

SYNTHESIS AND REACTIONS OF LITHIATED MONOCYCLIC AZOLES CONTAINING TWO OR MORE HETERO-ATOMS. PART VI: TRIAZOLES, TETRAZOLES, OXADIAZOLES, AND THIADIAZOLES[†]

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Abstract -The metallation and halogen → metal exchange reactions of 1,2,3- and 1,2,4-triazoles, tetrazoles, 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-oxadiazoles, and 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-thiadiazoles 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.

C 1,2,5-Oxadiazoles

D 1,3,4-Oxadiazoles

VI THIADIAZOLES

A 1,2,3-Thiadiazoles

B 1,2,4-Thiadiazoles

C 1,2,5-Thiadiazoles

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I INTRODUCTION

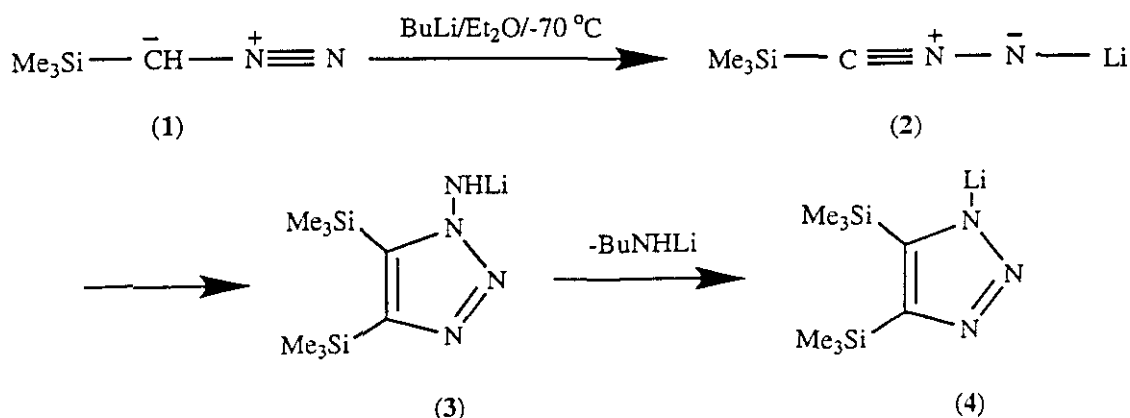
A general introduction to this series of reviews was given in Part I.² Since it appeared a review on "The Lateral Metallation of Isoxazoles" has been published³ which covers some references that we had overlooked. We would be pleased to hear from any other authors whose work we have inadvertently overlooked.

Part VI, like the other reviews in this Series, is intended to be comprehensive and covers the literature through June 1994.

II 1,2,3-TRIAZOLES

A Metallation in the ring

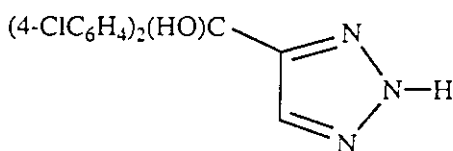
Substituted diazomethanes, e.g. **1**, react with organolithium reagents as shown in Scheme 1, to give *N*-lithiated



Scheme 1

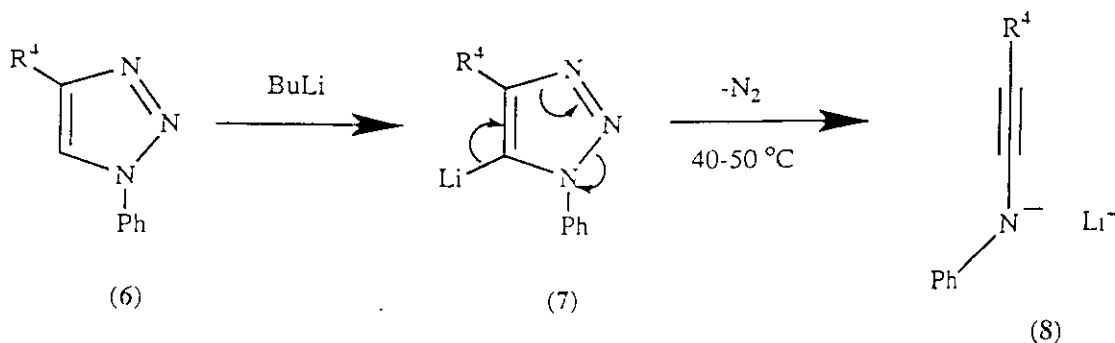
1*H*-1,2,3-triazoles, e.g. **4**.⁴ The key steps are the condensation of the lithiated diazomethane (**2**) with the starting material (**1**), to give triazole (**3**) which fragments to the product (**4**) in the presence of the excess of butyllithium.

As far as we are aware only two 1-protected 1*H*-1,2,3-triazoles have been metallated directly. The 1-trimethylsilyloxyethyl(SEM) derivative, with butyllithium [tetrahydrofuran (THF)/-70 °C], gives its 5-lithiated derivative which can be quenched with a number of electrophiles, but not *N,N*-dimethylformamide (DMF) (see Table I).⁵ Similar reactions with 2-trimethylsilyloxyethyl(SEM)-2*H*-1,2,3-triazole are not successful; the 4-lithiated derivative is not stabilized through co-ordination with the substituent in this case.⁵ A mixture of 1-1*H*- and 2-2*H*-diethoxyethyl-1,2,3-triazole has been metallated with butyllithium; after quenching the lithiated products with *bis*(4-chlorophenyl) ketone and deprotection, a low yield (17%) of compound (5) was obtained.⁶



(5)

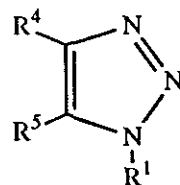
At ambient temperature, or slightly above, 1,4-diphenyl-1*H*-1,2,3-triazol-5-yl lithium (7, R⁴ = Ph) fragments to produce nitrogen and the *N*-phenylketenimine anion (8, R⁴ = Ph) (Scheme 2).⁷ 1-Phenyl- (7, R⁴ = H) and 4-methyl-1-phenyl-1*H*-1,2,3-triazol-5-yl lithium (7, R⁴ = Me) fragment similarly but at slightly higher temperatures, typical also of the fragmentation of 1,2,3-thiadiazoles (Section VI.A), 1,4-disubstituted tetrazolium salts (Section IV), and 5-chloro-1-phenyltetrazole (Section IV) in the presence of bases.^{8,9} A number of other 4-substituted 1-phenyl-1*H*-1,2,3-triazol-5-yl lithium compounds (7) lose nitrogen at ambient temperature (Scheme 2).¹⁰ Neither butyllithium nor *sec*-butyllithium appear to metallate the diethylamide (6, R⁴ = CONEt₂) but an excess of lithium



Scheme 2

diisopropylamide (LDA) at -78 °C accomplishes this metallation - at position-5. The 5-lithiated derivative of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole can be prepared similarly and quenching with methyl chloroformate yields the corresponding methyl ester; no fragmentation occurs.¹⁰ 4-Phenyl-1-styryl-1*H*-1,2,3-triazole forms a

Table I

1*H*-1,2,3-Triazoles from Lithium Compounds Prepared by Direct Metallation or Halogen → Lithium Exchange

R ¹	R ⁴	R ⁵	Reagent	Yield (%)	Ref.
H ^a	H	C(OH)(C ₆ H ₄ Cl-4) ₂	(4-ClC ₆ H ₄) ₂ CO	17	6
CH ₂ Ph	Ph	CO ₂ Me	ClCO ₂ Me	–	10
CH ₂ Ph	Br	SMe	Me ₂ S ₂	91.5	11
CH ₂ C ₆ H ₄ OMe-4	Br	SMe	Me ₂ S ₂	86.5	11
CH ₂ OMe ^b	Br	H	H ₂ O	84	11
CH ₂ OMe ^b	Br	C(OH)Ph ₂	Ph ₂ CO	93	11
CH ₂ OMe ^b	Br	CO ₂ H	CO ₂	71.5	11
CH ₂ OMe ^b	Br	CO ₂ Me	ClCO ₂ Me	–	11
CH ₂ OMe ^b	Br	SPh	Ph ₂ S ₂	71	11
SEM ^c	H	Me	MeI	30	5
SEM ^c	H	Cl	Cl ₃ CCCl ₃	50	5

SEM ^ε	H	CH(OH)Ph	PhCHO	45	5
SEM ^ε	H	COPh	PhCO ₂ Et	21	5
SEM ^ε	H	SPh	Ph ₂ S ₂	80	5
SEM ^ε	H	SiMe ₃	Me ₃ SiCl	37	5
MeC(OEt) ₂	H	C(OH)(C ₆ H ₄ Cl-4) ₂	(4-ClC ₆ H ₄) ₂ CO	17 ^d	6
Ph	H	Me	MeI	94	8
Ph	Me	Me	MeI	81	8
Ph	Me	Ph	MeI	99	8
Ph	H	Et	MeI	42	8
Ph	Ph	Me	MeI	78	8
Ph	Ph	CO ₂ H	CO ₂	62	8

^a A mixture of 1- and 2-diethoxymethyl-1,2,3-triazole was lithiated; yield given is that of the product isolated after deprotection. ^b The 2-methoxymethyl compounds reacted similarly. ^c SEM ≡ trimethylsilylethoxymethyl. ^d The starting material was a mixture of 1- and 2-diethoxymethyl-1,2,3-triazole; this yield is of the homogenous product obtained after deprotection of the mixture of products.

5-lithiated derivative which evolves nitrogen on warming; addition of methyl chloroformate appears to result in reaction at the styryl terminus. 4-Nitro-1-phenyl-1*H*-1,2,3-triazole (**6**, R⁴ = NO₂) is incapable of lithiation at position-5 without affecting the nitro group.¹⁰

Provided that the temperature is kept low it is usually possible to trap the 5-lithiated derivative with an electrophile (Table I).^{6,8,9,11} If position-5 is blocked, as in 1,5-diphenyl-1*H*-1,2,3-triazole, the 4-lithiated derivative can be formed.⁸

Begtrup¹² has reviewed the activation towards deprotonation (NaH/DMF) of *N*-substituted 1,2,3-triazoles through their quaternization or *N*-oxidation. Use of the *N*-oxides in particular has proved extremely useful for introduction of substituents into this ring system. However, with 3-substituted 1,2,3-triazole 1-oxides regio- and monoselectivity may be low. One of the unsymmetrical positions may be protected, however, with a removable protecting group, e.g. bromine, chlorine, or methylthio.^{12,13} Halogen atoms enhance the acidity of the adjacent proton. The anions formed react with carbon, silicon, halogen, and sulfur electrophiles. Initial products may react further, e.g. by nucleophilic displacement of a halogen atom (e.g. by MeS⁻ liberated from Me₂S₂) or through dealkylation of a methylthio group (SMe → SH).

The reactivity of 3-substituted 1,2,3-triazole 1-oxides can be enhanced in various other ways, e.g. by their *O*-alkylation.¹² Thus, e.g., 1-methoxy-2-phenyl-1,2,3-triazolium salts are deprotonated by bases such as ethyldiisopropylamine (EDIP), and the resulting anions can be quenched with various electrophiles.¹⁴

In certain cases high regio- and monoselectivity can be achieved, especially through conversion of the 1-oxides into their 1-trialkylsilyloxy derivatives.^{12,15}

3-Benzyl- and 3-phenyl-1,2,3-triazole 1-oxide and the 4- and 5-methyl derivatives of the latter can be *C*-silylated (in CHCl₃ or CH₂Cl₂) through their treatment with iodotrimethylsilane (TMSI), trimethylsilyl triflate (TMSTf), or *tert*-butyldimethylsilyl triflate (TBDMSTf) in the presence of EDIP, lithium 2,2,6,6-tetramethylpiperidide (LiTMP), or 1,2,2,6,6-pentamethylpiperidine (PMP).¹⁵ Substitution occurs in position-5 where this is free. An initial *O*-silylation enhances the acidity of the adjacent proton. For more acidic positions *C*-trimethylsilylation can be achieved with TMSI or TMSTf in the presence of EDIP or PMP but positions of low acidity require the use of TMSTf and LiTMP. Introduction of a *tert*-butyldimethylsilyl group requires more forcing conditions, i.e. use of TBDMSTf and LiTMP.

