

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

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

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- II MONOMETALLATION IN THE RING
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I INTRODUCTION

A general introduction to this topic was included in Part I.¹

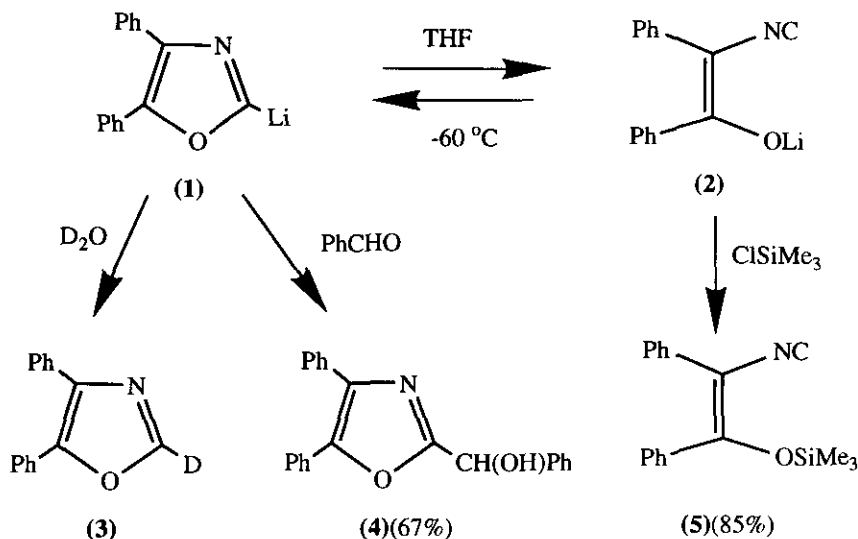
Oxazoles (1,3-oxazoles),²⁻⁶ like isoxazoles, have attracted considerable interest as starting materials for the synthesis of more complex molecules⁷⁻¹⁰ (and cross refs. to be found in refs. 11 and 12). This in turn has led to an interest in the introduction of substituents into oxazoles using metallation and halogen $\rightarrow$ metal exchange methodologies. As with isoxazoles¹ the fragility of the C-O bond gives rise to ring-cleavage processes.

II MONOMETALLATION IN THE RING

Bowie *et al.*, in 1968, first demonstrated that 4-phenyl-,¹³ 4-methyl-5-phenyl-,¹³ 5-methyl-4-phenyl-,¹³ and 4,5-diphenyloxazole¹⁴ could be metallated by butyllithium in position-2; the resulting 2-lithiated derivatives

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

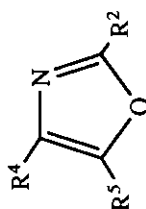
were trapped only with deuterium oxide (Table I). In 1975, however, Schröder *et al.*¹⁵ showed that 4,5-diphenyloxazol-2-yllithium (1) exists in equilibrium with the ring-opened lithium enolate (2) and that the choice of trapping agent determined the product (3)-(5) (Scheme 1) (Δ^2 -oxazolin-2-yllithium compounds behave analogously^{5,12,16-19}). So far isoxazol-2-yllithium²⁰ and its 4-methyl-,^{12,21,22} 4,5-dimethyl-,²³ 4-phenyl-,^{10,24} and various other 5-aryl-^{12,15} and 4,5-diaryl-derivatives⁹ have been shown to behave similarly



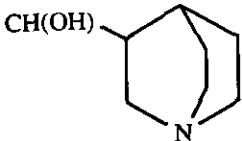
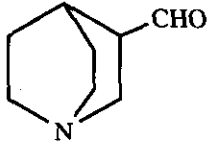
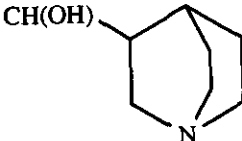
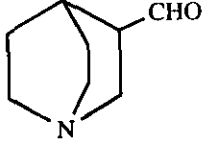
Scheme 1

(for a review see ref. 5). However, lithiation of 5-ethoxy-4-methyloxazole [BuLi/tetrahydrofuran (THF)/-78 °C] and ethyl 4-methyloxazole-5-carboxylate [lithium isopropylcyclohexylamide (LiICA)/THF/-78 °C]²⁵ apparently results in irreversible formation of a ring-opened species corresponding to 2.²³ Butyllithium, lithium diisopropylamide (LDA), and lithium 2,2,5,5-tetramethylpiperidide (LiTMP) have been used to metallate oxazoles in position-2. Quenching these equilibrium mixtures, e.g. $1 \rightleftharpoons 2$, with deuterium oxide or aromatic aldehydes (for 4-unsubstituted oxazoles; see later) invariably leads to the isolation of a 2-substituted oxazole (Table I) whilst quenching with chlorotrimethylsilane^{9,15,21} and acetyl^{12,21,24} or benzoyl chloride²⁴ appears to result in trapping of the ring-opened product. However, the reactions are more complicated than they appear from the earlier literature. Noteworthy is the synthesis of 2-aryloxazoles (Table I) by using *N*-methyl-*N*-(pyrid-2-yl)carboxamides as the quenching agents; a good yield of 5-phenyloxazole-2-carbaldehyde is available *via* this procedure.¹¹

Table I
Oxazoles Prepared from Oxazol-2-yllithium Derivatives

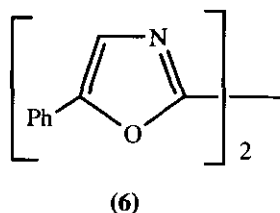


R ²	R ⁴	R ⁵	Reagent	Yield (%)	Ref.
D	H	H	D ₂ O	90	20
CHO	H	H	DMF	50 ^a	20
CH(OH)Ph	H	H	PhCHO	— ^b	20
C(OH)Ph ₂	H	H	Ph ₂ CO	73	20
	H	H		19	26
SiMe ₃	H	H	Me ₃ SiCl	—	27
D	H	Ph	D ₂ O	90	15
CHO	H	Ph	HCONMe(pyrid-2-yl)	61	11
COPh	H	Ph	PhCONMe(pyrid-2-yl)	18	11
COC ₆ H ₄ Me-4	H	Ph	4-MeC ₆ H ₄ CONMe(pyrid-2-yl)	67	11
COC ₆ H ₄ OMe-4	H	Ph	4-MeOC ₆ H ₄ CONMe(pyrid-2-yl)	46	11

COC ₆ H ₄ Cl-4	H	Ph	4-ClC ₆ H ₄ CONMe(pyrid-2-yl)	63	11
COC ₆ H ₄ F-4	H	Ph	4-FC ₆ H ₄ CONMe(pyrid-2-yl)	63	11
COC ₆ H ₄ NO ₂ -4	H	Ph	4-O ₂ NC ₆ H ₄ CONMe(pyrid-2-yl)	56	11
COC ₆ H ₄ CN-4	H	Ph	4-NCC ₆ H ₄ CONMe(pyrid-2-yl)	77	11
SiMe ₃	H	Ph	Me ₃ SiCl	50c	12
SiMe ₃	H	C ₆ H ₄ Cl-4	Me ₃ SiCl	50c	12
SiMe ₃	H	C ₆ H ₄ OMe-4	Me ₃ SiCl	35c	12
CH(OH)C ₆ H ₃ (OMe) ₂ -3,4	H	C ₆ H ₃ (OMe) ₂ -3,4	3,4-(MeO) ₂ C ₆ H ₃ CHO	50-90	28
CH(OH)C ₆ H ₃ (OCH ₂ O)-3,4	H	C ₆ H ₃ (OCH ₂ O)-3,4	3,4-(OCH ₂ O)C ₆ H ₃ CHO	50-90	28
CH(OH)C ₆ H ₃ (OMe) ₂ -3,4	H	C ₆ H ₃ (OCH ₂ O)-3,4	3,4-(MeO) ₂ C ₆ H ₃ CHO	50-90	28
CHO	Me	H	DMF or <i>N</i> -formylmorpholine	-	12
CH(OH)Ph	Me	H	PhCHO	30	21, 12
	Me	H		33	26
	Et	H		10	26
SiMe ₃	Me	H	Me ₃ SiCl	60c	21
SnMe ₃	Me	H	Me ₃ SiCl	60	22, 12

