SYNTHESIS AND REACTIONS OF LITHIATED MONOCYCLIC AZOLES CONTAINING TWO OR MORE HETERO-ATOMS. PART VI: TRIAZOLES, TETRAZOLES, OXADIAZOLES, AND THIADIAZOLES[1] †

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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.

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I INTRODUCTION

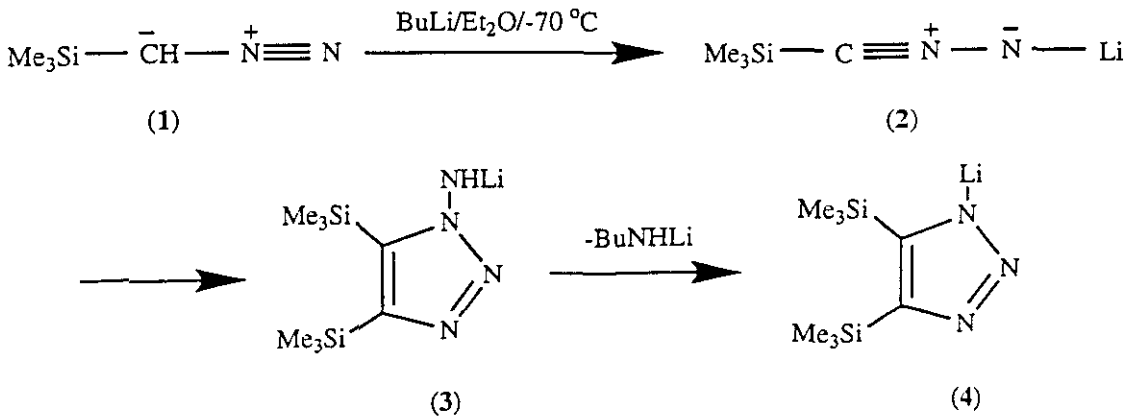
A general introduction to this series of reviews was given in Part I.[2] Since it appeared a review on "The Lateral Metallation of Isoxazoles" has been published[3] which covers some references that we had overlooked. We would be pleased to hear from any other authors whose work we have inadvertently 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

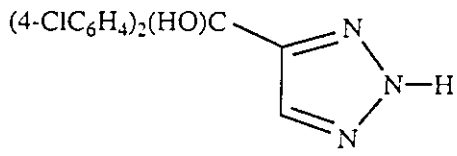
Substituted diazomethanes, e.g. **1**, react with organolithium reagents as shown in Scheme 1, to give *N*-lithiated



Scheme 1

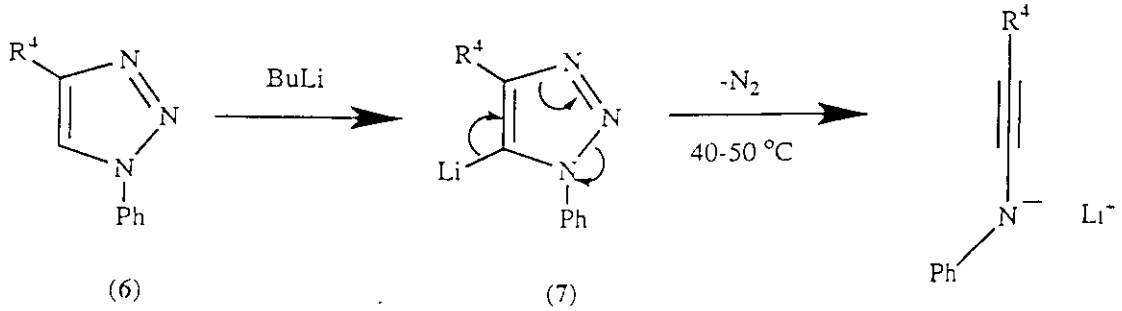
1*H*-1,2,3-triazoles, e.g. **4**.[4] The key steps are the condensation of the lithiated diazomethane (**2**) with the starting material (**1**), to give triazole (**3**) which fragments to the product (**4**) in the presence of the excess of butyllithium.

As far as we are aware only two 1-protected 1*H*-1,2,3-triazoles have been metallated directly. The 1-trimethylsilyethoxymethyl(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-trimethylsilylethoxymethyl(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-yllithium (**7**, R^4 = Ph) fragments to produce nitrogen and the *N*-phenylketenimine anion (**8**, R^4 = Ph) (Scheme 2).[7] 1-Phenyl- (**7**, R^4 = H) and 4-methyl-1-phenyl-1*H*-1,2,3-triazol-5-yllithium (**7**, R^4 = 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-yllithium compounds (**7**) lose nitrogen at ambient temperature (Scheme 2).[10] Neither butyllithium nor *sec*-butyllithium appear to metallate the diethylamide (**6**, R^4 = $CONEt_2$) but an excess of lithium



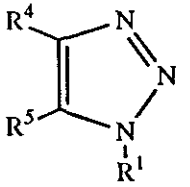
(**6**) (**7**) (**8**)

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	$C(OH)(C_6H_4Cl\text{-}4)_2$	$(4\text{-}ClC_6H_4)_2CO$	17	6
CH_2Ph	Ph	CO_2Me	$ClCO_2Me$	–	10
CH_2Ph	Br	SMe	Me_2S_2	91.5	11
$CH_2C_6H_4OMe\text{-}4$	Br	SMe	Me_2S_2	86.5	11
CH_2OMe[b]	Br	H	H_2O	84	11
CH_2OMe[b]	Br	$C(OH)Ph_2$	Ph_2CO	93	11
CH_2OMe[b]	Br	CO_2H	CO_2	71.5	11
CH_2OMe[b]	Br	CO_2Me	$ClCO_2Me$	–	11
CH_2OMe[b]	Br	SPh	Ph_2S_2	71	11
SEM[c]	H	Me	MeI	30	5
SEM[c]	H	Cl	Cl_3CCCl_3	50	5

SEM[c]	H	CH(OH)Ph	PhCHO	45	5
SEM[c]	H	COPh	$PhCO_2Et$	21	5
SEM[c]	H	SPh	Ph_2S_2	80	5
SEM[c]	H	$SiMe_3$	Me_3SiCl	37	5
$MeC(OEt)_2$	H	$C(OH)(C_6H_4Cl\text{-}4)_2$	$(4\text{-}ClC_6H_4)_2CO$	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_2H	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**, $R^4 = NO_2$) 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]

Begtrup[12] 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 Me_2S_2) 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 $CHCl_3$ or CH_2Cl_2) 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 susbtitution 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

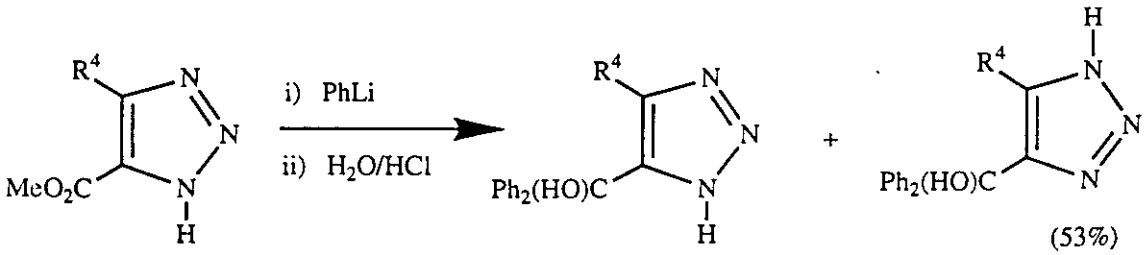
5-Methyl-1-phenyl-1*H*-1,2,3-triazole is lithiated preferentially in its methyl group (*cf.* Section II.A - 1,5-diphenyl-1*H*-1,2,3-triazole is lithiated at position-4); reaction of the α-(or laterally)lithiated derivative with iodomethane gives the corresponding ethyl derivative (42% yield).[8] A number 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-CH_2^-) 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