2-Substituted 1,2,3-triazole 1-oxides react with high regio- and monoselectivity since only position-5 is activated towards deprotonation.^{12,15} Thus, 2-methyl- and 2-phenyl-1,2,3-triazole 1-oxide and the 4-methyl derivative of

the latter are *C*-silylated at this position in high yields with TMSTf or TBDMSTf in the presence of EDIP or LiTMP.¹⁵ If position-5 is blocked with a chlorine-atom, then substitution is possible in position-4.

The trialkylsilyl groups in these products are replaceable through addition of various electrophilic reagents in the usual way.

Treatment of 1,2,3-triazolo[5,1-*b*]thiazole with butyllithium gives a mixture of the 3- and 6-lithiated derivatives with the product ratio dependent upon temperature and reaction time. Quenching with most electrophiles gives, as the only isolable compounds, 6-substituted products (in the thiazole ring).¹⁶

B Halogen → lithium exchange reactions

4,5-Dibromo-1(and -2)-methoxymethyl-1,2,3-triazole react with butyllithium (at -80 °C) at position-5 to give lithiated derivatives which react with a variety of electrophiles in moderate to good yields (except for DMF, which gives only about 5% yield of the corresponding aldehyde).¹¹ The chlorine atom in 5-chloro-1*H*-1,4-diphenyl-1,2,3-triazole is exchangeable with butyllithium (see also Section II.A)⁷ (see Table I for products).

C Lateral metallation

5-Methyl-1-phenyl-1*H*-1,2,3-triazole is lithiated preferentially in its methyl group (*cf.* Section II.A - 1,5-diphenyl-1*H*-1,2,3-triazole is lithiated at position-4); reaction of the α -(or laterally)lithiated derivative with iodomethane gives the corresponding ethyl derivative (42% yield).⁸ A number of benzotriazoles substituted at N-1 by a variety of substituted methyl functions are observed also to lithiate at the *N*-alkyl group.^{11,17-21}

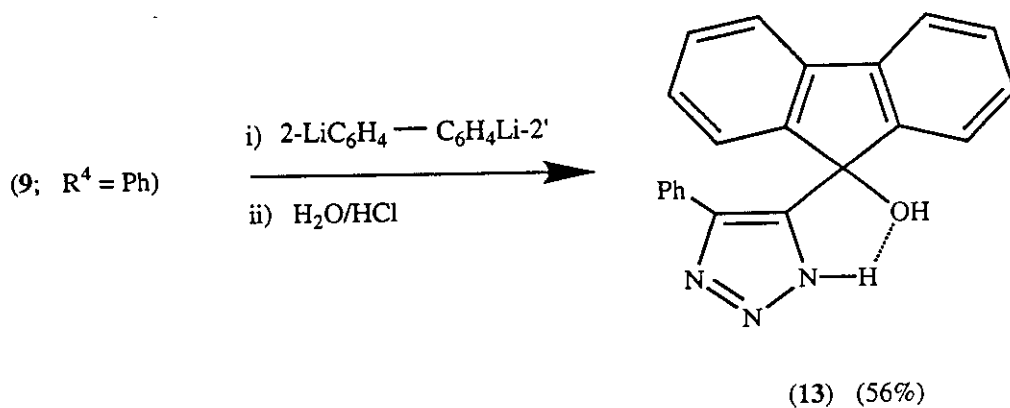
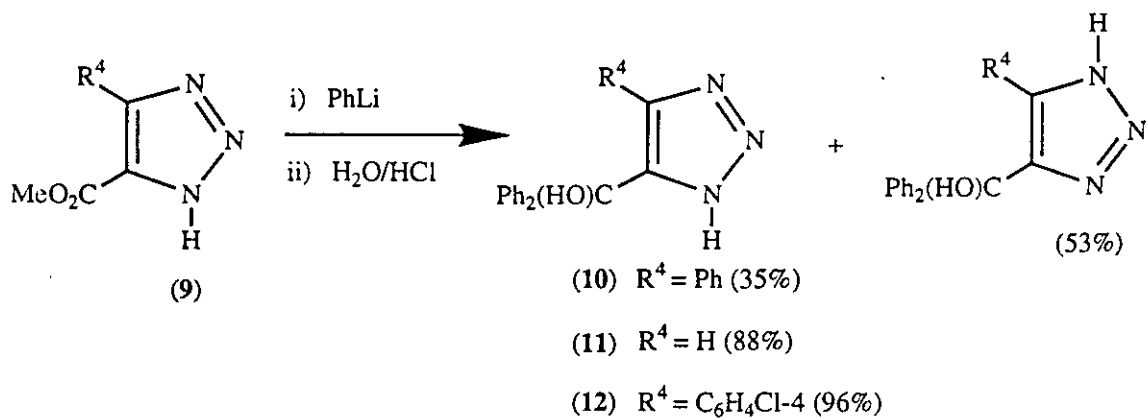
When 1-trimethylsilylmethyl-1*H*-1,2,3-triazoles are treated with tetrabutylammonium fluoride they are desilylated to give anions (Het-CH₂⁻) which react with electrophiles such as water or aldehydes.²²

Noteworthy are the reactions of 4-substituted 1*H*-1,2,3-triazole-5-carboxylates (**9**) with phenyllithium, or the 2,2'-dilithiated derivative of biphenyl, which yield products (**10**)-(**13**) arising from attack at the ester carbonyl group (Scheme 3).²³

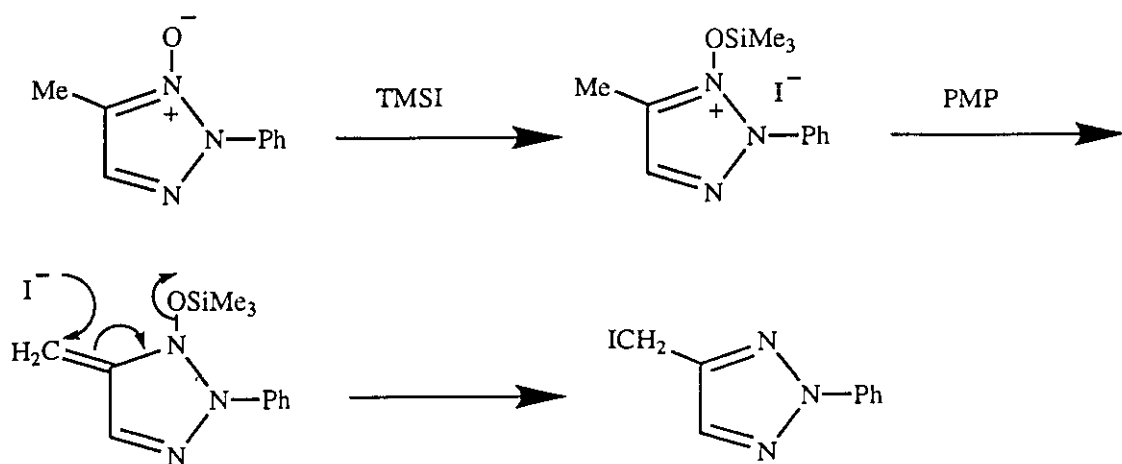
With TMSI in the presence of PMP (see Section II.A for an explanation of these abbreviations) 2-substituted 5-methyl-1,2,3-triazole 1-oxides give the corresponding 4-iodomethyl derivative, as shown in Scheme 4.^{12,24,25}

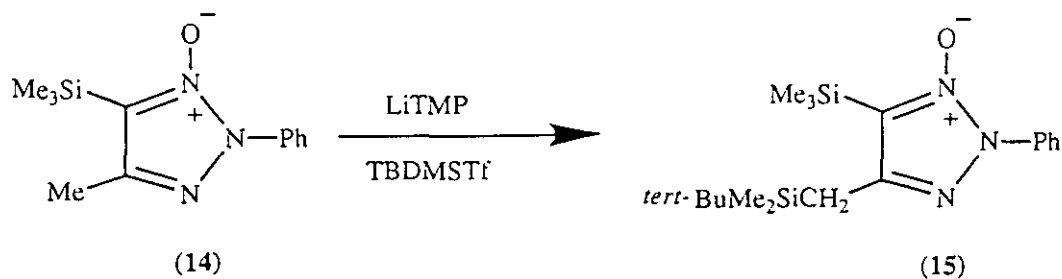
With 4,5-dimethyl-2-phenyl-1,2,3-triazole 1-oxide the 4-iodomethyl compound is the major product.²⁴

A 4-methyl group can be deprotonated in the presence of a stronger base. Thus, treatment of 4-methyl-2-phenyl-5-trimethylsilyl-1,2,3-triazole 1-oxide (**14**) with TBDMSTf in the presence of LiTMP results in the formation of the *C*-silylated product (**15**) (Scheme 5) but in only 14% yield.¹⁵ The 3-phenyl isomer (**16**) reacts similarly, to

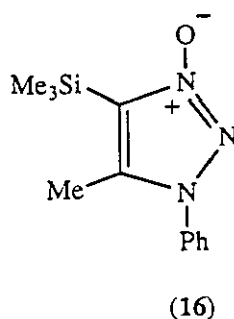


Scheme 3

Scheme 4²⁴



Scheme 5

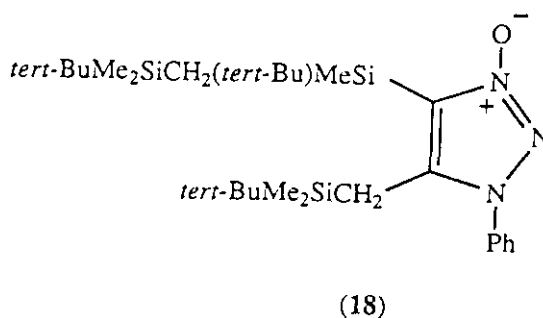
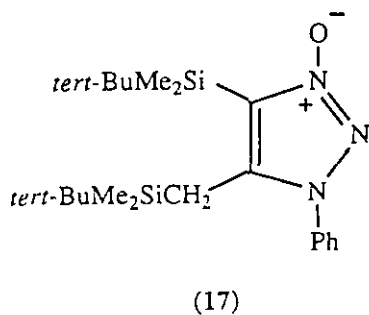


give a 38% yield of an analogous *C*-silylated product. In this case some (13%) *ortho*-substitution occurs also in the phenyl group.¹⁵

Milder conditions (TMSI/PMP) can be employed to *C*-silylate the methyl group in 5-chloro-4-methyl-3-phenyl-1,2,3-triazole 1-oxide (37% yield).¹⁵

Iterative *C*-silylation of 4-methyl-3-phenyl-1,2,3-triazole 1-oxide, first at *C*-5 (Section II.A) then in the *C*-4 methyl group, occurs when it is treated with TBDMSTf in the presence of LiTMP,¹⁵ to give compound (17).

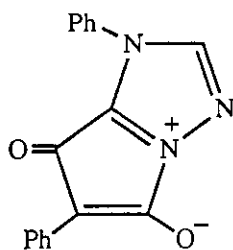
This product reacts further to give a small amount of compound (18).