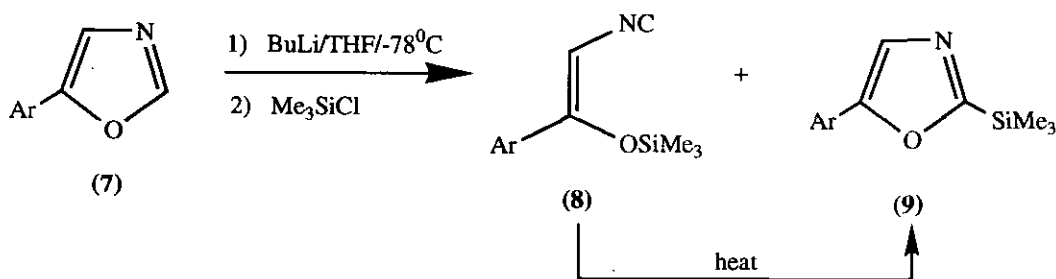
D	Ph	H	D ₂ O	low, -, -	24, 10, 13
CH(OH)Ph	Ph	H	PhCHO	75	24
C(OH)Ph ₂	Ph	H	Ph ₂ CO	96	24
D	Me	Me	D ₂ O	100	23
Cl	Me	CO ₂ Et	CCl ₄	29	25
Br	Me	CO ₂ Et	Br ₂	21	25
I	Me	CO ₂ Et	I ₂	42	25
D	Me	Ph	D ₂ O	-	13
D	Ph	Me	D ₂ O	-	13
D	Ph	Ph	D ₂ O	-, 95, 100	14, 15, 9
CH(OH)Ph	Ph	Ph	PhCHO	67	15
Et	C ₆ H ₄ OMe-4	C ₆ H ₄ OMe-4	EtI	21	9
Pr	C ₆ H ₄ OMe-4	C ₆ H ₄ OMe-4	PrI	23	9
CH ₂ Ph	C ₆ H ₄ OMe-4	C ₆ H ₄ OMe-4	PhCH ₂ Br	27	9
CH(OH)CHMe ₂	C ₆ H ₄ OMe-4	C ₆ H ₄ OMe-4	Me ₂ CHCHO	70	9
CH(OH)CH=CH ₂	C ₆ H ₄ OMe-4	C ₆ H ₄ OMe-4	CH ₂ =CHCHO	83	9
COPh	C ₆ H ₄ OMe-4	C ₆ H ₄ OMe-4	PhCN	85	9

^a Variable yields after work-up due to volatility of product. ^b Minor product, isolated only at ambient temperature or above; the major product is the 4-substituted isomer (Table II). ^c After distillation of a mixture of compounds (8) and (9) (Ar = Ph, C₆H₄Cl-4, or C₆H₄OMe-4).



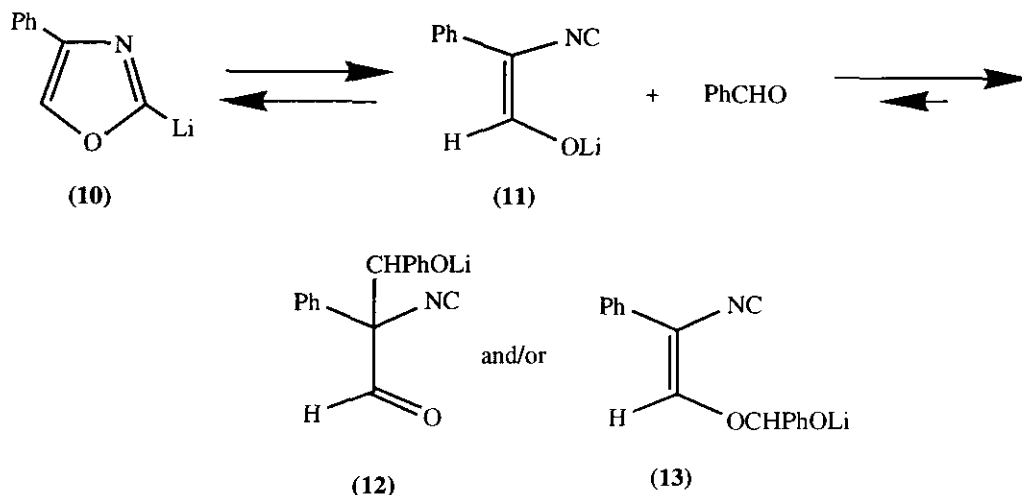
5-Phenyloxazol-2-ylidene reacts with tosyl fluoride in THF at low temperatures to give the coupled product (6); presumably the initially formed 2-tosyloxazole reacts with the unreacted 5-phenyloxazol-2-ylidene compound.¹⁵

A number of 5-aryloxazol-2-ylidene derivatives (derived from the corresponding 5-aryloxazole; 7) (Ar = Ph, C₆H₄Cl-4, or C₆H₄OMe-4) react with chlorotrimethylsilane to give comparable amounts of the ring-opened product (8) and the corresponding 2-trimethylsilyloxazole (9) (Scheme 2).¹² The former compounds are convertible into 2-trimethylsilyloxazoles by heating them in the presence of a base,^{5,12,20,21,29} (however, see



Scheme 2

also ref. 24). By contrast, when 4-methyloxazole is treated sequentially with butyllithium [diethyl ether (Et₂O)/-78 °C] and chlorotrimethylstannane, only 4-methyl-2-trimethylstannane is isolated (Table I)²² (but see ref. 12). In order to maximise the yields obtained from the reactions of 4-phenyloxazol-2-ylidene (10) (Scheme 3) with benzaldehyde or benzophenone it is necessary to allow 18-24 hours to elapse between addition of these reagents and quenching the reaction mixtures with acid prior to work-up.²⁴ The authors reasoned that addition of e.g. benzaldehyde to the initial equilibrium mixture, 10 $\rightleftharpoons$ 11, creates another equilibrium as shown in Scheme 3, generating either aldol salt (12) or hemiacetal salt (13). Overall this results in a reduced availability of oxazol-2-ylidene.