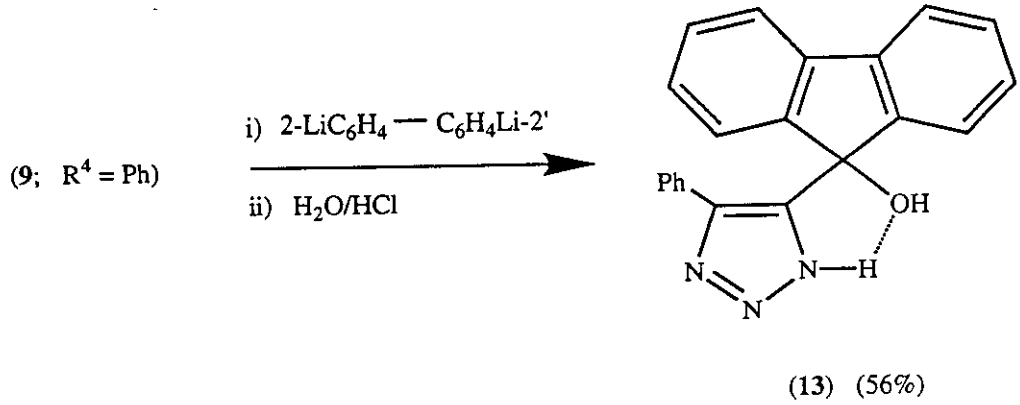


(9)

(10) R^4 = Ph (35%)

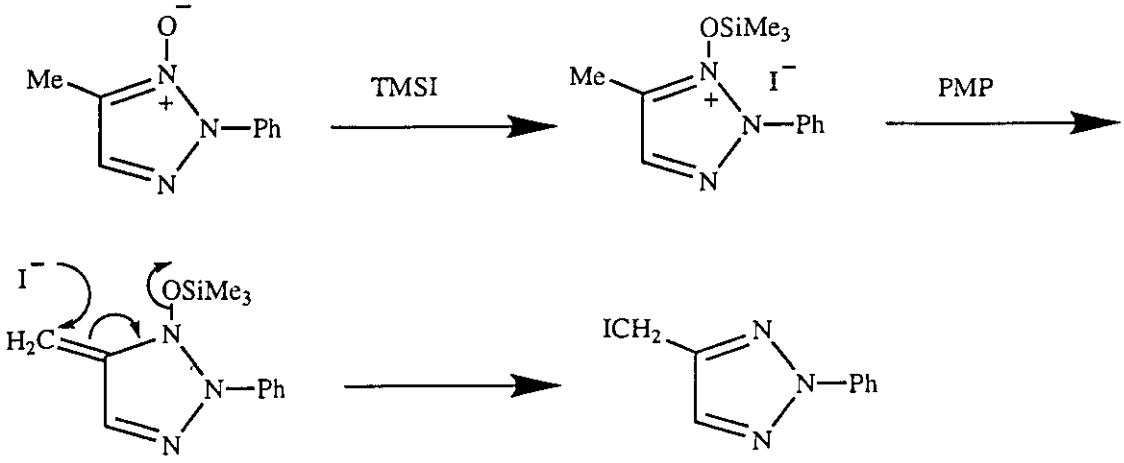
(11) R^4 = H (88%)

(12) R^4 = C_6H_4Cl-4 (96%)

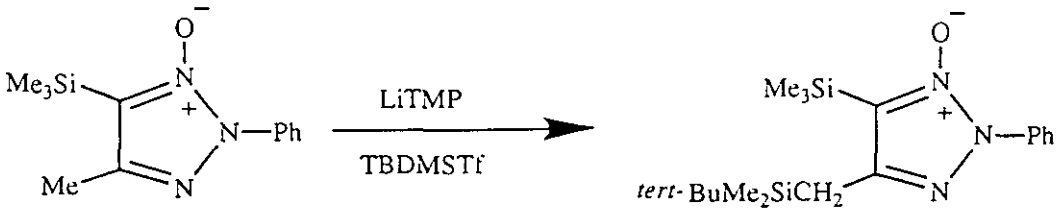


(13) (56%)

Scheme 3

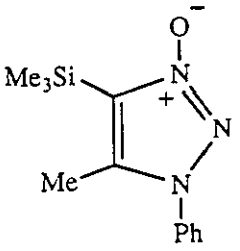


Scheme 4[24]



(14) (15)

Scheme 5

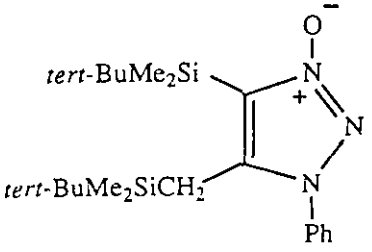


(16)

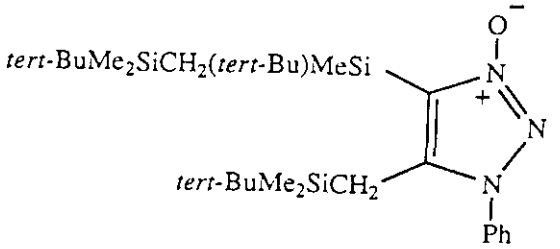
give a 38% yield of an analogous *C*-silylated product. In this case some (13%) *ortho*-substitution occurs also in the phenyl group.[15]

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**).



(17)

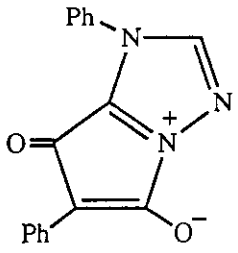


(18)

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 (Et_2O)/-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-yllithium.[30]



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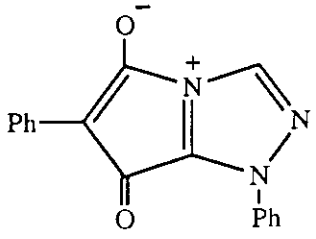


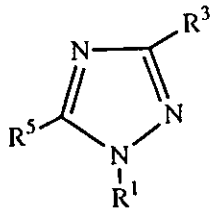
(20)

*N-Un*substituted 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-yllithium 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_2O	98	35
Me	H	COMe	$MeCONMe_2$	82	35
Me	H	COEt	$EtCONMe_2$	91	35
Me	H	COBu-*tert*	*tert*-$BuCONMe_2$	49	35
Me	H	$CO(CH_2)_5Me$	$Me(CH_2)_5CONMe_2$	91	35
Me	H	COC_6H_{11}-c	c-$C_6H_{11}CONMe_2$	77.5	35
Me	H	$COCH_2Ph$	$PhCH_2CONMe_2$	60	35
Me	H	$COCH_2C_6H_4Cl$-4	4-$ClC_6H_4CH_2CONMe_2$	43	35
Me	H	$CO(CH_2)_2$-2-furyl	2-furyl$(CH_2)_2CONMe_2$	84.5	35
Me	H	$O(CH_2)_2$tetrahydro-2-furyl	tetrahydro-2-furyl-$(CH_2)_2CONMe_2$	70	35

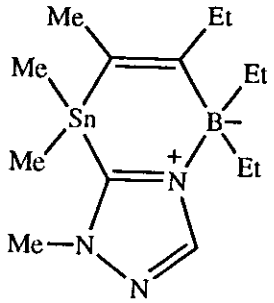
Me	H	COPh	$PhCONMe_2$	62	35
Me	H	COC_6H_4Cl-4	4-$ClC_6H_4CONMe_2$	55.5	35
Me	H	$COC_6H_3Cl_2$-2,4	2,4-$Cl_2C_6H_3CONMe_2$	78	35
Me	H	COC_6H_4OMe-4	4-$MeOC_6H_4CONMe_2$	83	35
Me	H	SPh	Ph_2S_2	98	35
Me	COMe	SPh	$MeCONMe_2$	35	35
Me	COEt	SPh	$EtCONMe_2$	67	35
Me	COBu-*tert*	SPh	*tert*-$BuCONMe_2$	55	35
Me	$CO(CH_2)_5Me$	SPh	$Me(CH_2)_5CONMe_2$	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]	$ClSnMe_2CMe{=}CEtBEt$	78	33
Et	H	COMe	$MeCONMe_2$	81	35
iso-Pr	H	COMe	$MeCONMe_2$	94	35
hexyl	H	COMe	$MeCONMe_2$	98	35
CH_2OMe	H	CO_2Me	$ClCO_2Me$	[c]	29
CH_2OMe	H	$CH(OH)CF{=}C(SMe)_2$	$(MeS)_2C{=}CFCHO$	74	39
$(CH_2)_2OMe$	H	CO_2Me	$ClCO_2Me$	[c]	29
$CH_2O_2C_6H_3$[d]	H	CO_2Et	$ClCO_2Et$	[c]	29