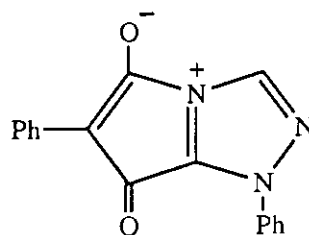
III 1,2,4-TRIAZOLES

A Metallation in the ring

In contrast to the 1,2,3-triazoles, which are quite prone to ring-opening on attempted lithiation (Section II.A), 1-substituted 1*H*-1,2,4-triazoles form much more stable 5-lithiated derivatives. Thus, 1-phenyl-1*H*-1,2,4-triazole is lithiated at position-5 with no evidence of co-lithiation at any other site.²⁶⁻³⁰ About 10-15% of ring-opening was noticed though during the lithiation of 1-benzyl-3-phenyl-1*H*-1,2,4-triazole.³¹ A number of other 1-substituted 1*H*-1,2,4-triazoles have been lithiated at position-5. The resulting products are quite stable at -78 °C and react cleanly with electrophiles (Table II). The variety of *N*-protecting groups used include methyl,³²⁻³⁵ ethyl,³⁵ isopropyl,³⁵ hexyl,³⁵ phenyl,^{28,29} benzyl,^{23,26,31,34-37} pyrid-2-yl,³⁸ trityl,³¹ methoxymethyl^{29,39} and similar ethers,²⁹ tetrahydro-2-furyl (THF in Table II),²⁹ tetrahydropyran-2-yl (THP in Table II),²⁹ SEM,⁴⁰ 1,1-diethoxyethyl,^{6,35} methylthiomethyl,⁴¹ *N,N*-dimethylsulfamoyl,⁴² pyrrolidinomethyl,^{43,44} and 1-azabicyclo-[2.2.2]oct-3-yl.⁴⁵ Ring-cleavage of 4-phenyl-4*H*-1,2,4-triazole is evidently preceded by metallation in positions-3 and -5.⁹ However, 4-phenyl-4*H*-1,2,4-triazole has been converted through lithiation in position-5 [BuLi/diethyl ether (Et₂O)/-78 °C] and condensation of the resulting 5-lithiated derivative with (chlorocarbonyl)phenylketene into the pseudocross-conjugated mesomeric betaine (**19**) (63% yield)³⁰ An analogous compound (**20**) (77%) has been prepared similarly from 1-phenyl-1*H*-1,2,4-triazol-5-yl lithium.³⁰



(19)

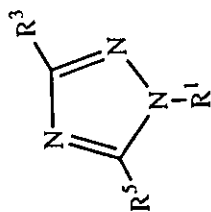


(20)

N-Unsubstituted 1,2,4-triazoles give only the *N*-lithiated species which are unreactive towards electrophiles.⁴⁴ A trityl group may sterically hinder lithiation at position-5. Thus, although benzophenone reacts with 1-trityl-1*H*-1,2,4-triazol-5-yl lithium to give a 61% yield of the carbinol, diethylchlorophosphate fails to form the corresponding 5-phosphate ester.³¹

Katritzky's group have found that use of a pyrrolidinomethyl group to protect *N*-1, despite the fact that it would be expected to stabilize the 5-lithiated derivative through co-ordination, results in formation of a mixture of the 3- and 5-lithiated derivatives (THF/-78 °C).^{43,44} It appears that a subsequent isomerisation produces the less sterically hindered 3-lithiated species. Analogous isomerisations occur in other *N*-substituted azoles including *N*-

Table II
 1*H*-1,2,4-Triazoles Prepared from 1*H*-1,2,4-Triazol-3(or -5)-yllithium Compounds^a

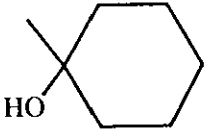


R ¹	R ³	R ⁵	Reagent	Yield (%)	Ref.
Me	H	D	D ₂ O	98	35
Me	H	COMe	MeCONMe ₂	82	35
Me	H	COEt	EtCONMe ₂	91	35
Me	H	COBu- <i>tert</i>	<i>tert</i> -BuCONMe ₂	49	35
Me	H	CO(CH ₂) ₅ Me	Me(CH ₂) ₅ CONMe ₂	91	35
Me	H	COC ₆ H ₁₁ - <i>c</i>	<i>c</i> -C ₆ H ₁₁ CONMe ₂	77.5	35
Me	H	COCH ₂ Ph	PhCH ₂ CONMe ₂	60	35
Me	H	COCH ₂ C ₆ H ₄ Cl-4	4-ClC ₆ H ₄ CH ₂ CONMe ₂	43	35
Me	H	CO(CH ₂) ₂ -2-furyl	2-furyl(CH ₂) ₂ CONMe ₂	84.5	35
Me	H	O(CH ₂) ₂ tetrahydro-2-furyl	tetrahydro-2-furyl-(CH ₂) ₂ CONMe ₂	70	35

Me	H	COPh	PhCONMe ₂	62	35
Me	H	COC ₆ H ₄ Cl-4	4-ClC ₆ H ₄ CONMe ₂	55.5	35
Me	H	COC ₆ H ₃ Cl ₂ -2,4	2,4-Cl ₂ C ₆ H ₃ CONMe ₂	78	35
Me	H	COC ₆ H ₄ OMe-4	4-MeOC ₆ H ₄ CONMe ₂	83	35
Me	H	SPh	Ph ₂ S ₂	98	35
Me	COMe	SPh	MeCONMe ₂	35	35
Me	COEt	SPh	EtCONMe ₂	67	35
Me	COBu- <i>tert</i>	SPh	<i>tert</i> -BuCONMe ₂	55	35
Me	CO(CH ₂) ₅ Me	SPh	Me(CH ₂) ₅ CONMe ₂	55	35
Me	COPh	SPh	PhCONMe ₂	57	35
Me	H	SnMe ₃	ClSnMe ₃	86	32
Me	H	PO(OEt) ₂	ClPO(OEt) ₂	72	34
Me	H	b	ClSnMe ₂ CMe=CEtBEt	78	33
Et	H	COMe	MeCONMe ₂	81	35
<i>iso</i> -Pr	H	COMe	MeCONMe ₂	94	35
hexyl	H	COMe	MeCONMe ₂	98	35
CH ₂ OMe	H	CO ₂ Me	ClCO ₂ Me	ε	29
CH ₂ OMe	H	CH(OH)CF=C(SMe) ₂	(MeS) ₂ C=CFCHO	74	39
(CH ₂) ₂ OMe	H	CO ₂ Me	ClCO ₂ Me	ε	29
CH ₂ O ₂ C ₆ H ₃ ^d	H	CO ₂ Et	ClCO ₂ Et	ε	29

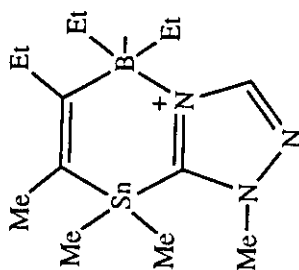
SEM ^g	H	D	D ₂ O	80	40
SEM ^g	H	Me	MeI	35	40
SEM ^g	H	Cl	Cl ₃ CCCl ₃	41	40
SEM ^g	H	CH(OH)Ph	PhCHO	39	40
SEM ^g	H	COPh	PhCOCl	30	40
SEM ^g	H	SPh	Ph ₂ S ₂	57	40
THF ^f	H	CO ₂ Et	ClCO ₂ Et	50	29
THP ^g	H	CO ₂ Me	ClCO ₂ Me	g	29
CH(OEt) ₂	H	COMe	MeCONMe ₂	96 ^h	35
CH(OEt) ₂	H	COPh	PhCONMe ₂	61 ^h	35
CH(OEt) ₂	H	CO(CH ₂) ₅ Me	Me(CH ₂) ₅ CONMe ₂	85 ^h	35
CH(OEt) ₂	H	COC ₆ H ₄ Cl-4	4-ClC ₆ H ₄ CONMe ₂	58 ^h	35
CH(OEt) ₂	H	COC ₆ H ₃ Cl ₂ -2,4	2,4-Cl ₂ C ₆ H ₃ CONMe ₂	48 ^h	35
CH(OEt) ₂	H	COC ₆ H ₄ OMe-4	4-MeOC ₆ H ₄ CONMe ₂	53 ^h	35
C(OEt) ₂ Me	H	C(OH)(C ₆ H ₄ Cl-4) ₂	(4-ClC ₆ H ₄) ₂ CO	72 ^h	6
CH ₂ SMe	H	D	MeOD	59	43, 44
CH ₂ Ph	H	D	MeOD	95	31
CH ₂ Ph	H	Me	MeI	77	31
CH ₂ Ph	H	Cl	Cl ₃ CCCl ₃	80	31

CH ₂ Ph	H	C(OH)Ph ₂	Ph ₂ CO	86	31
CH ₂ Ph	H	COMe	MeCONMe ₂	99	35
CH ₂ Ph	H	CO ₂ Me	ClCO ₂ Me	71	31
CH ₂ Ph	H	PO(OEt) ₂	ClPO(OEt) ₂	70	31, 34
CH ₂ Ph	H	SiMe ₂ Bu- <i>tert</i>	<i>tert</i> -BuMe ₂ SiCl	68	31
CH ₂ Ph	Ph	CH ₂ OH	HCHO	78	26
CH ₂ Ph	Ph	C(OH)Ph ₂	Ph ₂ CO	92	26
CH ₂ Ph	Ph	C(OH)(C ₆ H ₄ OMe-4) ₂	(4-MeOC ₆ H ₄) ₂ CO	94	26
CH ₂ Ph	Ph	C(OH)(C ₆ H ₄ NMe ₂ -4) ₂	(4-Me ₂ NC ₆ H ₄) ₂ CO	91	26
CH ₂ Ph	Ph	SPh	Ph ₂ S ₂	50, 92	31
CH ₂ Ph	Ph	SiMe ₂ Bu- <i>tert</i>	<i>tert</i> -BuMe ₂ SiCl	50	31
CH ₂ Ph	Ph	PO(OEt) ₂	ClPO(OEt) ₂	54	31
CH ₂ NC ₅ H ₁₀ ⁱ	D(H) ⁱ	H(D) ⁱ	D ₂ O	90	43, 44
CH ₂ NC ₅ H ₁₀ ⁱ	H	CH(OH)C ₆ H ₄ Me-4	4-MeC ₆ H ₄ CHO	78	44
CH ₂ NC ₅ H ₁₀ ⁱ	H	CONHBu- <i>tert</i>	<i>tert</i> -BuNCO	86	44
CH ₂ NC ₅ H ₁₀ ⁱ	H	CONHPh	PhNCO	91	44
CH ₂ NC ₅ H ₁₀ ⁱ	H	SPh	Ph ₂ S ₂	57k	44
CH ₂ NC ₅ H ₁₀ ⁱ	H	SCH ₂ Ph	(PhCH ₂) ₂ S ₂	54k	44
CH ₂ NC ₅ H ₁₀ ^l	Me	H	MeI	95	44
CH ₂ NC ₅ H ₁₀ ⁱ	CH(OH)Ph	H	PhCHO	87	44

CH ₂ NC ₅ H ₁₀ ^d		H	cyclohexanone	83	44
CPh ₃	H	D	MeOD	95	31
CPh ₃	H	C(OH)Ph ₂	Ph ₂ CO	61	31
l	H	Br	Br ₂	-	45
Ph	H	Me	MeI	68	28
Ph	H	Et	EtI	88	28
Ph	H	CH ₂ OMe	MeOCH ₂ Cl	78	28
Ph	H	CO ₂ H	CO ₂	95	28
Ph	H	CO ₂ Me	ClCO ₂ Me	b	29
Ph	H	COPh	PhCO ₂ Me	50	28
Ph	H	SMe	Me ₂ S ₂	55	28
Ph	H	SPh	PhSCl	79	28
pyrid-2-yl	H	C(OH)Ph ₂	Ph ₂ CO	70	38
pyrid-2-yl	H	m	CuCl ₂	18	38
SO ₂ NMe ₂	Ph	CHO	DMF	-	42
SO ₂ NMe ₂	C ₆ H ₄ Cl-3	CN	PhOCN	75	46
SO ₂ NMe ₂	C ₆ H ₃ Me ₂ -2,4	CN	TosCN	-	42
SO ₂ NMe ₂	C ₆ H ₄ OMe-4	CN	TosCN	-	42

^a See also text for the synthesis of compounds (19) and (20).³⁰ ^b Product has the formula shown below. ^c Compounds converted directly into amides in yields of 5-50%. ^d 1,3-Benzodioxol-5-yl. ^e SEM \equiv CH₂O(CH₂)₂SiMe₃. ^f THF \equiv tetrahydro-2-furyl. ^g THP \equiv tetrahydropyran-2-yl.