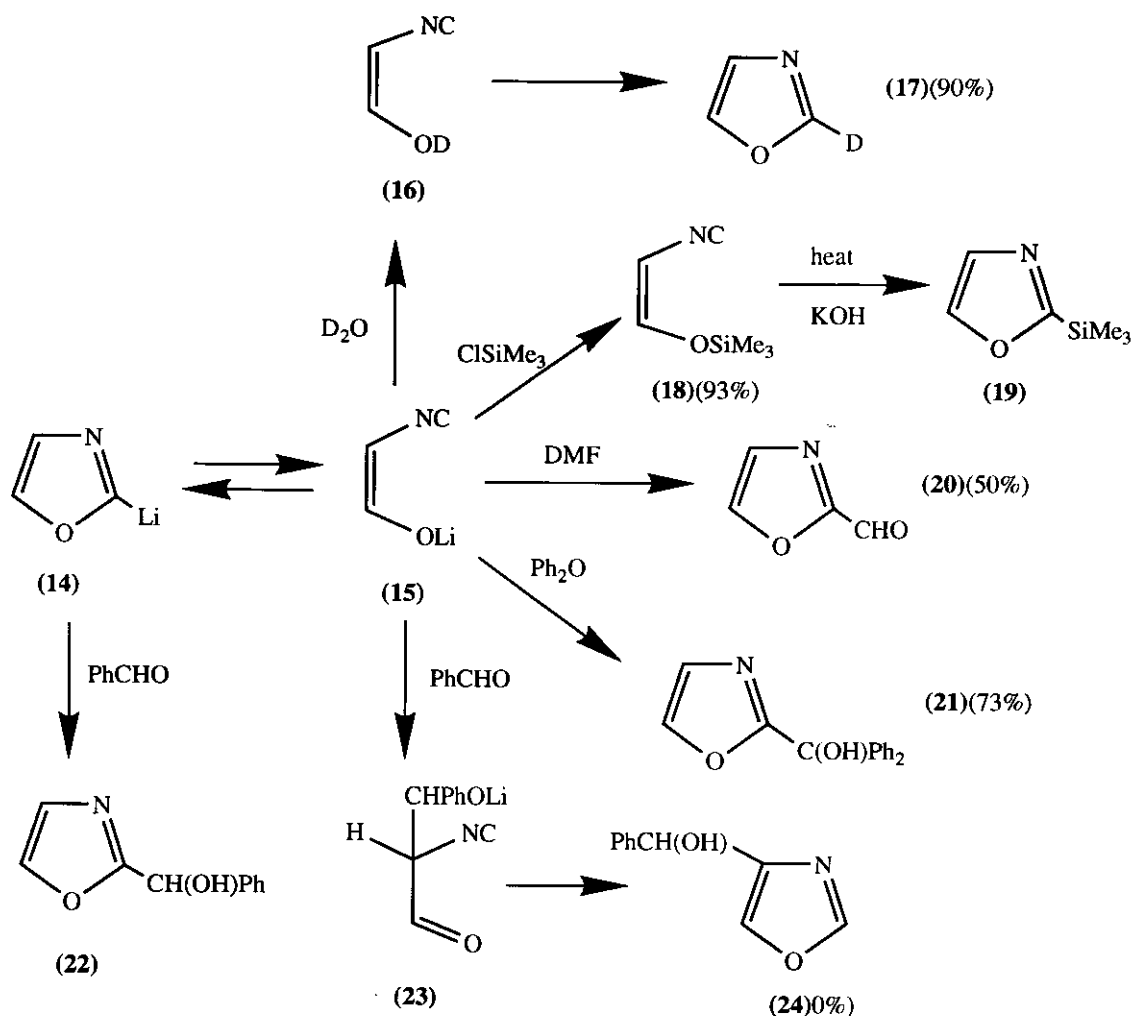


Scheme 3

Recent results with isoxazol-2-yl lithium, $14 \rightleftharpoons 15$ (Scheme 4), have added a new dimension to these studies.²⁰ Deuterium oxide quenches the lithium enolate at oxygen, to give product (16) which cyclizes to 2-deuterio-oxazole (17). Chlorotrimethylsilane reacts similarly, to yield compound (18) which can be rearranged to 2-trimethylsilyloxazole (19) by distillation from base (see before). Products of 2-substitution are observed with *N,N*-dimethylformamide (DMF) (20) and benzophenone (21) but, surprisingly, aldehydes such as benzaldehyde react with the lithium enolate at low temperatures, as shown in Scheme 4, to give an adduct (23) (analogous to 12) which cyclizes to give a 4-substituted oxazole (24). This last observation has not been seen before because all previous oxazoles studied have been 4-substituted. At higher temperatures small amounts of the 2-substituted oxazoles studied have been 4-substituted. At higher temperatures small amounts of the 2-substituted product (22) begin to appear. Iodobutane, benzyl bromide, and ethyl carbonate are unreactive towards oxazol-2-yl lithium (14).

In summary, depending on the structure of the oxazole under study, metallation of oxazoles can lead, after trapping with suitable reagents, to products of 2- or 4-substitution or of ring-opening via the formation of a lithium enolate.

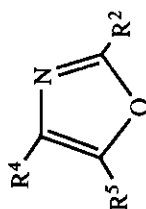
Few reports have appeared on the metallation of oxazoles in positions-4 and -5. Lithiation of 2,5-diphenyl-oxazole with butyllithium is complicated by metallation in the *ortho*-position of the 2-phenyl group²⁴ as well as by addition of the reagent to the C=N double bond,^{9,24} which leads to the isolation of valerophenone on work-



Scheme 4

up, and displacement of the 2-phenyl group by butyl.³⁰ Use of LDA or potassium diisopropylamide (KDA) at $-78^\circ C$,³⁰ or *sec*-butyllithium and a catalytic amount of LiTMP²⁴ leads to clean metallation at position-4. A number of 4-substituents (Table II) can be introduced by quenching the resulting 2,5-diphenyloxazol-4-yl lithium derivative with various electrophiles. We have mentioned already (Section II) that the lithium enolate (15) derived by the ring opening of oxazol-2-yl lithium (14) reacts with aldehydes to give 4-substituted oxazoles, e.g. 24 (Scheme 4) (Table II).²⁰

Table II
4-Substituted Oxazoles Prepared from Oxazol-4-yllithium Derivatives



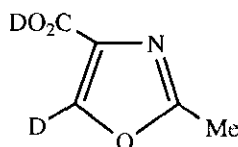
R ²	R ⁴	R ⁵	Reagent	Yield (%)	Ref.
H	CH(OH)C ₄ H ₉	H	C ₄ H ₉ CHO	28a	20
H		H		65a	20
H	CH(OH)Ph	H	PhCHO	20a,b	20
H	CH(OH)thiazol-2-yl	H	thiazol-2-ylCHO	65a	20
H	CH(OH)thiazol-4-yl	H	thiazol-4-ylCHO	62a	20
Ph	Br	Ph	Br ₂	58	24
Ph	Me	Ph	MeI	85	24
Ph	(CH ₂) ₆ OTMS ^c	Ph	TMSO(CH ₂) ₆ I	45	30
Ph	(CH ₂) ₈ OTBDMS ^d	Ph	TBDMSO(CH ₂) ₈ Br	60	30
Ph	CHO	Ph	DMF	50	9
Ph	COPh	Ph	PhCOCl	73	24