SEM[e]	H	D	D_2O	80	40
SEM[e]	H	Me	MeI	35	40
SEM[e]	H	Cl	Cl_3CCCl_3	41	40
SEM[e]	H	CH(OH)Ph	PhCHO	39	40
SEM[e]	H	COPh	PhCOCl	30	40
SEM[e]	H	SPh	Ph_2S_2	57	40
THF[f]	H	CO_2Et	$ClCO_2Et$	50	29
THP[g]	H	CO_2Me	$ClCO_2Me$	[c]	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	$CO(CH_2)_5Me$	$Me(CH_2)_5CONMe_2$	85[h]	35
$CH(OEt)_2$	H	COC_6H_4Cl-4	$4\text{-}ClC_6H_4CONMe_2$	58[h]	35
$CH(OEt)_2$	H	$COC_6H_3Cl_2$-2,4	$2,4\text{-}Cl_2C_6H_3CONMe_2$	48[h]	35
$CH(OEt)_2$	H	COC_6H_4OMe-4	$4\text{-}MeOC_6H_4CONMe_2$	53[h]	35
$C(OEt)_2Me$	H	$C(OH)(C_6H_4Cl\text{-}4)_2$	$(4\text{-}ClC_6H_4)_2CO$	72[h]	6
CH_2SMe	H	D	MeOD	59	43, 44
CH_2Ph	H	D	MeOD	95	31
CH_2Ph	H	Me	MeI	77	31
CH_2Ph	H	Cl	Cl_3CCCl_3	80	31

CH_2Ph	H	$C(OH)Ph_2$	Ph_2CO	86	31
CH_2Ph	H	COMe	$MeCONMe_2$	99	35
CH_2Ph	H	CO_2Me	$ClCO_2Me$	71	31
CH_2Ph	H	$PO(OEt)_2$	$ClPO(OEt)_2$	70	31, 34
CH_2Ph	H	$SiMe_2Bu$-*tert*	*tert*-$BuMe_2SiCl$	68	31
CH_2Ph	Ph	CH_2OH	HCHO	78	26
CH_2Ph	Ph	$C(OH)Ph_2$	Ph_2CO	92	26
CH_2Ph	Ph	$C(OH)(C_6H_4OMe\text{-}4)_2$	$(4\text{-}MeOC_6H_4)_2CO$	94	26
CH_2Ph	Ph	$C(OH)(C_6H_4NMe_2\text{-}4)_2$	$(4\text{-}Me_2NC_6H_4)_2CO$	91	26
CH_2Ph	Ph	SPh	Ph_2S_2	50, 92	31
CH_2Ph	Ph	$SiMe_2Bu$-*tert*	*tert*-$BuMe_2SiCl$	50	31
CH_2Ph	Ph	$PO(OEt)_2$	$ClPO(OEt)_2$	54	31
$CH_2NC_5H_{10}$[j]	D(H)[j]	H(D)[j]	D_2O	90	43, 44
$CH_2NC_5H_{10}$[j]	H	$CH(OH)C_6H_4Me$-4	$4\text{-}MeC_6H_4CHO$	78	44
$CH_2NC_5H_{10}$[j]	H	CONHBu-*tert*	*tert*-BuNCO	86	44
$CH_2NC_5H_{10}$[j]	H	CONHPh	PhNCO	91	44
$CH_2NC_5H_{10}$[j]	H	SPh	Ph_2S_2	57[k]	44
$CH_2NC_5H_{10}$[j]	H	SCH_2Ph	$(PhCH_2)_2S_2$	54[k]	44
$CH_2NC_5H_{10}$[j]	Me	H	MeI	95	44
$CH_2NC_5H_{10}$[j]	CH(OH)Ph	H	PhCHO	87	44

$CH_2NC_5H_{10}$[i]		H	cyclohexanone	83	44
CPh_3	H	D	MeOD	95	31
CPh_3	H	$C(OH)Ph_2$	Ph_2CO	61	31
I	H	Br	Br_2	-	45
Ph	H	Me	MeI	68	28
Ph	H	Et	EtI	88	28
Ph	H	CH_2OMe	$MeOCH_2Cl$	78	28
Ph	H	CO_2H	CO_2	95	28
Ph	H	CO_2Me	$ClCO_2Me$	[h]	29
Ph	H	COPh	$PhCO_2Me$	50	28
Ph	H	SMe	Me_2S_2	55	28
Ph	H	SPh	PhSCl	79	28
pyrid-2-yl	H	$C(OH)Ph_2$	Ph_2CO	70	38
pyrid-2-yl	H	[m]	$CuCl_2$	18	38
SO_2NMe_2	Ph	CHO	DMF	–	42
SO_2NMe_2	C_6H_4Cl-3	CN	PhOCN	75	46
SO_2NMe_2	$C_6H_3Me_2$-2,4	CN	TosCN	–	42
SO_2NMe_2	C_6H_4OMe-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-Benzdioxol-5-yl. [e] SEM ≡ $CH_2O(CH_2)_2SiMe_3$. [f] THF ≡ tetrahydro-2-furyl. [g] THP ≡ tetrahydropyran-2-yl. [h] Yield given for deprotected product (acid hydrolysis). [i] $CH_2NC_5H_{10}$ ≡ 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.



aminoalkylazoles[47-49] and *N*-trialkylstannylazoles.[50] 1,2,4-Triazoles protected by an aminal group at *N*-1 give *N-un*protected 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.

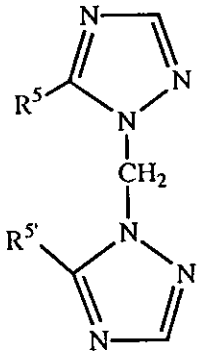
With one mol equiv. of butyllithium (THF/0 °C) *bis*(1,2,4-triazol-1-yl)methane lithiates predominantly in position-5 but a significant amount of the 5,5'-dilithiated derivative is produced also at this temperature.[51] Varying mixtures of the mono- or disubstituted product are isolated following addition 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 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% deuteriation in the *N*-substituent (methyl or

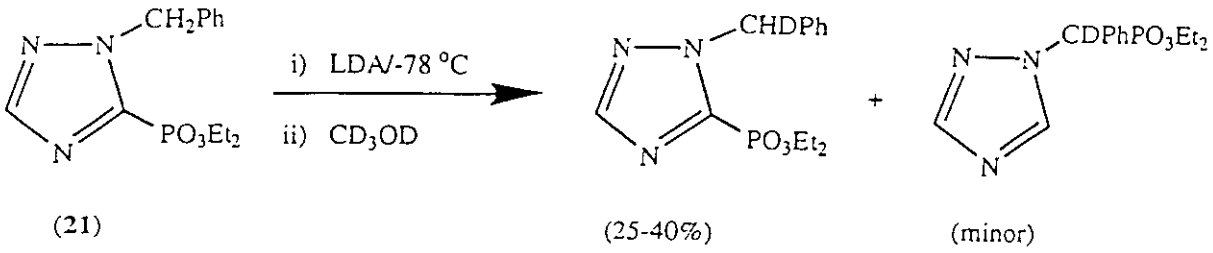
Table III

Metallation of *Bis*(1,2,4-Triazol-1-yl)methane[51]