^h Yield given for deprotected product (acid hydrolysis). ⁱ CH₂NC₅H₁₀ \equiv pyrrolidino-methyl. ^j 1:1 Ratio. ^k Yield of deprotected (NH) products (see Discussion). ^l 1-Azabicyclo[2.2.2]oct-3-yl. ^m 1-(Pyrid-2-yl)-1,2,4-tetrazol-5-yl.



aminoalkylazoles⁴⁷⁻⁴⁹ and *N*-trialkylstannylazoles.⁵⁰ 1,2,4-Triazoles protected by an aminal group at *N*-1 give *N*-unprotected products with diphenyl and dibenzyl sulfides. Nucleophilic cleavage of the aminal group, to form stable thioaminals, explains this behaviour.⁴⁴

Various 1-substituted 1*H*-1,2,4-triazoles have been acylated *via* lithiation at position-5 (BuLi/THF/0 °C) followed by addition of a *N,N*-dimethyl-substituted amide, e.g. *N,N*-dimethylacetamide (Table II).³⁵

Acylation of 1-methyl-1*H*-1,2,4-triazole at position-3 was achieved by the sequence: lithiation at position-5 (BuLi/THF/0 °C), addition of diphenyl disulfide, lithiation of the 1-methyl-5-phenylthio-1*H*-1,2,4-triazole produced with LiTMP (THF/-80 → -100 °C) in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), followed by addition of a *N,N*-dimethyl-substituted amide (yields: 35-67%).³⁵ The phenylthio group was cleaved reductively from the products.

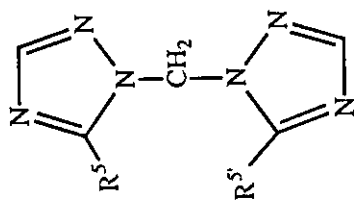
With one mol equiv. of butyllithium (THF/0 °C) *bis*(1,2,4-triazol-1-yl)methane lithiates predominantly in position-5 but a significant amount of the 5,5'-dilithiated derivative is produced also at this temperature.⁵¹

Varying mixtures of the mono- or disubstituted product are isolated following addition of one or more equivalents of the quenching reagent (Table III). Use of LDA or an increased temperature produces similar results and it can be concluded that ring metallation is both kinetically and thermodynamically favoured.

B Lateral metallation

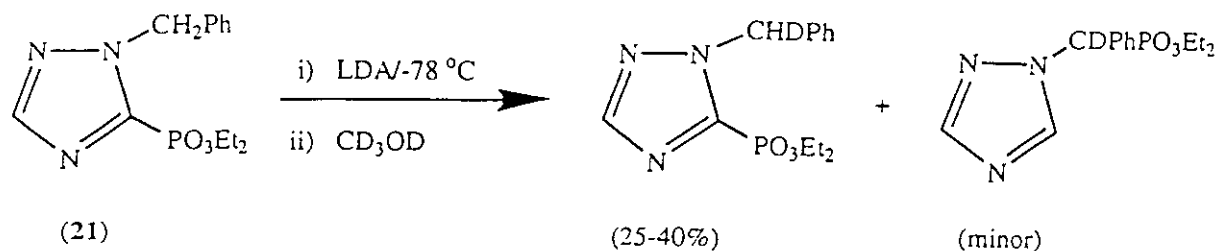
Although 5-lithiation of 1-substituted 1*H*-1,2,4-triazoles has been shown to be kinetically and thermodynamically favoured,^{31,37} with 1-benzyl-1*H*-1,2,4-triazoles there is usually a small amount of product present arising from α -(or lateral)metallation in the benzyl group. With certain electrophilic quenching reagents the isolated products are formed exclusively *via* the laterally lithiated species, e.g. 1-benzyl-1*H*-1,2,4-triazole with benzyl halides.³⁶ When position-5 is blocked, as in 5-phosphate esters of 1-benzyl-1*H*-1,2,4-triazole, lateral metallation becomes the favoured pathway.³⁴ The driving force for the novel phosphate migration observed when the 1-benzyl-1*H*-1,2,4-triazole-5-phosphate ester (**21**) is treated with LDA (THF/-78 °C) (Scheme 6) is doubtless the formation of the more stable lithiated species. This anion-mediated phosphonate migration process predominates at 0 °C. Identical results were obtained with the corresponding 1-methyl analogues.³⁴ The selective lithiation of the 1-alkyl groups may be a consequence of a "directing effect" of the adjacent phosphonate group [*cf.* ref. 52; phosphates are known to be excellent activators for lithiation]. To gain further insight the silyltriazoles (**22**) were lithiated. While use of LDA gave only about 5% deuterium incorporation into the *N*-substituent after quenching, *sec*-butyllithium gave greater than 90% deuteration in the *N*-substituent (methyl or

Table III
Metallation of Bis(1,2,4-Triazol-1-yl)methane⁵¹



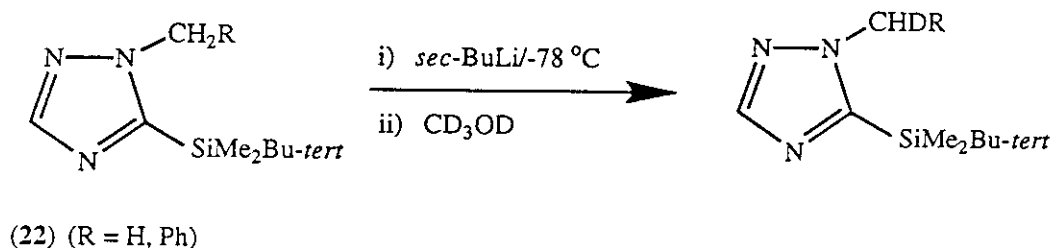
Electrophile (E)	SM : BuLi : E	Product Composition	
		Monosubstituted (%) ^a	Disubstituted (%) ^a
MeI	1 : 1 : 1	56	25
MeI	1 : 2.1 : 2.1	11	77
Me ₂ S ₂	1 : 1 : 1	67	14
Me ₂ S ₂	1 : 2.4 : 2.4	20	79
Me ₃ SiCl	1 : 1 : 1	80	0
Me ₃ SiCl	1 : 2.1 : 2.1	23	77
(HCHO) _{II} ^b	1 : 1 : 1	39	15
(HCHO) _{II} ^b	1 : 2.1 : 2.1	33	67

^a Determined by ¹H NMR spectroscopy. ^b Paraformaldehyde.



Scheme 6

or benzyl) (Scheme 7). 3-Deuteriation was not observed. These results suggest that phosphonate increases the acidity of the α -protons, but the increased acidity is not responsible for the selectivity of lithiation because α -(or lateral)metallation occurred even in the absence of the directing groups.^{31,34}

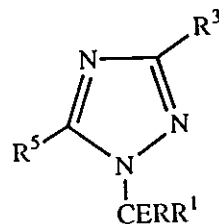


Scheme 7

In 5-methyl-1-phenyl-1*H*-1,2,4-triazole the methyl group is lithiated by butyllithium in hexane²⁸ as are the methylene groups in 5-ethyl-, 5-methylthio-, and 5-methoxymethyl-1*H*-1,2,4-triazole and 1-phenyl-1*H*-1,2,4-triazole-5-acetic acid.^{9,28} These reactions may be contrasted with those of 5-methyl- and 5-methylthio-1-phenylpyrazoles⁵³ which are *ortho*-lithiated. Apparently the inductive effect of *N*-4 in 1,2,4-triazoles is significant in directing metallation either to position-5 or to a methylene group at that site.²⁸ Tables IV and V list some examples.

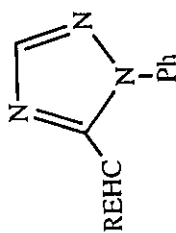
With 1-*bis*(methylthio)methyl-1*H*-1,2,4-triazole butyllithium in dimethoxyethane (DME) gives products of α -(or lateral)metallation, presumably because the resulting anion is doubly stabilized.⁴¹ The 1-methylthiomethyl analogue is conventionally 5-lithiated. When treated in turn with butyllithium (hexane/-60 °C) and benzyl halides 1-benzyl-1*H*-1,2,4-triazoles give products only of lateral metallation.³⁶ That metallation procedures are not the only way of generating such methylene anions was demonstrated by their generation in fluoride induced desilylation of 1-trimethylsilylmethyl-1*H*-1,2,4-triazole^{54,55} and 1-[phenylthio(trimethylsilyl)methyl]-, 1-[methyl-

Table IV

1*H*-1,2,4-Triazoles Prepared by Lateral Metallation in a Substituent at *N*-1

R	R ¹	R ³	R ⁵	E	Reagent	Yield (%)	Ref.
H	H	SiMe ₂ Bu- <i>tert</i>	H	D	CD ₃ OD	> 90	34
H	Ph	H	H	CH ₂ Ph	PhCH ₂ Cl	65	36
H	Ph	H	H	CH ₂ C ₆ H ₄ Me-4	4-MeC ₆ H ₄ CH ₂ Cl	61	36
H	Ph	H	H	CH ₂ C ₆ H ₄ Cl-4	4-ClC ₆ H ₄ CH ₂ Cl	49	36
H	Ph	SiMe ₂ Bu- <i>tert</i>	H	D	CD ₃ OD	> 90	34
H	Ph	H	PO(OEt) ₂	D	CD ₃ OD	25-40	34
SMe	SMe	H	H	C(OH)Ph ₂	Ph ₂ CO	65	41
SMe	SMe	H	H	C(OH)PhCOPh	(PhCO) ₂	63	41

Table V

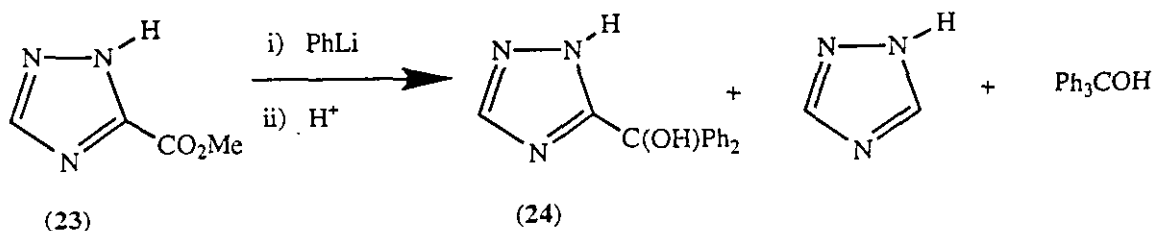
1-Phenyl-1*H*-1,2,4-triazoles Prepared by Lateral Metallation in a Substituent at Position-5^{28 a}

R	E	Reagent	Yield (%)
H	Me	MeI	75
H	CO ₂ H	CO ₂	70
Me	Me	MeI	50
CO ₂ H	Me	MeI	62
OMe	CO ₂ H	CO ₂	78

^a Reaction of 5-methylthio-1-phenyl-1*H*-1,2,4-triazole with BuLi, then MeI, gave the 5-ethylthio derivative (70%).

thio(trimethylsilyl)methyl]-, and 1-[methoxy(trimethylsilyl)-methyl]-1*H*-1,2,4-triazole.⁴¹ The anion derived from 1-trimethylsilylmethyl-1*H*-1,2,4-triazole in this way is basic enough to deprotonate position-5 of the starting material, thus leading to mixtures of products.^{41,54}

Methyl 1*H*-1,2,4-triazole-5-carboxylate (**23**) forms the carbinol (**24**) when treated with phenyllithium; retro-aldol reactions account for the other products (Scheme 8).²³ Phenyllithium reacts with 1-benzyl-3-phenyl-1*H*-1,2,4-triazole at position-5.²³



Scheme 8

With one mol equiv. of butyllithium 3,5-dimethyl-4-phenyl-1*H*-1,2,4-triazole gives products of lateral metallation, providing access to the 3-ethyl (33% yield) and some 3-(2'-hydroxyethyl) products [with acetone (26%) or 1-tetralone (51%)].⁵⁶

IV TETRAZOLES

A Metallation in the ring and halogen \rightarrow metal exchange reactions

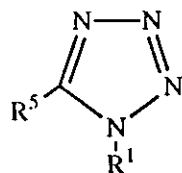
Provided that position-5 is free metallation takes place there preferentially^{45,57-62} either with a 1- (Table VI) or 2-substituted tetrazole (Table VII), and halogen \rightarrow metal exchange occurs when magnesium or butyllithium reacts with 5-chloro-1-phenyltetrazole.⁶³ Tetrazolium salts form anions at C-5 very readily with bases such as triethylamine^{64,65} and even more readily with butyllithium.⁶¹