Ph	CH(OH)C ₅ H ₁₁	Ph	C ₅ H ₁₁ CHO	82	9
Ph	CH(OH)(CH ₂) ₃ OTBDMS ^d	Ph	TBDMSO(CH ₂) ₃ CHO	47	30
Ph	CH(OH)Ph	Ph	PhCHO	94, 70	24, 9
Ph	C(OH)Me ₂	Ph	Me ₂ CO	80	9
Ph	SiMe ₃	Ph	Me ₃ SiCl	83, 92	24, 9
Ph	SiEt ₃	Ph	Et ₃ SiCl	71	24
C ₆ H ₄ OMe-4	D	C ₆ H ₄ OMe-4	D ₂ O	50	9
C ₆ H ₄ OMe-4	Me	C ₆ H ₄ OMe-4	MeI	30	9
C ₆ H ₄ OMe-4	Et	C ₆ H ₄ OMe-4	EtI	20	9
C ₆ H ₄ OMe-4	CH ₂ Ph	C ₆ H ₄ OMe-4	PhCH ₂ Br	26	9
C ₆ H ₄ OMe-4	CH(OH)CHMe ₂	C ₆ H ₄ OMe-4	Me ₂ CHCHO	35	9

^a These aldehydes react, as shown for PhCHO, in **Scheme 4** (i.e. *via* initial generation of oxazol-2-yl lithium, **14** $\rightleftharpoons$ **15**). ^b At ambient temperature PhCH₂OH is formed also in 34% yield along with a trace amount (2%) of the corresponding 2-isomer (amount dependent on temperature). ^c TMS = trimethylsilyl. ^d TBDMS = *tert*-butyldimethylsilyl.

2,4-Diphenyloxazole is metallated at position-5 with butyllithium (THF/-60 °C) in the presence of hexamethylphosphoric triamide (HMPA)³¹ or with *sec.*-butyllithium and a catalytic amount of LiTMP²⁴ and the resulting 5-lithiated derivative can be trapped with various electrophiles (Table III). 2-Phenyloxazole is deprotonated similarly and exclusively at position-5⁷ as shown by isolation of the 5-deuteriated derivative on addition of deuterium oxide. The same 5-deuteriated derivative is obtained following sequential treatment of 2-(2-bromophenyl)oxazole with butyllithium and deuterium oxide, showing that the C-5 proton is thermodynamically more acidic than the *ortho*-proton of the phenyl ring.⁷

Oxazole-4-carboxylic acid is metallated with butyllithium (2 mol. equiv. required: THF/-78 °C) in position-5 as shown by isolation of its 5-deuteriated derivative after addition of MeOD.^{8,32} Similarly, 2-methyloxazole-4-carboxylic acid^{8,32,33} and its methyl,³² ethyl³⁴ and *tert.*-butyl esters³⁵ were not metallated by butyl- (THF/-78 °C) or *tert.*-butyllithium (THF/-40 °C) or LDA in their methyl groups (Section IV) but in position-5 instead. The resulting oxazol-5-yl lithium derivatives can be trapped with various electrophiles (Table III). Even more surprising perhaps is the fact that compound (25), prepared in the manner just described, reacts with 2 mol. equiv. of *tert.*-butyllithium (butyllithium is reported not to react) at -78 °C only by deuterium extraction; addition



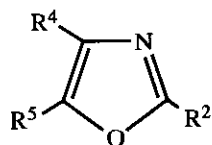
(25)

of iodomethane gives 2,5-dimethyloxazole-4-carboxylic acid together with 2-methyloxazole-4-carboxylic acid (ratio 10:90, which suggests that the dilithiated derivative of 2-methyloxazole-4-carboxylic is a very poor nucleophile).^{8,32}

III HALOGEN → LITHIUM EXCHANGE REACTIONS

Few have been reported in the oxazole area presumably due to the difficulties encountered in obtaining suitable halogeno-oxazoles. Bowie *et al.*¹⁴ obtained 2,5-diphenyloxazol-4-yl lithium (26) from the corresponding 4-bromo oxazole and quenched it with deuterium oxide.

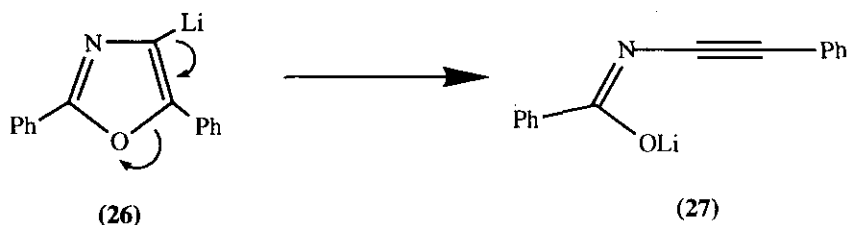
Table III
5-Substituted Oxazoles Prepared from Oxazol-5-yllithium Derivatives



R ²	R ⁴	R ⁵	Reagent	Yield (%)	Ref.
H	CO ₂ H	D	MeOD	—	32, 8
Ph	H	D	D ₂ O	—	7
Me	CO ₂ H	D	D ₂ O	92, 77	32, 8
Me	CO ₂ H	D → Me	MeI	~ 10% ^a	32, 8
Me	CO ₂ H	SiMe ₃	Me ₃ SiCl	86	33
Me	CO ₂ Me	D	D ₂ O	99, 92	32, 8
Me	CO ₂ Et	D	D ₂ O	—	34
Me	CO ₂ Bu- <i>t</i>	SiMe ₃	Me ₃ SiCl	62	35
Me	Ph	D	D ₂ O	—	13 ^b
Ph	H	H	H ₂ O	88	36 ^b
Ph	H	D	D ₂ O	84	36 ^b
Ph	H	Me	MeI	73	36 ^b
Ph	H	Et	EtI	70	36 ^b

Ph	H	CH ₂ Ph	PhCH ₂ Br	72	36 ^b
C ₆ H ₄ Cl-4	H	H	H ₂ O	84	36 ^b
C ₆ H ₄ Cl-4	H	D	D ₂ O	80	36 ^b
C ₆ H ₄ Bu ^t -4	H	H	H ₂ O	85	36 ^b
C ₆ H ₄ Bu ^t -4	H	D	D ₂ O	86	36 ^b
Ph	Ph	Me	MeI	85	31
Ph	Ph	CH(OH)Ph	PhCHO	—	31
Ph	Ph	SiMe ₃	Me ₃ SiCl	88	24

^a The methylated product comprised only 10% of the mixture; the remaining 90% was recovered **protonated** starting material. ^b Prepared via bromine → lithium exchange.



Scheme 5

Interestingly lithium derivative (26) undergoes a similar ring-opening reaction (Scheme 5) to that which oxazol-2-yllithium derivatives undergo (Section II) but under more forcing conditions (70 °C in hexane/HMPA); the product (27) can be trapped, e.g. with benzaldehyde.³⁷

Similarly, with butyllithium (Et₂O/-65 °C) 5-bromo-2-methyl-4-phenyloxazole yields the corresponding oxazol-5-yllithium derivative which has been trapped with deuterium oxide.¹³ Formation of 2-aryloxazol-5-yllithium (THF/-18 °C) compounds is reported³⁶ to require 5 mol. equiv. of butyllithium for good conversion; the resulting 5-lithiated derivatives have been treated with water, deuterium oxide, iodomethane and -ethane, and benzyl bromide (Table III).