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_2S_2	1 : 1 : 1	67	14
Me_2S_2	1 : 2.4 : 2.4	20	79
Me_3SiCl	1 : 1 : 1	80	0
Me_3SiCl	1 : 2.1 : 2.1	23	77
$(HCHO)_n$[b]	1 : 1 : 1	39	15
$(HCHO)_n$[b]	1 : 2.1 : 2.1	33	67

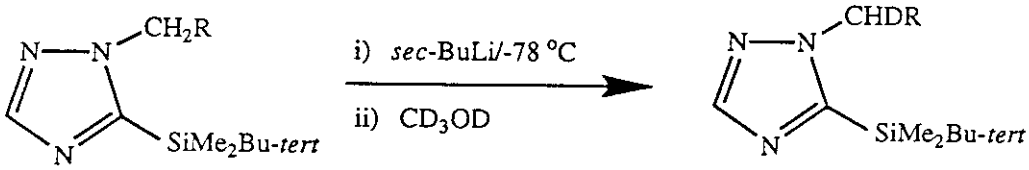
[a] Determined by ^1H NMR spectroscopy. [b] Paraformaldehyde.



(21) (25-40%) (minor)

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]



(22) (R = H, Ph)

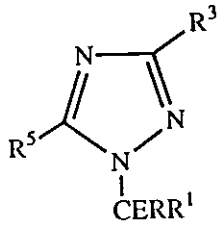
Scheme 7

In 5-methyl-1-phenyl-1*H*-1,2,4-triazole the methyl group is lithiated by butyllithium in hexane[28] 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-phenylpyrazoles[53] 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

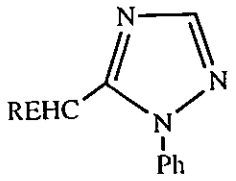
1*H*-1,2,4-Triazoles Prepared by Lateral Metallation in a Substituent at *N*-1



R	R^1	R^3	R^5	E	Reagent	Yield (%)	Ref.
H	H	$SiMe_2Bu$-*tert*	H	D	CD_3OD	> 90	34
H	Ph	H	H	CH_2Ph	$PhCH_2Cl$	65	36
H	Ph	H	H	$CH_2C_6H_4Me$-4	4-$MeC_6H_4CH_2Cl$	61	36
H	Ph	H	H	$CH_2C_6H_4Cl$-4	4-$ClC_6H_4CH_2Cl$	49	36
H	Ph	$SiMe_2Bu$-*tert*	H	D	CD_3OD	> 90	34
H	Ph	H	$PO(OEt)_2$	D	CD_3OD	25-40	34
SMe	SMe	H	H	$C(OH)Ph_2$	Ph_2CO	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]

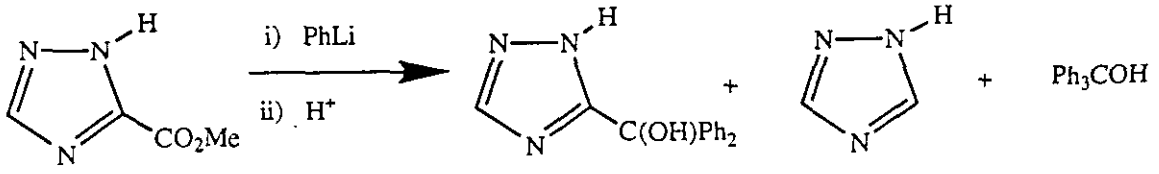


R	E	Reagent	Yield (%)
H	Me	MeI	75
H	CO_2H	CO_2	70
Me	Me	MeI	50
CO_2H	Me	MeI	62
OMe	CO_2H	CO_2	78

[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]



(23) (24)

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 → metal exchange reactions

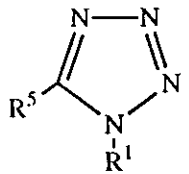
Provided that position-5 is free metallation takes place there preferentially[45,57-62] either with a 1- (Table VI) or 2-substituted tetrazole (Table VII), and halogen → metal exchange occurs when magnesium or butyllithium reacts with 5-chloro-1-phenyltetrazole.[63] Tetrazolium salts form anions at C-5 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-yllithium 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

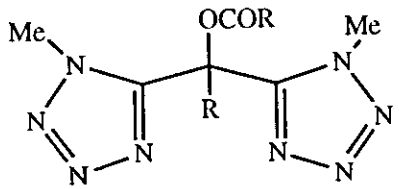
1,5-Disubstituted Tetrazoles Prepared from 1-Substituted Tetrazol-5-yllithium Compounds



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_2CO	75	59
Me	COPh	$PhCO_2Me$	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	$Ni(PEt_3)_2Cl_2$	80	57, 58
cyclohexyl	b	$Ni(PEt_3)_2Cl_2$	–	58
$CMe(OEt)_2$	$C(OH)(C_6H_4Cl\text{-}4)_2$	$(4\text{-}ClC_6H_4)_2CO$	86c	6

a Products were

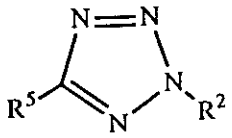


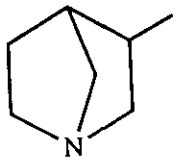
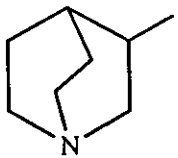
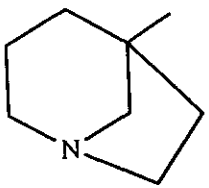
(R =Me, Ph)

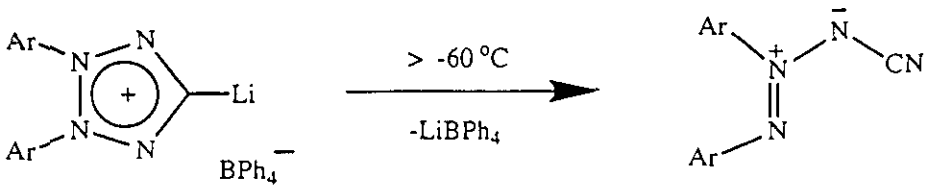
b *Bis*(1-methyltetrazol-5-yl)nickel(II) products formed. c After removal of the 1,1-diethoxyethyl protecting group.

Table VII

2,5-Disubstitued Tetrazoles Prepared from 2-Substituted Tetrazol-5-yllithium Compounds[45]



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_2CO	27
	Cl	Cl_2	50
	Br	Br_2	56



(25) (26)

Scheme 9

methylcyanamide, but is stable enough below -60 °C to react with a variety of electrophiles (Table VI).[59] 1-Phenyl-1*H*-1,2,3-triazol-5-yllithium is a little less stable, decomposing at temperatures as high as -60 °C to -70 °C, to give lithium phenylcyanamide.[59] In general tetrazol-5-yllithium compounds are more susceptible to fragmentation than their 1,2,3-triazolyllithium 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

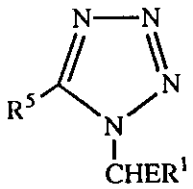
When position-5 of tetrazole is blocked anions can be formed by lateral metallation of alkyl or aryl substituents. Thus, 1- and 2-alkyl-5-phenyltetrazoles react with *tert*-butyllithium (THF/-78 °C) to give "dipole stabilized" α-lithioalkyl derivatives which react readily with a wide range of electrophiles (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 °C, and even briefly at 0 °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-alkyl-imidazoles).[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 -sodium[68] (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

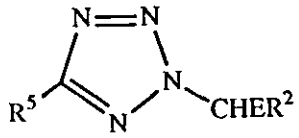


R^1	R^5	E	Reagent	Yield (%)	Ref.
H	Ph	D	D_2O	96	60, 62
H	Ph	Me	Me_2SO_4	90	60, 62
H	Ph	$C(OH)Ar_2$	Ar_2CO	84[a]	60, 62
H	Ph	$SiMe_3$	$ClSiMe_3$	96	60, 62
H	SH	CO_2H	CO_2	-	70
Ar	Ph	CH(OH)Ar	ArCHO	87[a]	60, 62
Ar	Ph	$C(OH)Ar_2$	Ar_2CO	95[a]	60, 62
Ar	Ph	$COAr_2$	PhCN	80[a]	60, 62