The species (**25**), which form when butyllithium or the more reactive *tert*-butyllithium react with 2,3-diaryltetrazolium tetraphenylborates, can be regarded as carbenoids, quite stable at -100°C .⁶¹ Above -60°C , however, they ring-open to form (2*Z*)-1-cyano-2,3-diaryltriaz-2-en-2-ium-1-idenes (**26**) (Scheme 9) but they can be trapped at -90°C by deuteriosulfuric acid, 4-methoxybenzenediazonium tetrafluoroborate (56% yield), or tosyl azide (43%) (but not with nitrous oxide, palladium dichloride, or oxidising electrophiles like chlorine and bromine).⁶¹ 1,4-Disubstituted tetrazolium salts cleave similarly to give carbodiimides.⁶⁵ 1-Methyltetrazol-5-yl lithium would not react with ferric chloride.⁵⁸

The 5-lithiated derivative of 1-methyltetrazole also fragments below -50°C to form nitrogen and lithium

Table VI

1,5-Disubstituted Tetrazoles Prepared from 1-Substituted Tetrazol-5-yllithium Compounds



R ¹	R ⁵	Reagent	Yield (%)	Ref
Me	Br	Br ₂	41	59
Me	Br	BrCN	55	59
Me	I	I ₂	36	59
Me	CH(OH)Ph	PhCHO	63	59
Me	C(OH)MePh	PhCOMe	67	59
Me	C(OH)Ph ₂	Ph ₂ CO	75	59
Me	COPh	PhCO ₂ Me	41	59
Me	SH	S ₈	67	59
Me	SiMe ₃	ClSiMe ₃	43	62
Me	a	MeCOCl	35	59
Me	a	PhCOCl	68	59

Me	b	Ni(PEt ₃) ₂ Cl ₂	80	57, 58
cyclohexyl	b	Ni(PEt ₃) ₂ Cl ₂	-	58
CMc(OEt) ₂	C(OH)(C ₆ H ₄ Cl-4) ₂	(4-ClC ₆ H ₄) ₂ CO	86 ^c	6

^a Products were ^b Bis(1-methyltetrazol-5-yl)nickel(II) products formed. ^c After removal of the 1,1-diethoxyethyl protecting group.

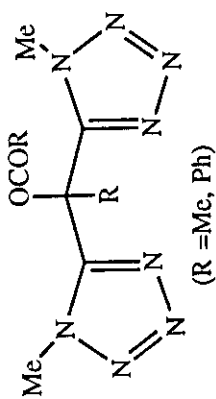
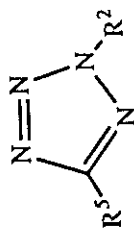
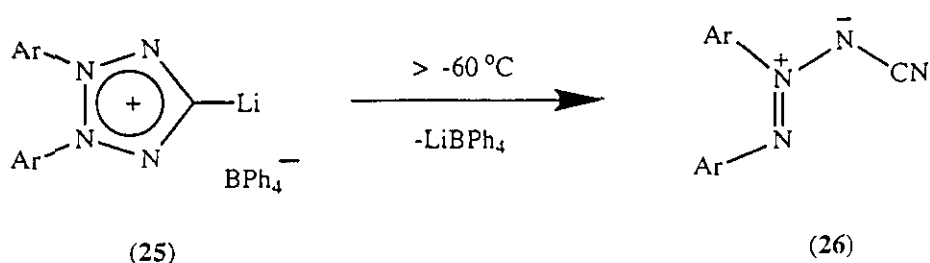


Table VII
2,5-Disubstituted Tetrazoles Prepared from 2-Substituted Tetrazol-5-yllithium Compounds⁴⁵



R ²	R ⁵	Reagent	Yield (%)
	Cl	Cl ₂	65
	Br	Br ₂	67
	I	I ₂	42
	Cl	Cl ₂	37
	Br	Br ₂	6
	I	I ₂	37
	CHO	PhNMeCHO	5
	C(OH)Ph ₂	Ph ₂ CO	27
	Cl	Cl ₂	50
	Br	Br ₂	56



Scheme 9

methylcyanamide, but is stable enough below $-60\text{ }^{\circ}\text{C}$ to react with a variety of electrophiles (Table VI).⁵⁹ 1-Phenyl-1*H*-1,2,3-triazol-5-yl lithium is a little less stable, decomposing at temperatures as high as $-60\text{ }^{\circ}\text{C}$ to $-70\text{ }^{\circ}\text{C}$, to give lithium phenylcyanamide.⁵⁹ In general tetrazol-5-yl lithium compounds are more susceptible to fragmentation than their 1,2,3-triazolyl lithium analogues.^{59,63}

Noteworthy is the fact that 1-phenyltetrazole is mercurated by mercuric acetate and the resulting 5-mercuriacetate can be used to introduce halogen (Cl, Br, I) at this position.⁶⁶

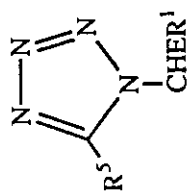
B Lateral metallation

When position-5 of tetrazole is blocked anions can be formed by lateral metallation of alkyl or aryl substituents. Thus, 1- and 2-alkyl-5-phenyltetrazoles react with *tert*-butyllithium (THF/ $-78\text{ }^{\circ}\text{C}$) to give "dipole stabilized" α -lithioalkyl derivatives which react readily with a wide range of electrophiles (Tables VIII and IX).^{60,62,67} No lithiation occurs in the *ortho*-position of the 5-phenyl substituent. These lithiomethyl derivatives are stable at $-23\text{ }^{\circ}\text{C}$, and even briefly at $0\text{ }^{\circ}\text{C}$.⁶²

Ketones capable of enolisation will not react as quenching reagents for these anions. 2-Alkyltetrazoles with groups other than phenyl at position-5 enter the process less readily, although satisfactory yields are achieved with phenylthio, aminomethyl, and trimethylsilyl groups at position-5.⁶² It has been suggested that 2-alkyltetrazoles are more acidic than their 1-isomers. Hence, the lithioalkyl derivatives are less stabilized and more nucleophilic. The presence of extra pyridine-like N-atoms adjacent to the pyrrole-type N-atom greatly facilitates deprotonation of an *N*-alkyl group (1-alkylpyrazoles are more readily laterally metallated than 1-alkylimidazoles).⁶² A number of 1,5-dialkyl- and 5-benzyl-1-methyl- and 5-methyl-1-phenyl-tetrazoles are converted also into anions at the 5-alkyl side chain by phenyllithium^{68,69} or -sodium⁶⁸ (Table X).

That ring-lithiation is preferred can be deduced from the reaction of 1-methyltetrazole (**27**) with butyllithium. Quenching the product with chlorotrimethylsilane initially gives the 5-trimethylsilyl derivative (**28**) (Scheme

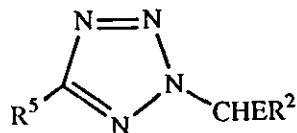
Table VIII
1,5-Disubstituted Tetrazoles Prepared by Lateral Lithiation in a Substituent at N-1



R ¹	R ⁵	E	Reagent	Yield (%)	Ref.
H	Ph	D	D ₂ O	96	60, 62
H	Ph	Me	Me ₂ SO ₄	90	60, 62
H	Ph	C(OH)Ar ₂	Ar ₂ CO	84 ^a	60, 62
H	Ph	SiMe ₃	ClSiMe ₃	96	60, 62
H	SH	CO ₂ H	CO ₂	-	70
Ar	Ph	CH(OH)Ar	ArCHO	87 ^a	60, 62
Ar	Ph	C(OH)Ar ₂	Ar ₂ CO	95 ^a	60, 62
Ar	Ph	COAr ₂	PhCN	80 ^a	60, 62

^a Ar = C₆H₄Me-4

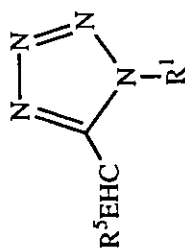
Table IX

2,5-Disubstituted Tetrazoles Prepared by Lateral Lithiation in a Substituent at N-2⁶⁰, ⁶²

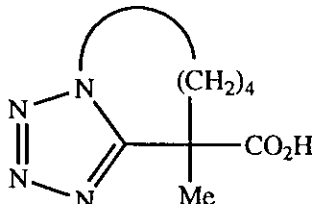
R ²	R ⁵	E	Reagent	Yield (%)
H	Ph	CH ₂ OH	HCHO	33
H	Ph	CH(OH)Et	EtCHO	85
H	Ph	CH(OH)C ₆ H ₄ OMe-4	4-MeOC ₆ H ₄ CHO	77
H	Ph	Me ₃ SiCl	ClSiMe ₃	70
H	SPh	CH(OH)C ₆ H ₄ OMe-4	4-MeOC ₆ H ₄ CHO	57
H	CH ₂ NH ₂	CH(OH)C ₆ H ₄ OMe-4	4-MeOC ₆ H ₄ CHO	37
Me	Ph	CO ₂ H	CO ₂	53
Me	Ph	CH(OH)Ph	PhCHO	98 ^a
Et	SiMe ₃	SiMe ₃	ClSiMe ₃	51
SiMe ₃	Ph	=CHEt	EtCHO	68
SiMe ₃	Ph	=CHBu- <i>tert</i>	<i>tert</i> -BuCHO	88

^a See also ref. 67

Table X
1,5-Disubstituted Tetrazoles Prepared by Lateral Lithiation of 5-Substituted Tetrazoles

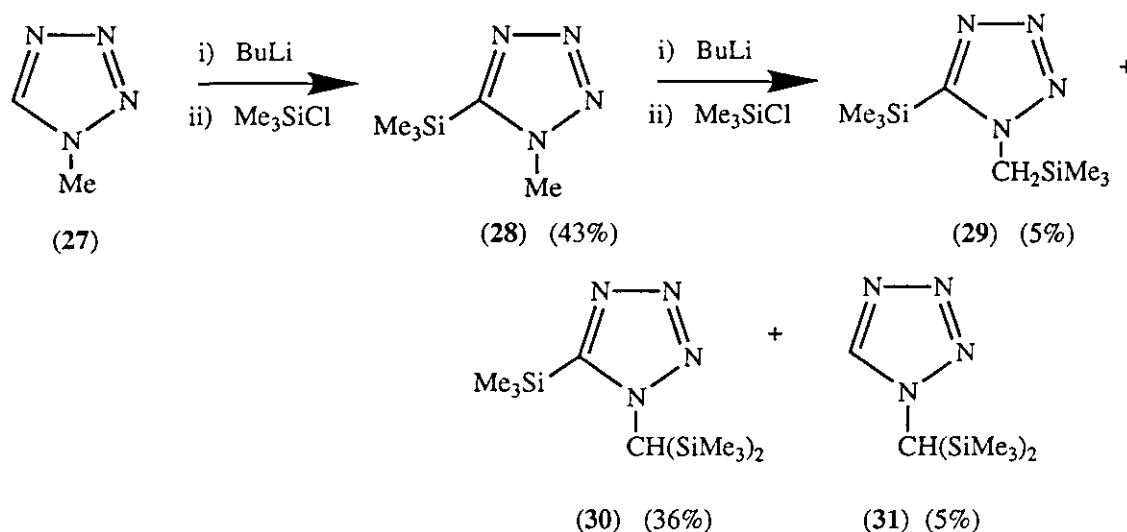


R ¹	R ⁵	E	Reagent	Yield (%)	Ref.
Me	Ph	CO ₂ H	CO ₂	62	68
Me	Ph	(CH ₂) ₂ NMe ₂	Me ₂ N(CH ₂) ₂ Cl	34	69
Me	Ph	(CH ₂) ₂ NEt ₂	Et ₂ N(CH ₂) ₂ Cl	48	69
Me	Ph	(CH ₂) ₂ NC ₅ H ₁₀ ^a	C ₅ H ₁₀ N(CH ₂) ₂ Cl ^a	29	69
Me	Ph	CH(OH)CMe ₂ CH ₂ NEt ₂	Et ₂ NCH ₂ CMe ₂ CHO	41	69
Me	Ph	CH(OH)CMe ₂ CH ₂ NC ₅ H ₁₀ ^a	C ₅ H ₁₀ NCH ₂ CMe ₂ CHO ^a	53	69
Me	Ph	C(OH)Ph(CH ₂) ₂ NMe ₂	Me ₂ N(CH ₂) ₂ COPh	23	69
Ph	H	CO ₂ H	CO ₂	66	68
Ph	H	COMe	MeCN	29	69
Ph	H	CH(OH)CMe ₂ CH ₂ NC ₅ H ₁₀ ^a	C ₅ H ₁₀ NCH ₂ CMe ₂ CHO ^a	26	69

Ph	H	C(OH)Ph(CH ₂) ₂ NMe ₂	Me ₂ N(CH ₂) ₂ COPh	17	69
Ph	H	C(OH)Me(CH ₂) ₂ NC ₅ H ₁₀ ^a	C ₅ H ₁₀ N(CH ₂) ₂ COMe ^a	27	69
naphth-1-yl	H	CO ₂ H	CO ₂	low	68
cyclohexyl	^b	CO ₂ H	CO ₂	64	68
R ¹ → R ⁵					
-(CH ₂) ₄ -		CO ₂ H	CO ₂	57	68
-(CH ₂) ₃ CHMe-		CO ₂ H	CO ₂	57	68
-(CH ₂) ₂ CH(Me)CH ₂ -		CO ₂ H	CO ₂	51	68
-(CH ₂) ₂ CH(Bu- <i>tert</i>)CH ₂ -		CO ₂ H	CO ₂	75	68
		CO ₂ H	CO ₂	36	68

^a NC₅H₁₀ is a piperidino substituent. ^b The 5-substituent in the substrate was isopropyl; the product in this case was α -(1-cyclohexyltetrazol-5-yl)isobutyric acid.