IV LATERAL METALLATION

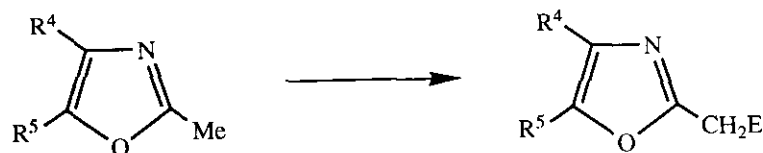
Modification of oxazoles at position-2 *via* metallation is complicated by ring-opening of oxazol-2-yllithium compounds (Section II). Another way of preparing 2-substituted oxazoles is through α -(or lateral)metallation of 2-alkyloxazoles.

The first reported lateral metallation of an oxazole was the 2- α -deuteration of 2-methyl-4-phenyloxazole through its sequential treatment with butyllithium (Et₂O/-65 °C) and deuterium oxide.¹³ The same anion can be trapped also with 5-bromopent-1-ene (see Table IV).²⁴

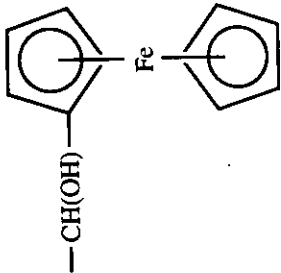
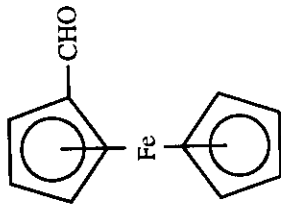
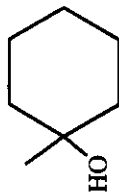
Kashima *et al.*³⁸ has generated anion (28) through treatment of the 2-methyl compound with LDA (THF/-78 °C) and trapped it with 4-methylbenzaldehyde, methyl 4-methylbenzoate and with varying amounts of iodomethane, iodoethane, and benzyl bromide (Table IV). The products obtained on alkylation depend upon the ratio of 2-methyl compound : LDA : RI; one, two, or three alkyl groups can be introduced successively. More than one mol. equiv. of LDA is required due to the formation of RNPri₂ on addition of the alkylating reagent; attempted

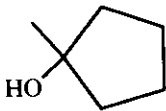
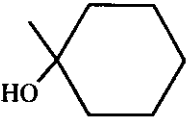
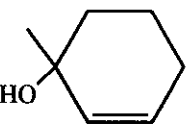
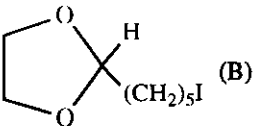
Table IV

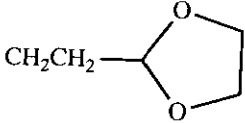
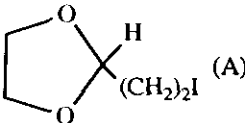
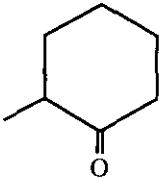
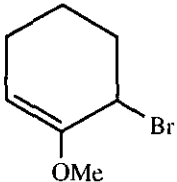
2-Substituted Oxazoles Prepared by Lateral Metallation of 2-Methyloxazoles^a



R ⁴	R ⁵	E	Quenching Reagent	Yield (%)	Ref.
Ph	H	D	D ₂ O (A)	–	13
Ph	H	(CH ₂) ₃ CH=CH ₂	CH ₂ =CH(CH ₂) ₃ Br (A)	65	24
Ph	H	CH ₂ E ≡ CPh(OMOM)COMe	MeCOCl	30	24
H	Ph	Me	MeI (B)	68 ^b	38
H	Ph	Et	EtI (B)	60 ^b	38
H	Ph	CHMe ₂	MeI (B)	70 ^c	38
H	Ph	CHEt ₂	EtI (B)	58 ^d	38
H	Ph	CH ₂ Ph	PhCH ₂ Br (B)	62 ^b	38
H	Ph	CH(CH ₂ Ph) ₂	PhCH ₂ Br (B)	65	38
H	Ph	CH(OH)C ₆ H ₄ Me-4	4-MeC ₆ H ₄ CHO (B)	63	38
H	Ph	CH(OH)C ₆ H ₄ Me-4	4-MeC ₆ H ₄ CO ₂ Me (B)	58	38
Me	Me	CH ₂ Ph	PhCH ₂ Cl (B)	92	39
Me	Me	CH ₂ (naphth-2-yl)	naphth-2-ylCH ₂ Br (B)	70	39

Me	Me	CH(OH)Ph	PhCHO (B)	89	39
Me	Me	CH(OH)(2-furyl)	2-furylCHO (B)	73	39
Me	Me			57	39
Me	Me		cyclohexanone (B)	95	39, 9
Me	Me	CH ₂ CH(OH)Ph	2-phenyloxirane (B)	72	39, 9
Ph	Me	CH ₂ CH=CH ₂	CH ₂ =CHCH ₂ Br (A, B)	80, 80	39, 9
Ph	Me	SiMe ₃	Me ₃ SiCl (A)	75	39
Me	Ph	CH(OH)C ₆ H ₁₃	C ₆ H ₁₃ CHO (A, B)	80, 80	39, 9
Me	Ph	CHMe ₂	Me ₂ CHI (A)	86	39
Ph	Ph	Me	MeI (A, B)	84, 73	39-41, 9
Ph	Ph	Pr	PrI (B)	82	40, 41, 9
Ph	Ph	Bu	BuI (A)	93	42

Ph	Ph	$(CH_2)_{11}OH$	THPO $(CH_2)_{11}I$ (B)	57c	40, 41, 9
Ph	Ph	$(CH_2)_{12}OH$	THPO $(CH_2)_{12}I$ (B)	43c	40, 41, 9
Ph	Ph	$(CH_2)_{11}CH(OH)Me$	THPOCHMe $(CH_2)_{11}I$ (B)	40c	40, 41, 9
Ph	Ph	$(CH_2)_5CH=CHCH_2CH(OH)Me$	THPOCHMe $CH_2CH=CH(CH_2)_5I$ (B)	43c	40, 41, 9
Ph	Ph	CH_2CH_2OH	oxirane (B)	85	43
Ph	Ph	$CH_2CH(OH)Me$	2-methyloxirane (B)	45	40
Ph	Ph	$CH(OH)Ph$	PhCHO (C)	—	44
Ph	Ph	$C(OH)Ph_2$	Ph ₂ CO (C)	—	44
Ph	Ph		cyclopentanone (A, B)	90, 90	39, 9
Ph	Ph		cyclohexanone (C)	—	44
Ph	Ph		cyclohexenone (A)	—	39
Ph	Ph	$(CH_2)_5CHO$	 (B)	62	41