[a] Ar = C_6H_4Me-4

Table IX

2,5-Disubstituted Tetrazoles Prepared by Lateral Lithiation in a Substituent at *N*-2[60, 62]

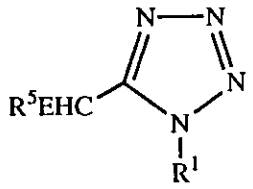


R^2	R^5	E	Reagent	Yield (%)
H	Ph	CH_2OH	HCHO	33
H	Ph	CH(OH)Et	EtCHO	85
H	Ph	$CH(OH)C_6H_4OMe$-4	4-$MeOC_6H_4CHO$	77
H	Ph	Me_3SiCl	$ClSiMe_3$	70
H	SPh	$CH(OH)C_6H_4OMe$-4	4-$MeOC_6H_4CHO$	57
H	CH_2NH_2	$CH(OH)C_6H_4OMe$-4	4-$MeOC_6H_4CHO$	37
Me	Ph	CO_2H	CO_2	53
Me	Ph	CH(OH)Ph	PhCHO	98[a]
Et	$SiMe_3$	$SiMe_3$	$ClSiMe_3$	51
$SiMe_3$	Ph	=CHEt	EtCHO	68
$SiMe_3$	Ph	=CHBu-*tert*	*tert*-BuCHO	88

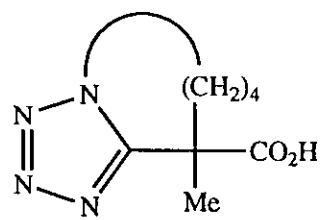
[a] See also ref. 67

Table X

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

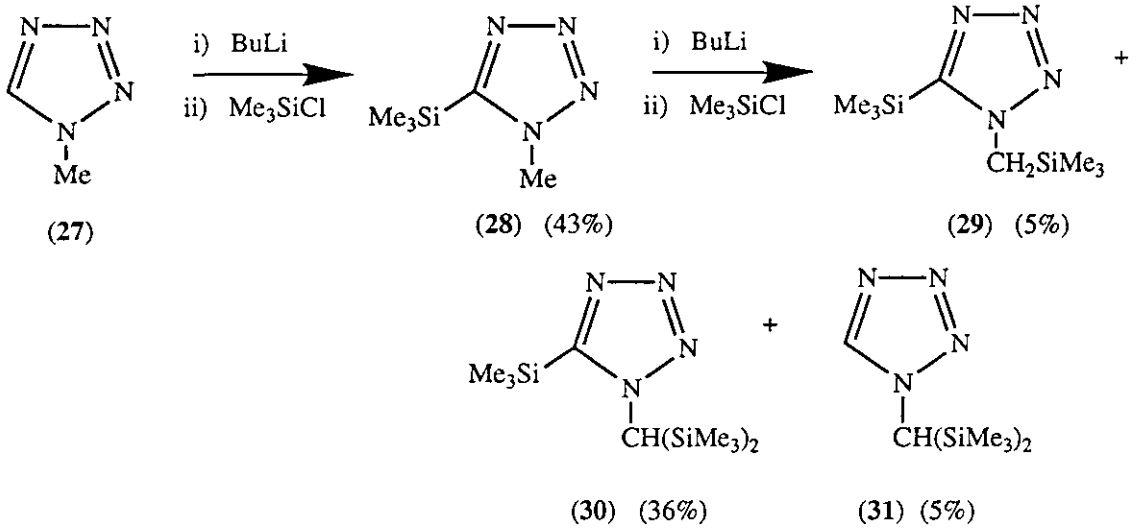


R^1	R^5	E	Reagent	Yield (%)	Ref.
Me	Ph	CO_2H	CO_2	62	68
Me	Ph	$(CH_2)_2NMe_2$	$Me_2N(CH_2)_2Cl$	34	69
Me	Ph	$(CH_2)_2NEt_2$	$Et_2N(CH_2)_2Cl$	48	69
Me	Ph	$(CH_2)_2NC_5H_{10}$[a]	$C_5H_{10}N(CH_2)_2Cl$[a]	29	69
Me	Ph	$CH(OH)CMe_2CH_2NEt_2$	$Et_2NCH_2CMe_2CHO$	41	69
Me	Ph	$CH(OH)CMe_2CH_2NC_5H_{10}$[a]	$C_5H_{10}NCH_2CMe_2CHO$[a]	53	69
Me	Ph	$C(OH)Ph(CH_2)_2NMe_2$	$Me_2N(CH_2)_2COPh$	23	69
Ph	H	CO_2H	CO_2	66	68
Ph	H	COMe	MeCN	29	69
Ph	H	$CH(OH)CMe_2CH_2NC_5H_{10}$[a]	$C_5H_{10}NCH_2CMe_2CHO$[a]	26	69

Ph	H	$C(OH)Ph(CH_2)_2NMe_2$	$Me_2N(CH_2)_2COPh$	17	69
Ph	H	$C(OH)Me(CH_2)_2NC_5H_{10}$[a]	$C_5H_{10}N(CH_2)_2COMe$[a]	27	69
naphth-1-yl	H	CO_2H	CO_2	low	68
cyclohexyl	[b]	CO_2H	CO_2	64	68
R^1 ⟶ R^5					
$-(CH_2)_4-$		CO_2H	CO_2	57	68
$-(CH_2)_3CHMe-$		CO_2H	CO_2	57	68
$-(CH_2)_2CH(Me)CH_2-$		CO_2H	CO_2	51	68
$-(CH_2)_2CH(Bu\text{-}tert)CH_2-$		CO_2H	CO_2	75	68
		CO_2H	CO_2	36	68

[a] NC_5H_{10} 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 transmetallation occurs since the methylene group in compound (**29**) is more acidic than the methyl group in compound (**28**).



(**27**) (**28**) (43%) (**29**) (5%) (**30**) (36%) (**31**) (5%)

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

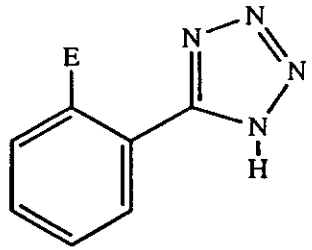
A 1,2,3-Oxadiazoles (Sydnones)

Lithiation of 3-phenylsydnone (**32**) (BuLi/Et_2O/-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/Et_2O/-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 acids[74-76](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-Aryltetrazoles[71]

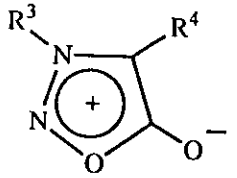


E	Reagent	Yield (%)
Me	MeI[a]	78
CH(OH)Me	MeCHO	95
$CH(OH)CH{=}CH_2$	$CH_2{=}CHCHO$	51
Et	MeI	71
$(CH_2)_5Me$	$Me(CH_2)_4I$	92
$(CH_2)_2Ph$	$PhCH_2Br$	73

[a] No reaction with alkyl halides more complex than MeI.