10).⁶² This is followed by lateral metallation. The product mixture isolated, compounds (29)-(31) (Scheme 10), infers that transmetalation occurs since the methylene group in compound (29) is more acidic than the methyl group in compound (28).



Scheme 10

5-Phenyltetrazole reacts with *sec*-butyllithium in the *ortho*-position of the substituent whilst 5-(*o*-tolyl)tetrazole is laterally metallated in the methyl group (Table XI).⁷¹ Whilst reaction of the *ortho*-lithiated derivative derived from 5-phenyltetrazole is straightforward with iodomethane, its reaction with 1-iodopentane or 1-chloro-3-iodopropane failed. Benzyl bromide gives 5-(*o*-bromophenyl)tetrazole and bibenzyl. The dianion derived from 5-(*o*-tolyl)-tetrazole reacts with 1-iodopentane and benzyl bromide in addition to iodomethane.⁷¹

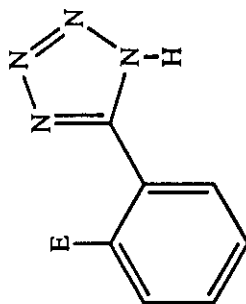
V OXADIAZOLES

A 1,2,3-Oxadiazoles (Sydnones)

Lithiation of 3-phenylsydnone (32) (BuLi/Et₂O/-20 °C) followed by carbonation gives the 4-carboxylic acid (35) (Scheme 11).⁷² The same product is formed with equal success from 4-bromo-3-phenylsydnone (33) *via* bromine → lithium exchange (BuLi/Et₂O/-50 °C) and treatment of the 4-lithiated intermediate with carbon dioxide.⁷² Other examples of sydnone 4-lithiation have been reported,⁷³ while the bromine → lithium exchange route has been used to prepare a number of 4-carboxylic acids⁷⁴⁻⁷⁶(Table XII).

3-Benzylaminosydnone reacts at the exocyclic NH functionality with one mol equiv. of butyllithium (THF/< -20 °C) but two mol equiv. lithiate position-4 as well, to give a red dianionic species which reacts with a variety of

Table XI
Tetrazoles Prepared by Lateral Metallation of 5-Aryltetrazoles⁷¹

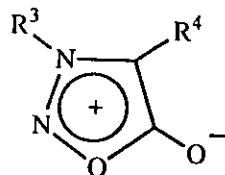


E	Reagent	Yield (%)
Me	MeI ^a	78
CH(OH)Me	MeCHO	95
CH(OH)CH=CH ₂	CH ₂ =CHCHO	51
Et	MeI	71
(CH ₂) ₅ Me	Me(CH ₂) ₄ I	92
(CH ₂) ₂ Ph	PhCH ₂ Br	73

^a No reaction with alkyl halides more complex than MeI.

Table XII

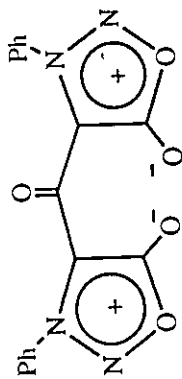
4-Substituted 1,2,3-Oxadiazoles Prepared from 1,2,3-Oxadiazol-4-yllithium Compounds

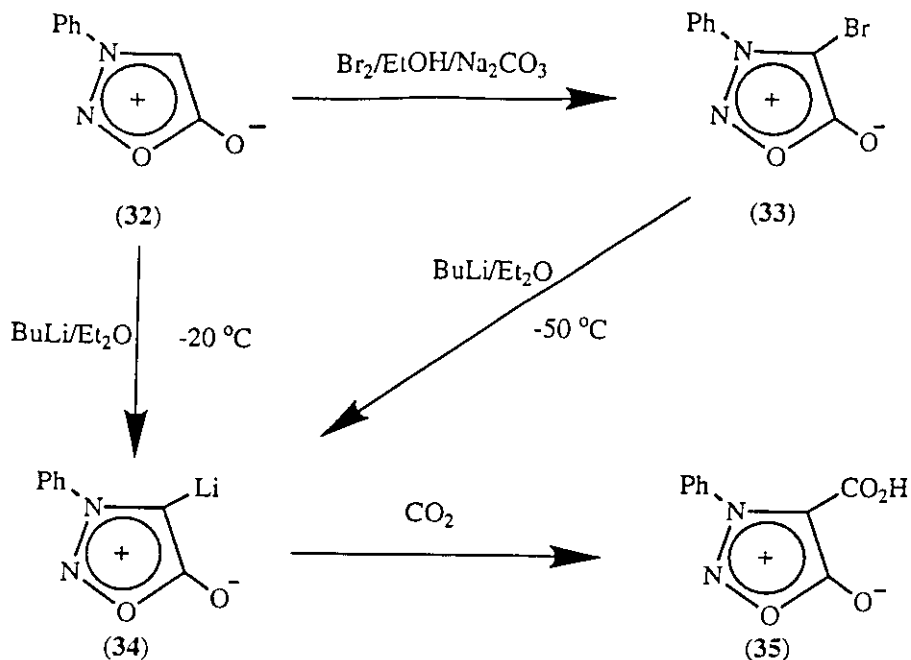


R ³	R ⁴	Reagent	Yield (%)	Ref
<i>iso</i> -Pr	CO ₂ H	CO ₂	60	75, 76
<i>sec</i> -Bu	CO ₂ H	CO ₂	75, 57	75, 76
Ph	CO ₂ H	CO ₂	61, 62	72, 74, 76
Ph	^a	COCl ₂	^a	73
C ₆ H ₄ Me-2	CO ₂ H	CO ₂	78	76
C ₆ H ₄ Me-4	CO ₂ H	CO ₂	40	76
C ₆ H ₄ Cl-2	CO ₂ H	CO ₂	65	76
C ₆ H ₄ Cl-4	CO ₂ H	CO ₂	50	76
C ₆ H ₄ OMe-2	CO ₂ H	CO ₂	39	76
C ₆ H ₄ OMe-4	CO ₂ H	CO ₂	47	76
NHCH ₂ Ph	Me ^b	MeI	85	77

NHCH ₂ Ph	CHO	DMF	90	77
NHCH ₂ Ph	COPh	PhCONMe ₂	76	77

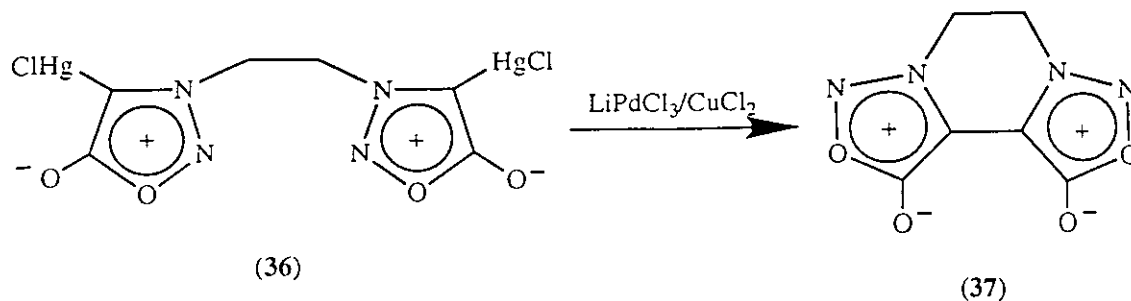
a Products were Ph- and small amounts of the corresponding carbinol. b Two mol equiv. MeI gave the N,4-dimethyl derivative (75% yield).





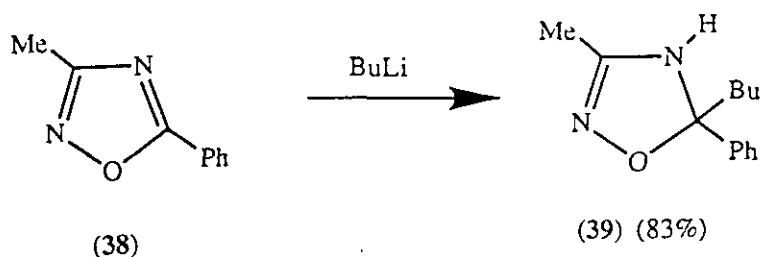
electrophiles.⁷⁷ Selective C-acylation has been observed with *N,N*-dimethylbenzamide and with DMF, but acyl halides give only decomposition products. One mol equiv. of iodomethane yields the 4-methyl product; two mol equiv. give the *N*,4-dimethyl derivative (Table XII).

4-Lithiated 3-phenylsydnone (**34**) reacts with cuprous iodide, to give a copper derivative which can be employed to obtain 4-acyl- or 4-arylsydnes.⁷⁸ Palladium(0) catalysed cross coupling of 4-cupro-3-phenylsydnone with aryl iodides and vinyl bromides similarly introduced aryl and vinyl groups at the 4-position.⁷⁹ A Grignard reagent has been obtained from 4-bromo-3-phenylsydnone (**33**).^{72,80,81,82} The bismercurated derivative **36** is coupled in the presence of $\text{LiPdCl}_3/\text{CuCl}_2$, to give the tricyclic product (**37**) (Scheme 12).⁸¹

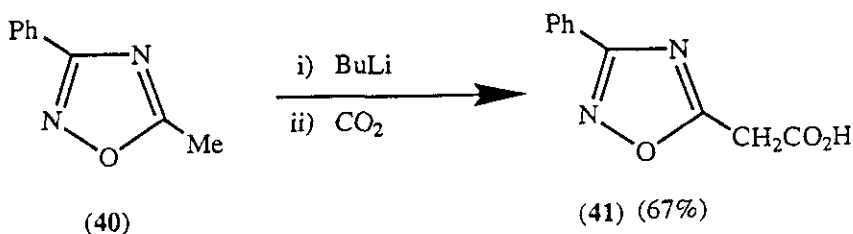


B 1,2,4-Oxadiazoles

3-Methyl-5-phenyl-1,2,4-oxadiazole (**38**) reacts with butyllithium to give the product (**39**) of addition across the 4,5-azomethine double bond (Scheme 13).⁸³ In contrast, its isomer (**40**) is laterally metallated in its