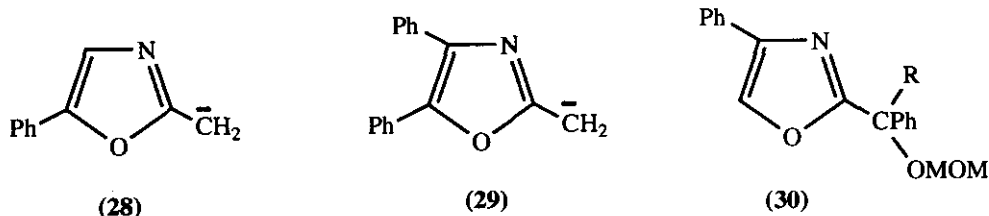
Ph	Ph	CH ₂ CH ₂ OH	Me ₃ SiOCH ₂ CH ₂ I (A)	77 ^d	45
Ph	Ph		 (A)	84	45
Ph	Ph	CH ₂ SnMe ₃	Me ₃ SnCH ₂ I (B)	70	46
Ph	Ph	CH ₂ COMe	CH ₂ =C(OMe)CH ₂ Br (A)	59	47
Ph	Ph			96	47
CO ₂ H	SiMe ₃	D	MeOD (A)	77	33
CO ₂ H	SiMe ₃	Me	MeI (A)	86	33
CO ₂ H	SiMe ₃	CH(OH)CHMe ₂	Me ₂ CHCHO (A)	88	33
CO ₂ H	SiMe ₃	C(OH)Me ₂	Me ₂ CO (A)	90	33
Me	CO ₂ H	Me	MeI (A, B)	87	48, 49
Me	CO ₂ H	Et	EtI (A, B)	66	49
Me	CO ₂ H	CH ₂ CH=CH ₂	CH ₂ =CHCH ₂ Br (A, B)	79	49
Me	CO ₂ H	CH(OH)Ph	PhCHO (A, B)	87	48, 49
Me	CO ₂ H	CH(OH)C ₆ H ₁₃	C ₆ H ₁₃ CHO (A, B)	80	48, 49

Me	CO ₂ H	CH(OH)C ₆ H ₄ OMe-4	4-MeOC ₆ H ₄ CHO (A, B)	50	48
Me	CO ₂ H	C(OH)Ph ₂	Ph ₂ CO (A, B)	78	48, 49

^a Metallation reagents: A = BuLi/Et₂O or THF/low temperatures (e.g. -78 °C); B = LDA/THF/-78 °C; C = LiNH₂/liquid NH₃; D = *tert*-BuLi (2 mol. equiv. in THF/-78 °C). ^b The product obtained depends on the ratio of starting material : LDA : RX; polyalkylation occurs under certain conditions. ^c Yield of alcohol after hydrolysis of THP ether. ^d Yield of alcohol after hydrolysis during work-up of TMS-protected alcohol.

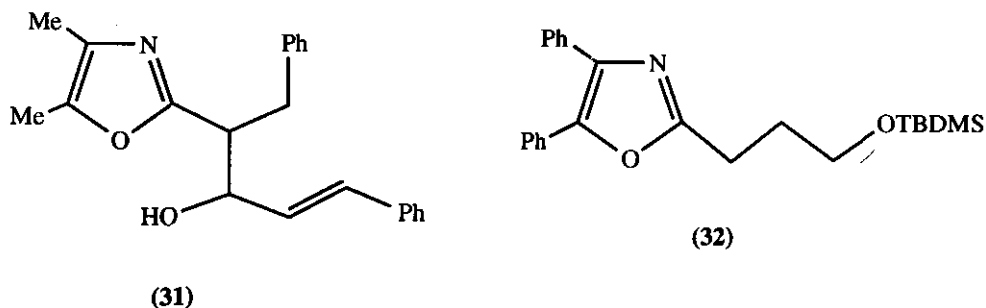
use of butyllithium resulted in failed reactions. Noteworthy is a comment by Meyers and Walker³⁴ that it is difficult to deprotonate (some) 2-methyloxazoles.

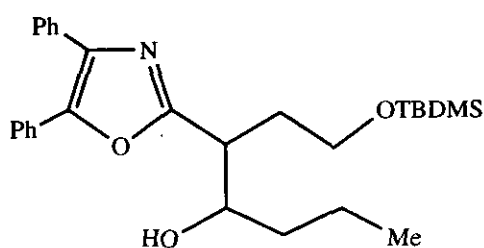
The most studied anion (29) (see ref. 50) is generated from the corresponding 2-methyl compound using either butyllithium (THF/-78 °C or -90 °C),^{42,45,47} LDA (THF/-78 °C or -50 °C),^{9,39-41,46} LDA in the presence of HMPA,⁴³ or sodamide in liquid ammonia.⁴⁴ This anion (29) has been trapped with a number of different electrophiles (Table IV). A number of other 4,5-disubstituted 2-methyloxazoles behave similarly; the products obtained after quenching the resulting anion are listed in Table IV.^{9,39}



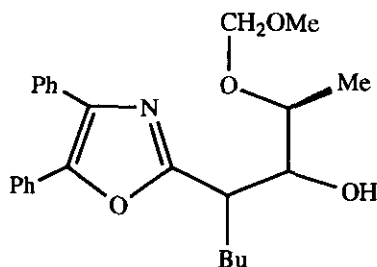
Noteworthy is the fact that the methoxymethyl (MOM) protected ether (30; R = H) undergoes α -deprotonation with butyllithium (THF/-78 °C) rather than metallation at position-5 and the resulting anion can be trapped with acetyl chloride to give compound (30; R = COCH₃) (Table IV).²⁴

Sequential treatment of 4,5-dimethyl-2-phenethyloxazole with LDA (THF/-78 °C) and cinnamaldehyde yields compound (31) (60% yield) as a mixture of diastereoisomers³⁹ whilst similar reactions between the TBDMS-protected ether (32) and butyraldehyde⁴³ and between 2-pentyl-4,5-diphenyloxazole and *S*-2-methoxymethyloxopropanal⁴² yield compound (33) (75% yield) and compound (34) (58%), respectively, also as mixtures of diastereoisomers. (+)-(1*R*,2*R*,3*S*)-34 was obtained pure from the mixture by flash chromatography. Likewise, 5-methyl-4-phenyl-2-trimethylsilylmethyloxazole is α -metallated at position-2 and the α -lithiated product has been treated with benzaldehyde.³⁹



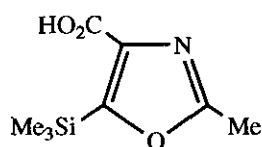


(33)

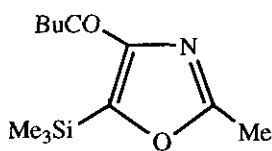


(34)

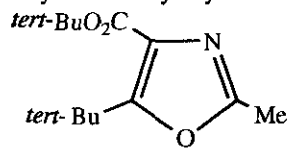
In order to substitute the methyl group in 2-methyloxazole-4-carboxylic acid it is necessary first to protect position-5 with a trimethylsilyl group (Section II; Table III). The product (35) can be metallated with *tert*-butyllithium (2 mol. equiv. in THF/-78 °C); after 2 min the appropriate trapping agent can be added (Table IV)³³ and the trimethylsilyl group removed with cesium fluoride. When *tert*-butyl 2-methyl-5-trimethylsilyloxazole-4-



(35)



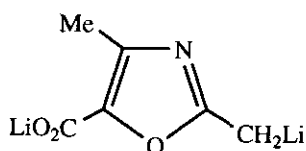
(36)



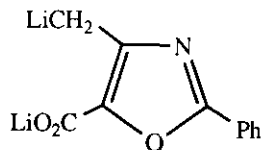
(37)

carboxylate is treated sequentially with butyllithium (THF/-78 °C) and iodomethane, the ketone (36) is unexpectedly produced (51% yield).³⁵ Its sequential treatment with *tert*-butyllithium (THF/-90 °C) and iodomethane results in displacement of the trimethylsilyl group, to give compound (37) (72%).³⁵