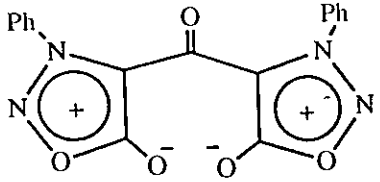
Table XII

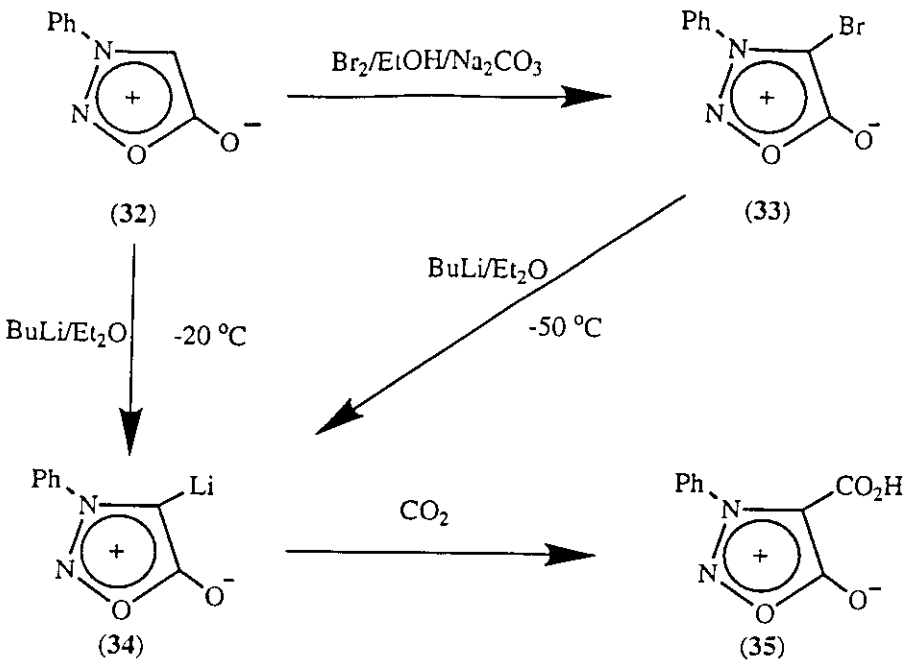
4-Substituted 1,2,3-Oxadiazoles Prepared from 1,2,3-Oxadiazol-4-yllithium Compounds



R^3	R^4	Reagent	Yield (%)	Ref
iso-Pr	CO_2H	CO_2	60	75, 76
sec-Bu	CO_2H	CO_2	75, 57	75, 76
Ph	CO_2H	CO_2	61, 62	72, 74, 76
Ph	[a]	$COCl_2$	[a]	73
C_6H_4Me-2	CO_2H	CO_2	78	76
C_6H_4Me-4	CO_2H	CO_2	40	76
C_6H_4Cl-2	CO_2H	CO_2	65	76
C_6H_4Cl-4	CO_2H	CO_2	50	76
C_6H_4OMe-2	CO_2H	CO_2	39	76
C_6H_4OMe-4	CO_2H	CO_2	47	76
$NHCH_2Ph$	Me[b]	MeI	85	77

$NHCH_2Ph$	CHO	DMF	90	77
$NHCH_2Ph$	COPh	$PhCONMe_2$	76	77

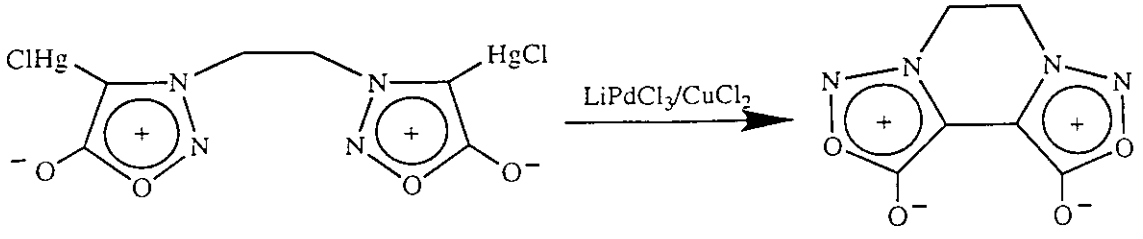
[a] Products were  (38%) and small amounts of the corresponding carbinol. [b] Two mol equiv. MeI gave the *N*,4-dimethyl derivative (75% yield).



Scheme 11

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-aroylsydnones.[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 *bis*mercurated derivative **36** is coupled in the presence of $LiPdCl_3/CuCl_2$, to give the tricyclic product (**37**) (Scheme 12).[81]

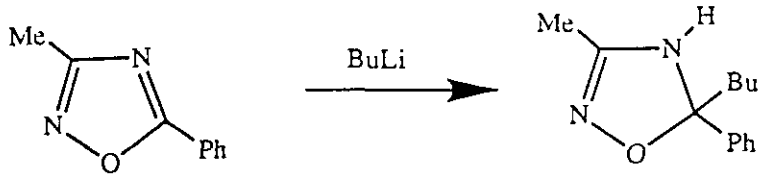


(36) (37)

Scheme 12

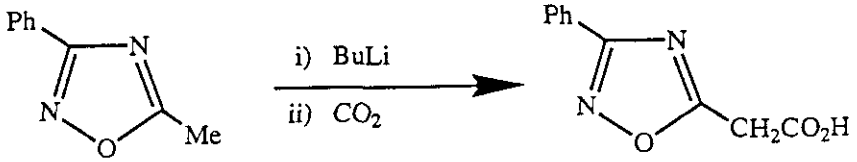
B 1,2,4-Oxadiazoles

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



(38) (39) (83%)

Scheme 13



(40) (41) (67%)

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]

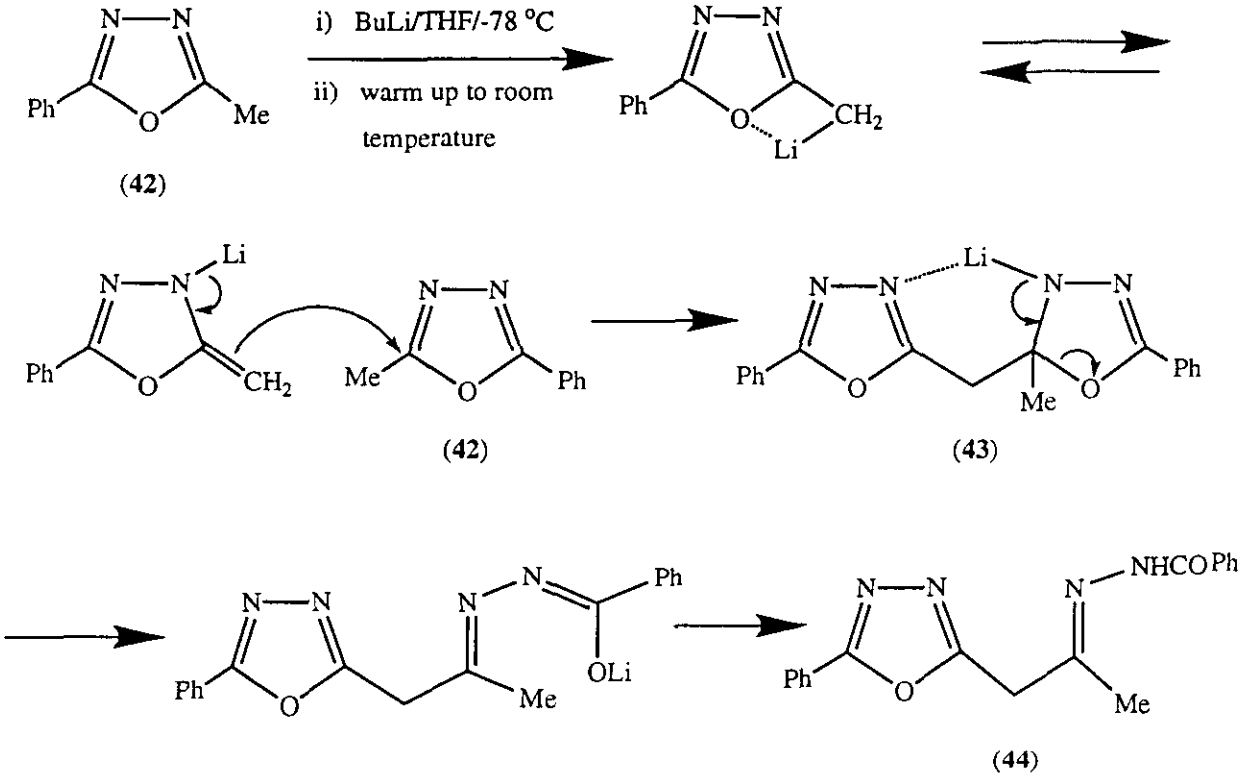
3-Methyl- and 3-phenyl-1,2,4-oxadiazole are mercurated with mercuric chloride at position-5 and the resulting mercurated derivatives can be used to introduce halogen (Cl, 10-15% yield; Br, 50%; and I, 90%) at this position.[85]