Scheme 13



Scheme 14

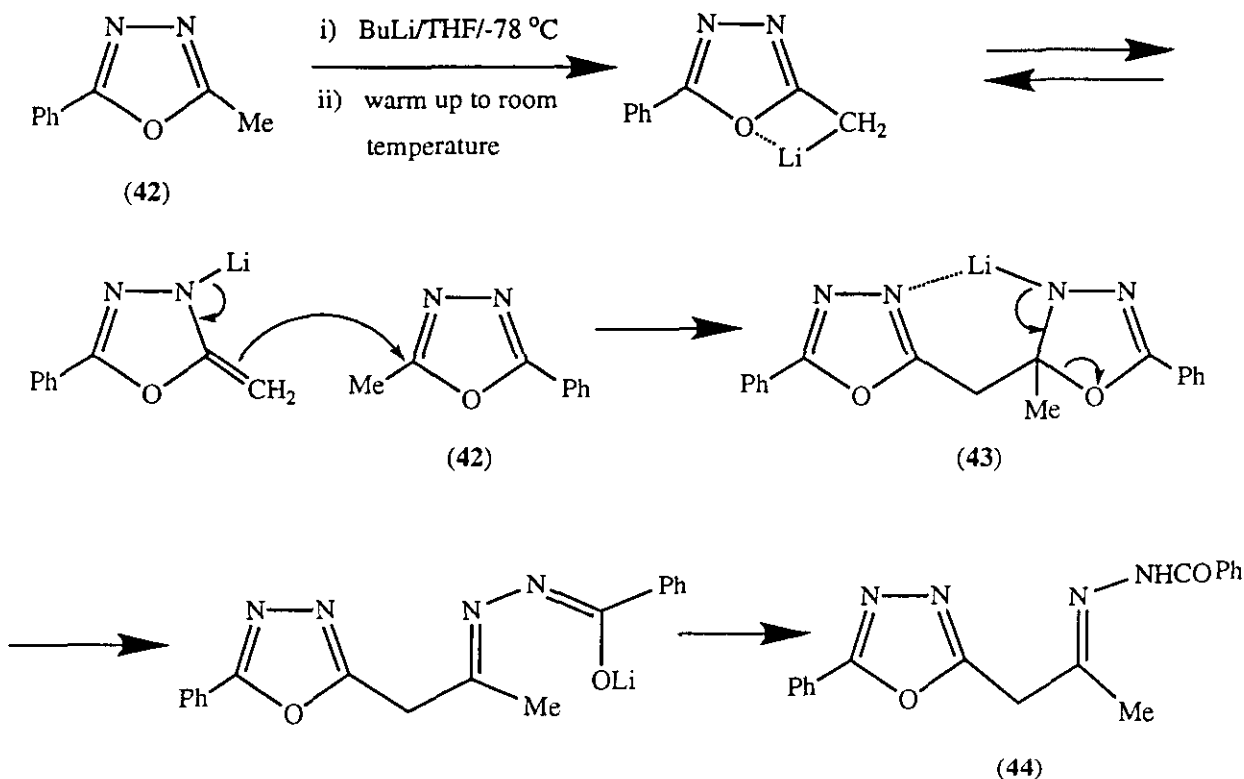
methyl group; carbonation of the intermediate yields acid (41) (Scheme 14).⁸³ A methyl group at position-5 is much more acidic than one at position-3. Thus, 3,5-dimethyl-1,2,4-oxadiazole reacts with butyllithium (*Et*₂O/-60 °C) followed by addition of chlorotrimethylsilane, to give the 5-trimethylsilyl derivative (60% yield).⁸⁴ With butyllithium in THF a lower yield of this product is obtained together with a little of the 3,5-bis(trimethylsilyl) product. These results were rationalised in terms of butyllithium being a tetramer in ether and a dimer in THF. In THF the reagent is more basic and less selective. There may also be some co-ordination of the lithium cation at all three heteroatoms, leading to lithiation at both the 3- and 5-methyl groups ("ortho effect").⁸⁴ 3-Methyl- and 3-phenyl-1,2,4-oxadiazole are mercuroated with mercuric chloride at position-5 and the resulting mercuroated derivatives can be used to introduce halogen (Cl, 10-15% yield; Br, 50%; and I, 90%) at this position.⁸⁵

C 1,2,5-Oxadiazoles

3,4-Dimethyl-1,2,5-oxadiazole has been laterally metallated in one of its methyl groups as a route to the monoacetic acid derivative (93% yield) *via* carbonation of the lithiated intermediate.^{9,83}

D 1,3,4-Oxadiazoles

In common with 2-methyl-thiazoles¹ and -1,3,4-thiadiazoles (Section VI.D), lithiation of 2-methyl-5-phenyl-1,3,4-oxadiazole (**42**) results in dimer (**43**) formation which is followed by a ring opening process (Scheme 15);

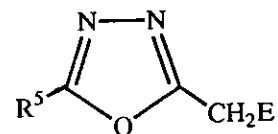


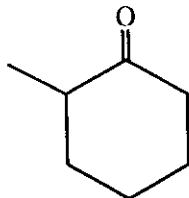
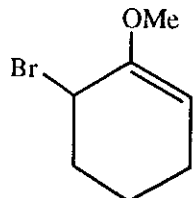
Scheme 15

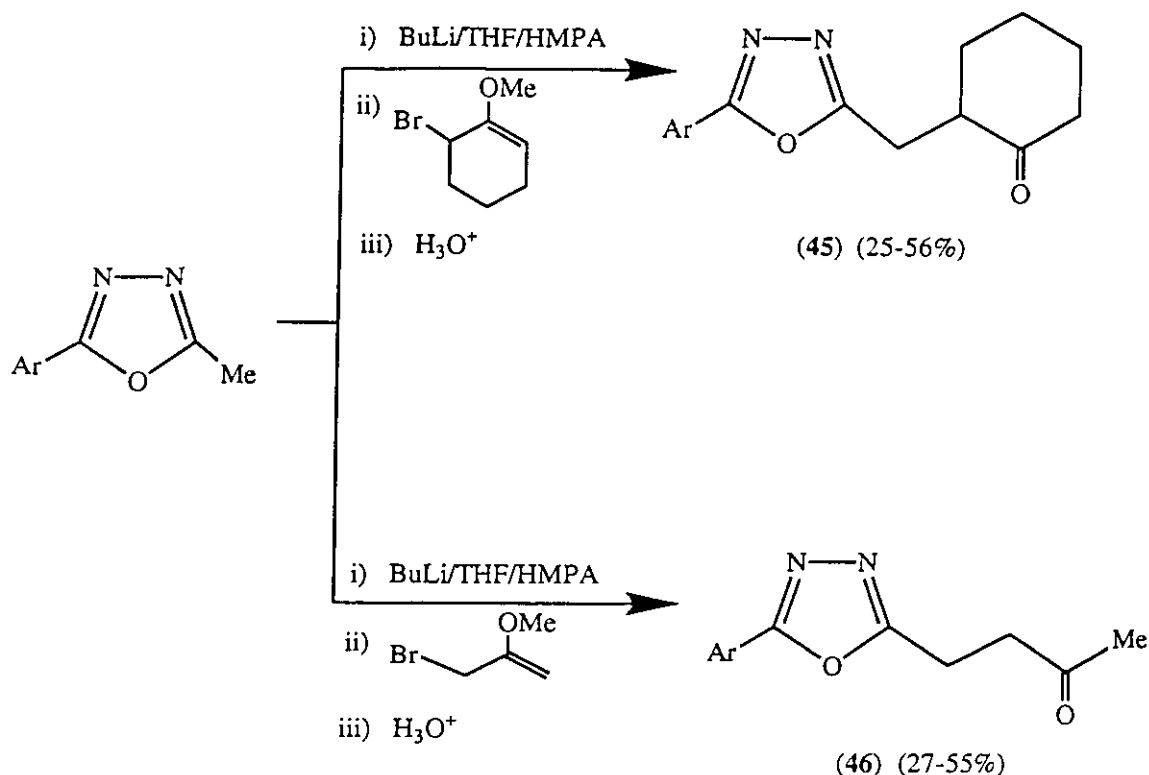
addition of water allows compound (**44**) to be isolated.^{86,87} 2,5-Dimethyl-1,3,4-oxadiazole also appears to be quite prone to ring-cleavage in the presence of butyllithium.^{9,83} The mechanism of this process has been discussed earlier.¹

A number of 5-substituted 2-methyl-1,3,4-oxadiazoles have been laterally metallated [BuLi/THF/-78 °C with hexamethylphosphoric triamide (HMPA) as co-solvent (8:1 v/v)] and the anions quenched with suitable enol ethers, to give compounds of type (**45**) or (**46**) (Scheme 16) (Table XIII).⁸⁸ The reaction appears to require an aryl substituent at position-5, for the 2,5-dimethyl compound gives no products.

Table XIII

1,3,4-Oxadiazoles Prepared by Lateral Metallation of a 5-Substituted 2-Methyl-1,3,4-oxadiazole⁸⁸

R ⁵	E	Reagent	Yield (%)
Ph	CH ₂ COMe	CH ₂ =C(OMe)CH ₂ Br	38
C ₆ H ₄ Me-4	CH ₂ COMe	CH ₂ =C(OMe)CH ₂ Br	55
C ₆ H ₄ Cl-4	CH ₂ COMe	CH ₂ =C(OMe)CH ₂ Br	27
C ₆ H ₄ OMe-4	CH ₂ COMe	CH ₂ =C(OMe)CH ₂ Br	46
Ph			35
C ₆ H ₄ Me-4	"	"	53
C ₆ H ₄ Cl-4	"	"	25
C ₆ H ₄ OMe-4	"	"	53

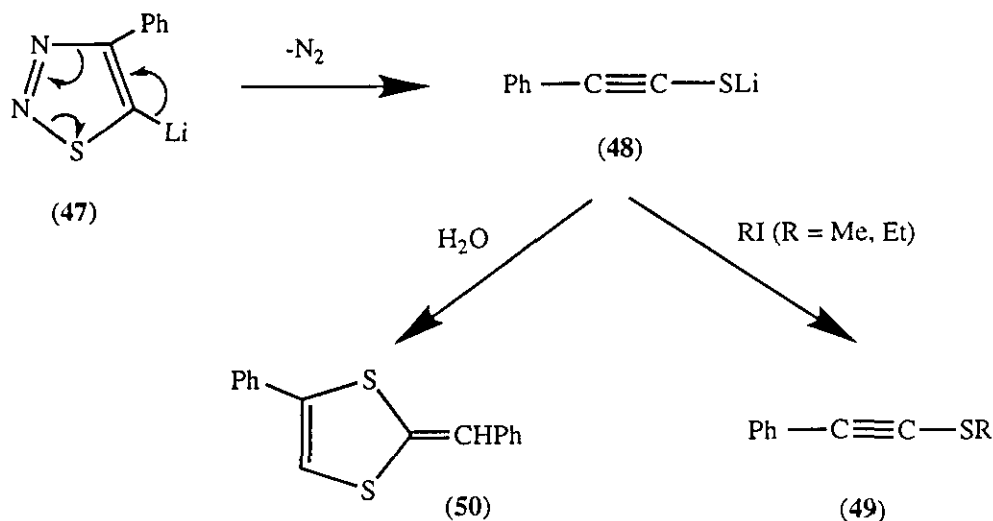


Scheme 16

VI THIADIAZOLES

A 1,2,3-Thiadiazoles

The ring was cleaved when butyllithium was reacted with 4-methyl-5-phenyl-1,2,3-thiadiazole.⁸³ 4,5-Diphenyl-1,2,3-thiadiazole forms diphenylacetylene under similar conditions (ref. 4 in our ref. 8 and ref. 89). Thiadiazoles unsubstituted in position-4 or -5 can be lithiated. Thus, 4-phenyl-1,2,3-thiadiazole forms the 5-lithiated species (47) with LDA⁹⁰ or with butyllithium at -65 °C⁹¹ (see also ref. 92). With butyllithium at higher temperatures, however, ring-opening occurs with elimination of nitrogen and the alkynthiolate anion (48) which forms can be trapped with iodo-methane or -ethane, to give the corresponding thioether (49, R = Me or Et) (Scheme 17)⁹¹ (see also ref. 92), or hydrolysed with water, to give 2-benzylidene-4-phenyl-1,3-dithiole (50) (74% yield).⁹³ 4-Phenyl-1,2,3-thiadiazole is cleaved similarly with methylolithium at low temperature.⁹⁰ It was thought that a more covalent carbon-metal bond might retard the decomposition, but reaction with methylmagnesium bromide was unsuccessful. 4-Phenyl-1,2,3-thiadiazol-5-ylolithium, prepared using LDA, has been trapped in 55% yield with chlorotrimethylsilane.⁹⁰



Scheme 17

5-Phenyl-1,2,3-thiadiazole is lithiated at position-4 with methyllithium in THF;^{90,91} addition of iodomethane yields the 4-methyl derivative in 64% yield.⁹⁰ With phenyllithium the yield of alkylated product drops to 34% and to a mere trace with butyllithium, presumably because N-S bond cleavage (see refs. 83 and 91) occurs in this case. Reactions of 5-phenyl-1,2,3-thiadiazol-4-yllithium with bromo- or iodo-butane were unsuccessful but this anion has been trapped with a wide range of other electrophiles⁹⁰ (Table XIV).