The powerful *ortho*-directing capabilities of a 4-carboxyl group in promoting lithiation at position-5 in oxazoles with a free position-2 or carrying a 2-methyl group has been mentioned before (Section II). However, when 2,4-dimethyloxazole-5-carboxylic acid is metallated with butyllithium or LDA (2 mol. equiv.; THF/-78 °C) only dianion (38) is formed.^{48,49} This can be trapped with various electrophiles (Table IV). When position-2 is blocked, lateral metallation is possible in another position, as shown by generation of dianion (39).^{48,49} At -78 °C in THF (with BuLi or LDA) conversion is poor and LDA at a temperature of -35 °C is preferred if good

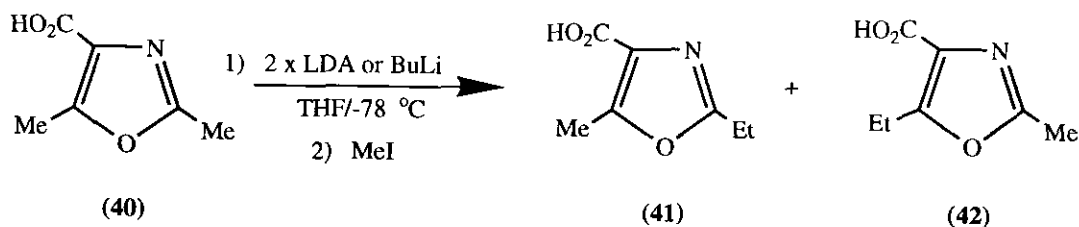


(38)



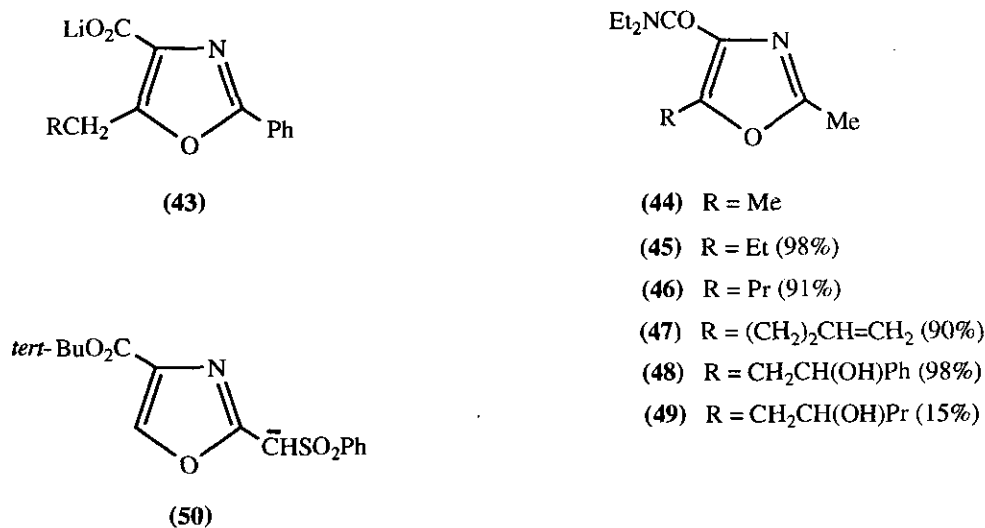
(39)

yields (68%) of 4-ethyl-2-phenyloxazole-5-carboxylic acid are to be obtained following addition of iodomethane. 2,5-Dimethyloxazole-4-carboxylic acid (40) reacts at both methyl groups. Comparable amounts of compounds (41) and (42) (Scheme 6) are produced with LDA but, with butyllithium, the ratio 41:42 is 3:7,^{48,49} indicating the importance of complexation of the metallating agent with the carboxyl group. When position-2 is blocked a 4-carboxyl group is capable of directing an adjacent alkyl group, as shown by generation of dianion (43; R = Li)



Scheme 6

(BuLi/THF/-78 °C), which can be quenched with iodomethane, to give 5-ethyl-2-phenyloxazole-4-carboxylic acid (43; R = Me, Li = H) (86% yield).^{48,49} Compounds [43; R = CH₂CH=CH₂, Li = H (75%) and R = CH₂CH(OH)Et, Li = H (60%)] can be prepared similarly.⁴⁸ Ethyl 4-methyloxazole-5-carboxylate is metallated with LiICA exclusively in position-2.²⁵ The amide group in compound (44) is a much more powerful *ortho*-directing group which allows selective introduction of substituents into the 5-methyl group; compounds (45)-(49) can be synthesised in this way (using BuLi/THF/-78 °C).^{48,49}



Noteworthy is the generation of anion (50) *via* treatment of the corresponding 2-phenylsulfonylmethyl compound with sodium hydride in THF at $-15 \rightarrow -10^\circ\text{C}$ ³⁵; it has been allowed to react with various acylating electrophiles.

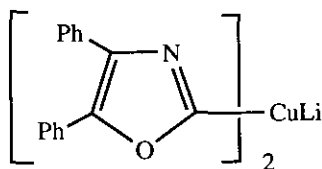
V POLYLITHIATED DERIVATIVES

No oxazole ring dianions are known. The only dianions studied to date are those described in the previous Section involving ring and side-chain metallation of oxazolecarboxylic acids.

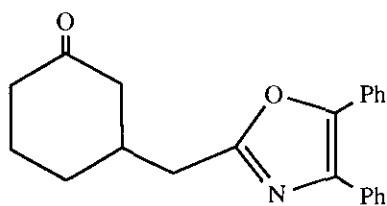
VI OTHER ORGANOMETALLIC DERIVATIVES

2-Methyl-4,5-diphenyloxazole reacts sequentially with butyllithium (THF/ -100°C) and cuprous iodide ($\text{Et}_2\text{O}/-45^\circ\text{C}$) in the presence of dimethyl sulfide to give organocopper derivative (51) which undergoes conjugate addition with 2-cyclohexenone, to give adduct (52) (> 80% yield).³⁹

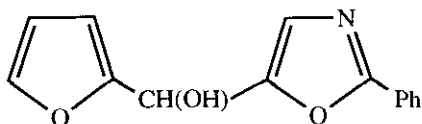
2,4-, 2,5-, and 4,5-Diphenyloxazole and 2-methyl-5-phenyloxazole are mercurated by mercuric acetate in the vacant ring-position^{51,52} and the resulting mercurated derivatives react with bromine or iodine^{51,53} to give moderate (55%) to high (85%) yields of the corresponding halogen derivative (see also ref. 54). The mercurated derivatives derived from 2,4- or 2,5-diphenyloxazole give the corresponding [oxazol-5(or 4)-yl]₂Hg derivative with sodium stannite.^{51,52} Each of the mercurated derivatives is hydrolysed back to the corresponding oxazole with dilute mineral acid.^{51,52}



(51)



(52)



(53)

Grignard derivatives of oxazoles are almost unknown.⁴ Noteworthy, however, is a report that the Grignard reagent prepared from 2-(2-bromophenyl)oxazole and activated magnesium rearranged to the isomeric 2-phenyloxazol-5-ylmagnesium bromide, as shown by isolation of compound (53) following addition of furan-2-carbaldehyde (furfural).⁷