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-thiazoles[1] 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);



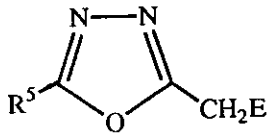
Scheme 15

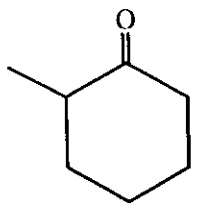
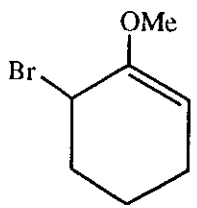
addition of water allows compound (**44**) to be isolated.[86,87] 2,5-Dimethyl-1,3,4-oxadiazole also appears to be quite prone to ring-cleavage in the presence of butyllithium.[9,83] The mechanism of this process has been discussed earlier.[1]

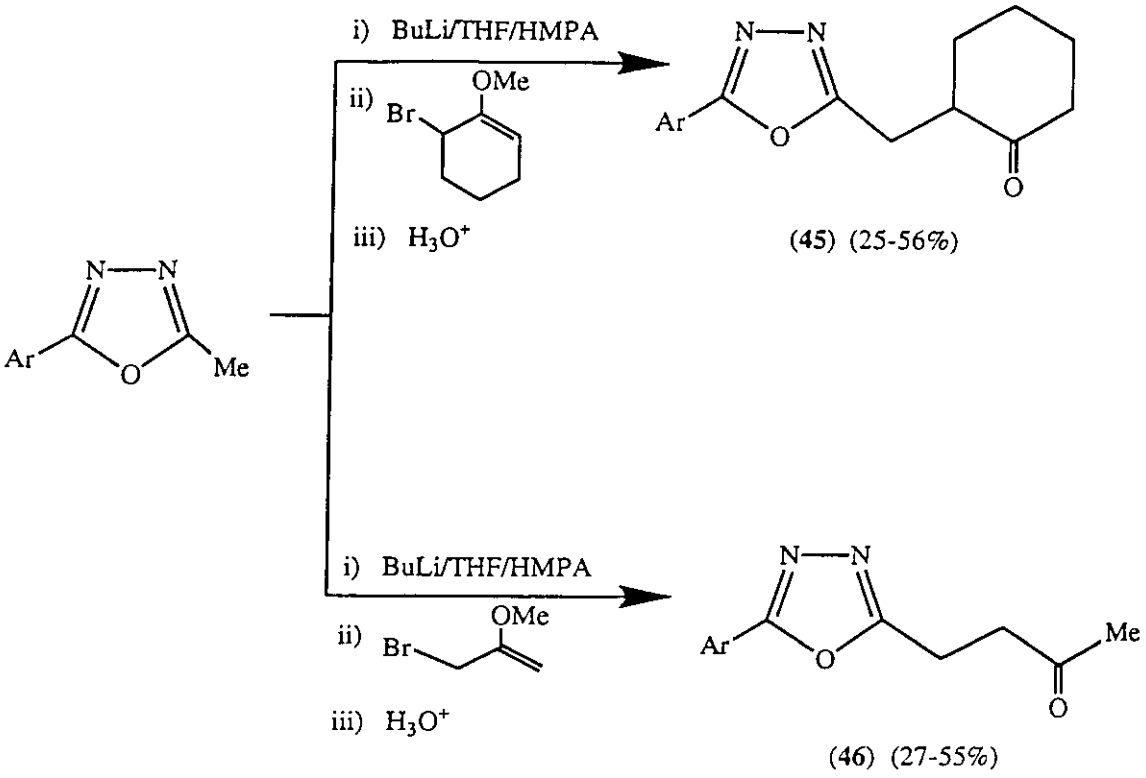
A number of 5-substituted 2-methyl-1,3,4-oxadiazoles have been laterally metallated [BuLi/THF/-78 °C with hexamethylphosphoric triamide (HMPA) as co-solvent (8:1 v/v)] and the anions quenched with suitable enol ethers, to give compounds of type (**45**) or (**46**) (Scheme 16) (Table XIII).[88] The reaction 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-oxadiazole[88]



R^5	E	Reagent	Yield (%)
Ph	CH_2COMe	$CH_2=C(OMe)CH_2Br$	38
C_6H_4Me-4	CH_2COMe	$CH_2=C(OMe)CH_2Br$	55
C_6H_4Cl-4	CH_2COMe	$CH_2=C(OMe)CH_2Br$	27
C_6H_4OMe-4	CH_2COMe	$CH_2=C(OMe)CH_2Br$	46
Ph			35
C_6H_4Me-4	"	"	53
C_6H_4Cl-4	"	"	25
C_6H_4OMe-4	"	"	53



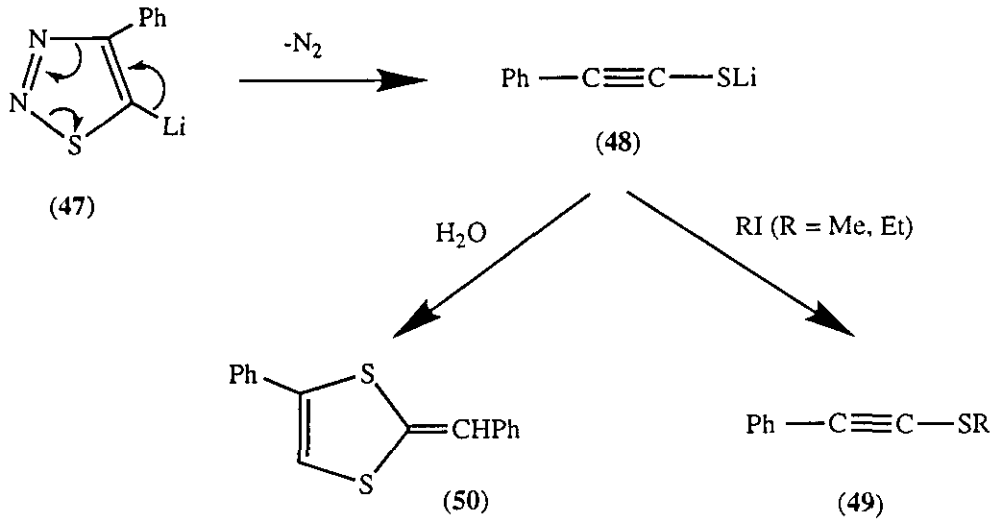
Scheme 16

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 LDA[90] or with butyllithium at -65 °C[91] (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 methyllithium 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-yllithium, 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 electrophiles[90] (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]

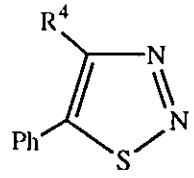
C 1,2,5-Thiadiazoles

The nucleophilic ring-cleavage reactions of 1,2,5-thiadiazoles(and -selenadiazoles) have been studied in some detail. Grignard reagents and alkyllithium compounds deprotonate these heterocycles,[83,94-96] even at temperatures as low at -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**) → (**52**) (Scheme 19).[98,99] Benzo-2,1,3-thiadiazole is cleaved similarly by phenyllithium.[100]

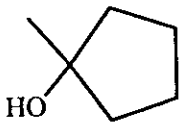
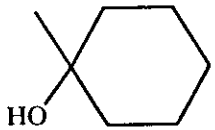
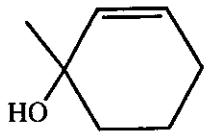
1,2,5-Thiadiazole and 3-substituted 1,2,5-thiadiazoles react in turn with Grignard reagents and sulfur dichloride to give mixtures of 3-mono- or 3,4-disubstituted 1,2,5-thiadiazoles (Table XV), thiols, and thioethers. It is likely

Table XIV

4-Substituted 5-Phenyl-1,2,3-thiadiazoles Prepared from 5-Phenyl-1,2,3-thiadiazol-4-yllithium Compounds



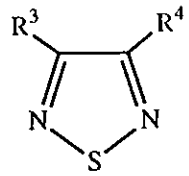
R^4	Reagent	Yield (%)	Ref.
D	D_2O	–	90
Me	MeI	64, 34	90a, 91a,b
CH_2Ph	$PhCH_2Br$	12	90
CO_2H	CO_2	45	90
CH(OH)Et	EtCHO	72	90
CH(OHPr	PrCHO	85	90
$CH(OH)C_7H_{15}$	$C_7H_{15}CHO$	83	90
CH(OH)Ph	PhCHO	90	90
$C(OH)Me_2$	Me_2CO	76	90

	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%.

