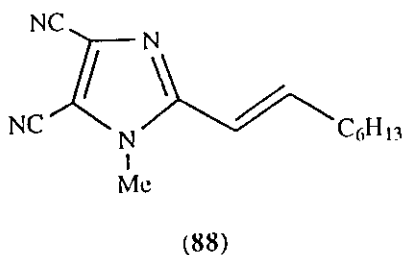
Potassium diisopropylamide-lithium *tert*-butoxide (KDA) (THF/-78 °C) metallates compound (**83**; $R = \text{H}$) in position-4; the resulting imidazol-4-yl anion was quenched with dimethyl disulfide, to give the tetrasubstituted imidazole (**83**; $R = \text{SMe}$).^{12,117}

4-Allyl-1-triphenylmethylimidazole (91% yield) can be prepared by successive addition of $\text{CuCN} \cdot 2\text{LiCl}$ (THF in this case) and allyl bromide to 1-triphenylmethylimidazol-4-ylmagnesium bromide (see below).¹⁵⁸ Addition of zinc chloride to the Grignard compound to give the 4-zincate, followed by addition of tetrahydropyranyl (**84**) or

(84) $X = \text{O}$ (85) $X = \text{NCHO}$ (86) $X = \text{O}$ (87) $X = \text{NCHO}$

piperidyl sulfone (**85**), gave the corresponding derivative (**86**; 53%) or (**87**; 65%), respectively.¹⁵⁸ Addition of zinc bromide followed by a catalytic quantity of $\text{Pd}(\text{PPh}_3)_4$, then 2-bromopyridine gave 4-pyrid-2-yl-1-triphenylmethylimidazole (66% yield).¹⁵⁸

The presence of two cyano groups in 2-bromo-4,5-dicyano-1-methylimidazole allows insertion of zinc into the C-Br bond.¹⁶⁰ The resulting organozinc bromide can be coupled with 1-iodooct-1-ene using *bis*(benzylideneacetone)palladium(0) [$\text{Pd}(\text{dba})_2$] and triphenylphosphine as catalyst, to give the alkene (**88**) (41% yield).



2-Fluoro-1-triphenylmethylimidazol-4-ylcopper has been synthesised by reacting the corresponding lithium derivative with cuprous iodide and quenching with allyl bromide (see previously in this Section).¹⁰⁵

Imidazole is mercurated in the 4(5)-position and its 4(5)-alkyl derivatives are mercurated adjacent to the alkyl group.^{161,162} These mercurated derivatives react with $^{211}\text{At}/\text{I}_2$ to give ^{211}At astatoimidazoles.

We have referred throughout this review to the synthesis and application of various silicon and tin derivatives of imidazole.

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† 19 References not covered in this review can be found in the Tables of our earlier review.⁸

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