This review does not cover the important metallated Δ^2 -oxazolines.^{5,12,17,19,55-57}

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REFERENCES

1. Part I: B. Iddon, *Heterocycles*, 1994,
2. R. Lakhan and B. Ternai, *Adv. Heterocycl. Chem.*, 1974, **17**, 99.
3. I.J. Turchi and M.J.S. Dewar, *Chem. Rev.*, 1975, **75**, 389.
4. I.J. Turchi, *Chem. Heterocycl. Compd.*, 1986, **45**, 1.
5. A. Dondoni, G. Fantin, M. Fogagnolo, A. Mastellari, A. Medici, E. Negrini, and P. Pedrini, *Gazz. Chim. Ital.*, 1988, **118**, 211.
6. A. Hassner and B. Fischer, *Heterocycles*, 1993, **35**, 1441.
7. J.I. Levin and S.M. Weinreb, *J. Org. Chem.*, 1984, **49**, 4325.
8. A.I. Meyers, J.P. Lawson, D.G. Walker, and R.J. Linderman, *J. Org. Chem.*, 1980, **51**, 5111.
9. H.H. Wasserman, K.E. McCarthy, and K.S. Prowse, *Chem. Rev.*, 1986, **86**, 845.
10. S.E. Whitney, M. Winters, and B. Rickborn, *J. Org. Chem.*, 1990, **55**, 929.
11. L.N. Pridgen and S.C. Shilcrat, *Synthesis*, 1984, 1048.
12. A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, *J. Org. Chem.*, 1987, **52**, 3413.
13. J.H. Bowie, P.F. Donaghue, H.J. Rodda, R.G. Cooks, and D.H. Williams, *Org. Mass Spectrom.*, 1968, **1**, 13.
14. J.H. Bowie, P.F. Donaghue, H.J. Rodda, and B.K. Simons, *Tetrahedron*, 1968, **24**, 3965.
15. R. Schröder, U. Schöllkopf, E. Blume, and I. Hoppe, *Liebigs Ann. Chem.*, 1975, 533.
16. F. Gerhart and U. Schöllkopf, *Tetrahedron Lett.*, 1968, 6231.
17. A.I. Meyers and E.W. Collington, *J. Am. Chem. Soc.*, 1970, **92**, 6676.

18. D. Hoppe and U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 300.
19. U. Schöllkopf, F. Gerhart, I. Hoppe, R. Harms, K. Hantke, K.H. Scheunemann, E. Eilers, and E. Blume, *Liebigs Ann. Chem.*, 1976, 183.
20. J.C. Hodges, W.C. Patt, and C.J. Connolly, *J. Org. Chem.*, 1991, **56**, 449.
21. A. Dondoni, T. Dall'Occo, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, *J. Chem. Soc., Chem. Commun.*, 1984, 258.
22. A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, *Synthesis*, 1987, 693.
23. P.A. Jacobi, S. Ueng, and D. Carr, *J. Org. Chem.*, 1979, **44**, 2042.
24. S.E. Whitney and B. Rickborn, *J. Org. Chem.*, 1991, **56**, 3058.
25. R.K. Howe and L.F. Lee, U.S. Patent 4,360,678/1982.
26. R. Baker, R.J. Snow, J. Saunders, and G.A. Showell, Europ. Pat. Appl. 0-307-141-A2/1988 (*Chem. Abstr.*, 1989, **111**, 153786).
27. P.D. Edwards, J.J. Lewis, C.W. Perkins, D.A. Trainor, and R.A. Wildonger, Europ. Pat. Appl. 0-291 234-A2/1988 (*Chem. Abstr.*, 1989, **110**, 232092).
28. A.P. Kozikowski and A. Ames, *J. Org. Chem.*, 1980, **45**, 2548.
29. A. Dondoni, *Phosphorus, Sulfur, Silica*, 1989, **43**, 25.
30. H.H. Wasserman, R.W. DeSimone, W.-B. Ho, K.E. McCarthy, K.S. Prouse, and A.P. Spada, *Tetrahedron Lett.*, 1992, **33**, 7207.
31. I. Hoppe and U. Schöllkopf, *Liebigs Ann. Chem.*, 1979, 219.
32. A.I. Meyers and J.P. Lawson, *Tetrahedron Lett.*, 1981, **22**, 3163.
33. R.D. Wood and B. Ganem, *Tetrahedron Lett.*, 1983, **24**, 4391.
34. A.I. Meyers and D.G. Walker, *J. Org. Chem.*, 1982, **47**, 2999.
35. Y. Nagao, S. Yamada, and E. Fujita, *Tetrahedron Lett.*, 1983, **24**, 2287.
36. C. Kashima and H. Arao, *Synthesis*, 1989, 873.
37. T.L. Gilchrist and D.P.J. Pearson, *J.C.S., Perkin Trans. 1*, 1976, 989.
38. C. Kashima, H. Arao, and R. Okada, *Heterocycles*, 1990, **30**, 487.
39. B.H. Lipshutz and R.W. Hungate, *J. Org. Chem.*, 1981, **46**, 1410.
40. H.H. Wasserman, R.J. Gambale, and M.J. Pulwer, *Tetrahedron Lett.*, 1981, **22**, 1737.
41. H.H. Wasserman, R.J. Gambale, and M.J. Pulwer, *Tetrahedron*, 1981, **37**, 4059.

42. H.H. Wasserman and R.J. Gambale, *Tetrahedron*, 1992, **48**, 7059.
43. H.H. Wasserman and T-J. Lu, *Recl. Trav. Chim. Pays-Bas*, 1986, **105**, 345.
44. V. Dryanska and K. Ivanov, *God. Sofii. Univ. Khim. Fak.*, **63**, 105 [1968-1969 (Publ. 1971)] (*Chem. Abstr.*, 1972, **76**, 126844).
45. L.N. Pridgen, S.C. Shilcrat, and I. Lantos, *Tetrahedron Lett.*, 1984, **25**, 2835.
46. W.R. Baker, *J. Org. Chem.*, 1985, **50**, 3942.
47. T. Sasaki, M. Ohno, and E. Ito, *J. Chem. Soc., Perkin Trans. 1*, 1983, 3027.
48. P. Cornwall, C.P. Dell, and D.W. Knight, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2417.
49. P. Cornwall, C.P. Dell, and D.W. Knight, *Tetrahedron Lett.*, 1987, **28**, 3585.
50. H.H. Wasserman and K.S. Prowse, *Tetrahedron*, 1992, **48**, 8199.
51. O.P. Shvaika and G.P. Klimisha, *Dopovidi Akad. Nauk. Ukr. RSR*, 1965, 1479 (*Chem. Abstr.*, 1966, **65**, 7159).
52. O.P. Shvaika and G.P. Klimisha, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1966, **2**, 14.
53. O.P. Shvaika and G.P. Klimisha, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1966, **2**, 517.
54. W.J. Hammar and M.A. Rustad, *J. Heterocycl. Chem.*, 1981, **18**, 885.
55. A.I. Meyers and E.D. Mihelich, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 270.
56. J. ApSimon and A. Holmes, *Heterocycles*, 1977, **6**, 731.
57. B.E. Marynoff, *Chem. Heterocycl. Compd.*, 1986, **45**, 963.

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