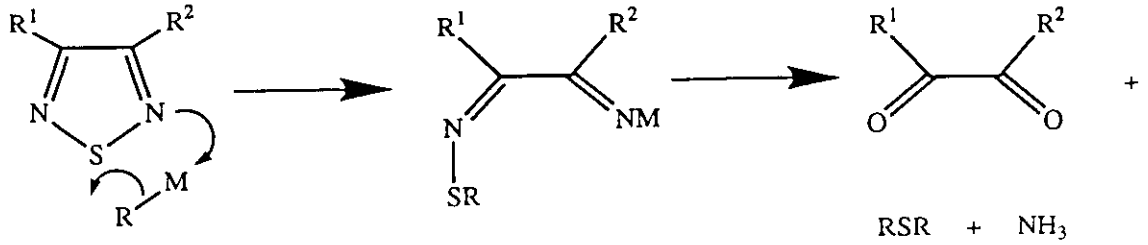
Table XV

1,2,5-Thiadiazoles Prepared by Reacting Grignard Reagents (R^4MgX) with 1,2,5-Thiadiazole or a 3-Substituted Derivative[101]

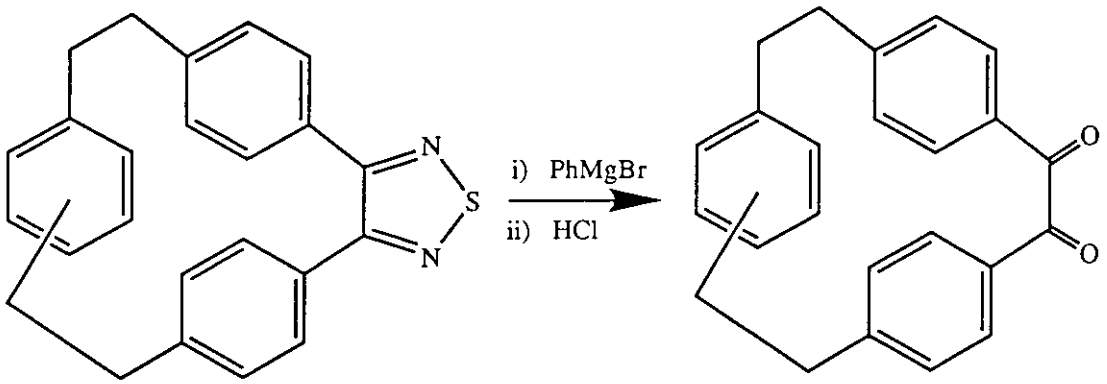


R^3	R^4	Grignard Reagent	Product Yield (%)	Starting material (%)
H	Me	MeMgBr	21	6
H	Me	MeMgI	7	13
H	Et	EtMgBr	30	11
H	cyclohexyl	cyclohexylMgBr	38	3
H	Ph	PhMgBr	60	4
H	naphth-1-yl	naphth-1-ylMgBr	55	7
H	$C_6H_4CH=CH_2$	$CH_2=CHC_6H_4MgCl$	27	6
H	$CH=CH_2$	$CH_2=CHMgCl$	19	traces
Me	Me	MeMgI	8	10
Me	Ph	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



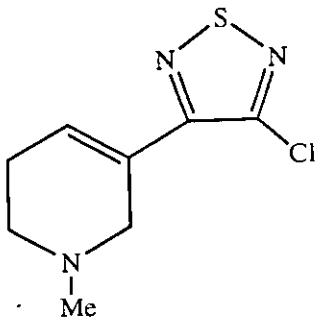
Scheme 18



(51) (52)

Scheme 19

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



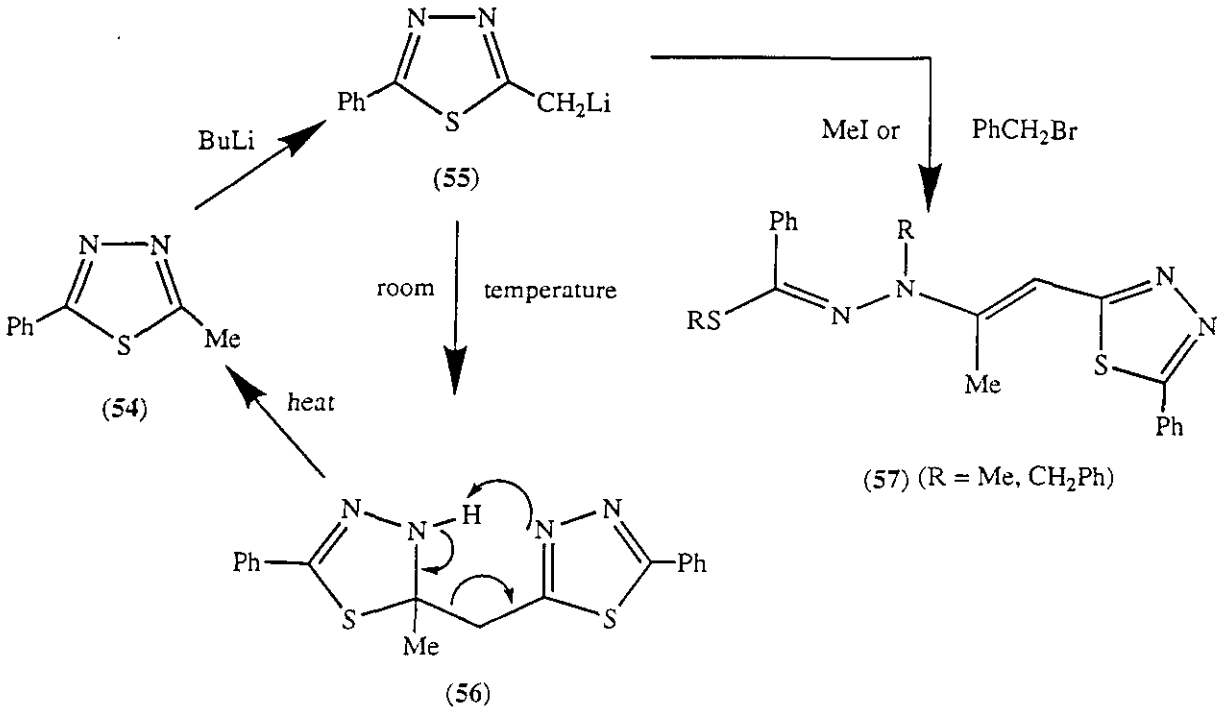
(53)

thiadiazole ring by its reaction with various Grignard reagents [RMgX; R = *n*-Pr (75%), R = *n*-C_5H_{11} (24%), R = *n*-C_7H_{15} (72%), R = *n*-C_8H_{17} (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



Scheme 20

bromide was added at ambient temperature compounds (**57**, R = Me or CH_2Ph) (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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