B 1,2,4-Thiadiazoles

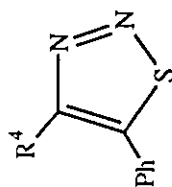
3,5-Dimethyl-1,2,4-thiadiazole can be laterally metallated in one of its methyl groups and the resulting anion converted by carbonation into the corresponding 5-acetic acid derivative (62% yield).⁸³

C 1,2,5-Thiadiazoles

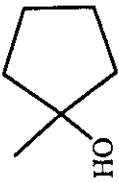
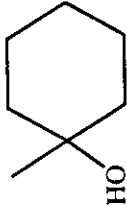
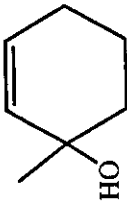
The nucleophilic ring-cleavage reactions of 1,2,5-thiadiazoles (and -selenadiazoles) have been studied in some detail. Grignard reagents and alkylolithium compounds deprotonate these heterocycles,^{83,94-96} even at temperatures as low as -70°C ; the reaction products, after hydrolysis, are thioethers, ammonia, and 1,2-dicarbonyl compounds (Scheme 18). It is believed that the reactions proceed through metal insertion into the N-S bond, as shown.⁹⁷ With phenylmagnesium bromide 1,2,4-thiadiazolocyclophanes also give 1,2-diketones, e.g. (51) \rightarrow (52) (Scheme 19).^{98,99} Benzo-2,1,3-thiadiazole is cleaved similarly by phenyllithium.¹⁰⁰

1,2,5-Thiadiazole and 3-substituted 1,2,5-thiadiazoles react in turn with Grignard reagents and sulfur dichloride to give mixtures of 3-mono- or 3,4-disubstituted 1,2,5-thiadiazoles (Table XV), thiols, and thioethers. It is likely

Table XIV
 4-Substituted 5-Phenyl-1,2,3-thiadiazoles Prepared from 5-Phenyl-1,2,3-thiadiazol-4-ylithium Compounds

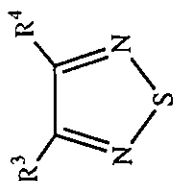


R ⁴	Reagent	Yield (%)	Ref.
D	D ₂ O	-	90
Me	MeI	64, 34	90a, 91ab
CH ₂ Ph	PhCH ₂ Br	12	90
CO ₂ H	CO ₂	45	90
CH(OH)Et	EtCHO	72	90
CH(OH)Pr	PrCHO	85	90
CH(OH)C ₇ H ₁₅	C ₇ H ₁₅ CHO	83	90
CH(OH)Ph	PhCHO	90	90
C(OH)Me ₂	Me ₂ CO	76	90

	cyclopentanone	83	90
	cyclohexanone	80	90
	cyclohex-2-enone	62	90
COPh	PhCOCl	10	90

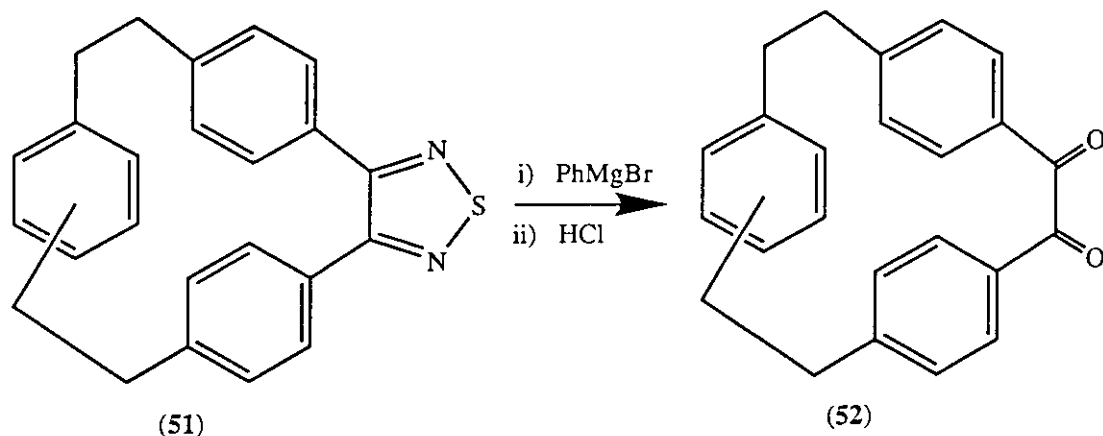
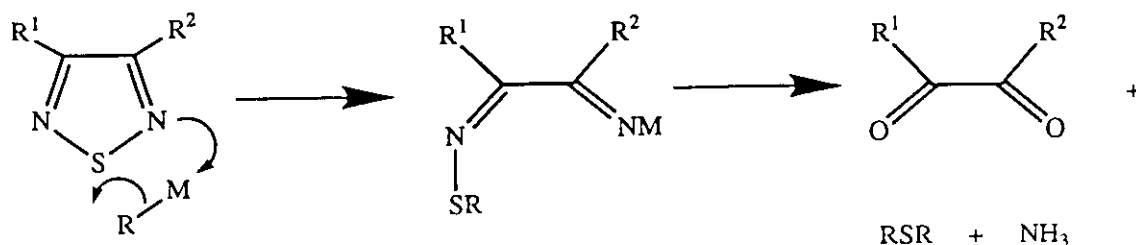
^a With MeLi. ^b With BuLi only a trace of the methyl compound was obtained; with PhLi the yield dropped to 34%.

Table XV
 1,2,5-Thiadiazoles Prepared by Reacting Grignard Reagents (R⁴MgX) with 1,2,5-Thiadiazole or a 3-Substituted Derivative¹⁰¹

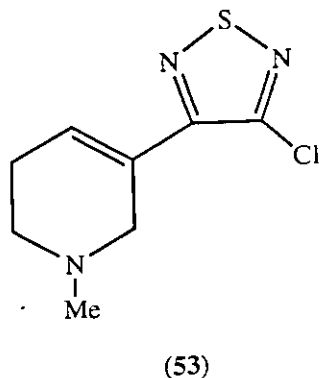


R ³	R ⁴	Grignard Reagent	Product Yield (%)	Starting material (%)
H	Me	MeMgBr	21	6
H	Me	MeMgI	7	13
H	Et	EtMgBr	30	11
H	cyclohexyl	cyclohexylMgBr	38	3
H	Ph	PhMgBr	60	4
H	naphth-1-yl	naphth-1-ylMgBr	55	7
H	C ₆ H ₄ CH=CH ₂	CH ₂ =CHC ₆ H ₄ MgCl	27	6
H	CH=CH ₂	CH ₂ =CHMgCl	19	traces
Me	Me	MeMgI	8	10
Me	Ph	PhMgBr	31	11
Me	naphth-1-yl	naphth-1-ylMgBr	42	11

Me	$C_6H_4CH=CH_2$	$CH_2=CHC_6H_4MgCl$	23	-
Me	$CH=CH_2$	$CH_2=CHMgCl$	18	2
Ph	Me	MeMgI	10	10
Ph	Ph	PhMgBr	18	29
Ph	$CH=CH_2$	$CH_2=CHMgCl$	23	25



that the heterocyclic products arise from a sequential ring-opening and recyclisation process.¹⁰¹ By contrast, 3-(3-chloro-1,2,5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine (**53**) is alkylated at position-3 of the

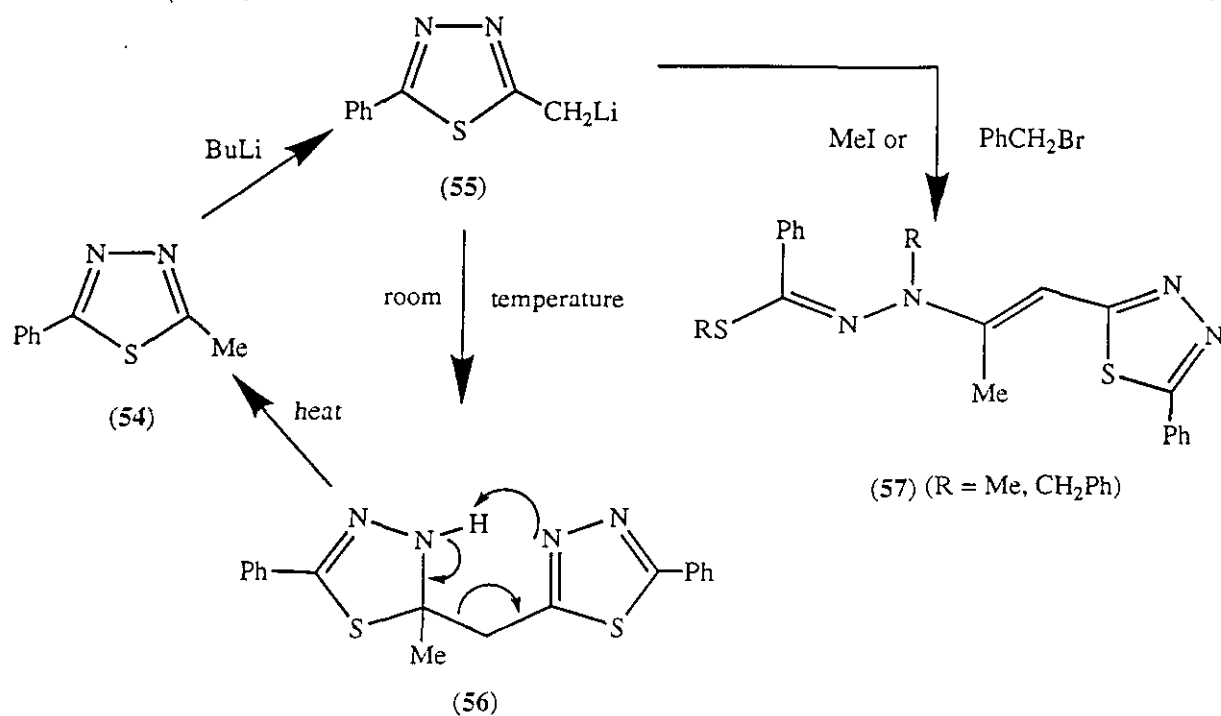


thiadiazole ring by its reaction with various Grignard reagents [RMgX; R = *n*-Pr (75%), R = *n*-C₅H₁₁ (24%), R = *n*-C₇H₁₅ (72%), R = *n*-C₈H₁₇ (75%)].¹⁰²

D 1,3,4-Thiadiazoles

2,5-Dimethyl-1,3,4-thiadiazole can be laterally metallated in one of its methyl groups and, with carbon dioxide, the resulting lithiated derivative is converted into the corresponding 2-acetic acid (80% yield).⁸³ By contrast, 2,5-

dimethyl-1,3,4-oxadiazole is cleaved by alkyllithium reagents (Section V.D). 2-Methyl-5-phenyl-1,3,4-thiadiazole (**54**) is metallated similarly by butyllithium (THF/-78 °C) and the resulting anion (**55**) can be quenched with iodomethane, to give the corresponding ethyl derivative (97% yield).^{86,87} When this experiment was repeated, however, without addition of iodomethane and the resulting mixture was allowed to warm up to ambient temperature prior to addition of water the dimer (**56**) was isolated (75%). When iodomethane or benzyl



bromide was added at ambient temperature compounds (**57**, R = Me or CH₂Ph) (38-47%) were formed.^{86,87} The dimer (**56**) reverted to starting material (**54**) on being heated at > 150 °C, as shown (Scheme 20). When 2-*iso*-propyl-5-phenyl-1,3,4-thiadiazole was metallated similarly and the resulting laterally metallated intermediate allowed to warm up prior to quenching the mixture with iodomethane, only the *tert*-butyl-1,3,4-thiadiazole (90%) was obtained and no products arising from a ring-opening sequence could be detected.⁸⁷

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