SYNTHESIS AND REACTIONS OF LITHIATED MONOCYCLIC AZOLES CONTAINING TWO OR MORE HETERO-ATOMS. PART I: ISOXAZOLES†

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Abstract: *The metallation and halogen → metal exchange reactions of isoxazoles (1,2-oxazoles) and the reactions of the resulting organometallic derivatives, particularly lithiated derivatives, are reviewed comprehensively.*

CONTENTS

I INTRODUCTION

Recently, in order to promote the use of organometallic derivatives of imidazoles in synthesis, we reviewed their synthesis and reactions.[1†] Since interest in this field of chemistry has expanded considerably, we have written a series of comprehensive reviews on the organometallic derivatives of the *mono*cyclic aromatic azoles containing two or more heteroatoms. In each we discuss first monolithiated derivatives, prepared either by metallation (either in the ring or in a side-chain) or by halogen → lithium exchange, then polylithiated derivatives, prepared by either method. Some mention is made of other organometallic derivatives, e.g. Grignard reagents, although our coverage of these compounds may not be complete. No attempt is made to cover metal complexes. Some coverage of this subject can be found in monographs and reviews on the individual heterocyclic systems [the literature on heterocyclic chemistry is reviewed comprehensively elsewhere[2-5]] and on the various aspects of

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

heterocyclic or organolithium chemisry.[6-20] Gilchrist[15] covers the ring-opening of some 5-membered azoles in his review of the ring-opening of 5-membered heteroaromatic anions whilst Rewcastle and Katritzky[21] have reviewed recently the "Generation and Reactions of sp^2 Carbanionic Centers in the Vicinity of Heterocyclic Nitrogen Atoms", though their coverage is not comprehensive. Each of our reviews, on isoxazoles, oxazoles, pyrazoles, imidazoles, isothiazoles, thiazoles, 1,2,3- and 1,2,4-triazoles, tetrazoles, and 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-oxa(and thia)diazoles will be comprehensive (this one covers the literature through June 1993). Isoxazoles (1,2-oxazoles)[10,11,22-30] have served as important building blocks in the construction of more complex molecular systems[30,31] including a variety of natural products.[28,29] Particular emphasis has been given to the α-(or lateral)metallation reactions of 3,5-dialkylisoxazoles, especially the 3,5-dimethyl derivative (Section IV). Following suitable modification of isoxazoles *via* metallation and halogen → lithium exchange reactions the fragility of the N-O bond enables their conversion into several non-cyclic intermediates. Consequently, this area of chemistry is dominated by ring-cleavage processes. Indeed, attempted metallation of some isoxazoles results in direct ring-cleavage.

II MONOMETALLATION IN THE RING

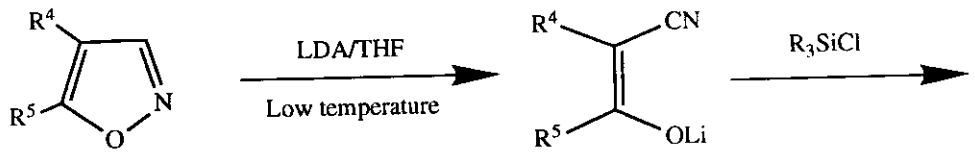
Attempts to lithiate 5-substituted isoxazoles in position-3 have resulted in ring cleavage. The ring-opened lithium enolates (**1**) can be trapped as silyl derivatives (**2**) (Table I) with *Z*-stereochemistry providing that reactions are carried out at -78 °C; at higher temperatures (> -30 °C) mixtures of *E*- and *Z*-products (**2**) are obtained (ratio 1:1).[32] Acetoacetonitrile dianion (**3**; R = H) is obtained when 5-methylisoxazole is reacted with 2 mol. equiv. of lithium diisopropylamide (LDA) at -10 °C in tetrahydrofuran (THF); it can be trapped at the C-atom italicised with various electrophiles.[33] 4,5-Dimethylisoxazole behaves similarly.[33]

The ability of isoxazoles to metallate in position-4 depends on the nature of the substituents present at positions-3 and -5. Halogen atoms, dialkylaminomethyl groups, and alkoxy or thioalkoxy groups in these positions facilitate metallation (BuLi/THF/-70 °C) at position-4 and high yields of trapped products can be obtained (Table II). However, whereas 3-(2,6-dichlorophenyl)-5-dimethylaminomethylisoxazole metallates at position-4 (co-ordination of BuLi stronger with the -NMe_2 functionality than with the ring *O*-atom), 5-alkoxymethyl- and 5-alkylthiomethyl substituted isoxazoles undergo lateral metallation (co-ordination of BuLi with ring *O*-atom predominates) (see Section IV).[34] 3-Hydroxy-5-methylisoxazole (**4**) reacts with 2 mol. equiv. of butyllithium in THF at -10 °C to give a dianion which, on quenching with carbon dioxide, gives a mixture of the 4-carboxylic

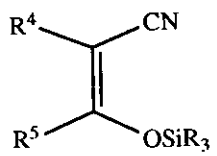
Table I

PRODUCTS (2) DERIVED *VIA* RING-CLEAVAGE OF ISOXAZOL-3-YLLITHIUM INTERMEDIATES[32]

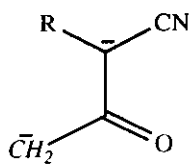
R^4	R^5	R_3	Yield (%)
H	Me	Me_3	72
H	Me	*t*-$BuMe_2$	88
H	Ph	Me_3	92



(1)



(2)



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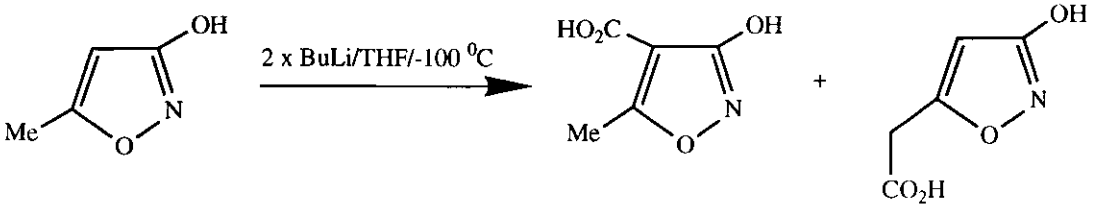
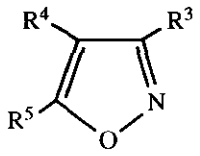


(4) (5) (6)

Scheme 1

Table II

4-SUBSTITUTED ISOXAZOLES PREPARED *VIA* METALLATION OF 3,5-DISUBSTITUTED ISOXAZOLES IN POSITION-4



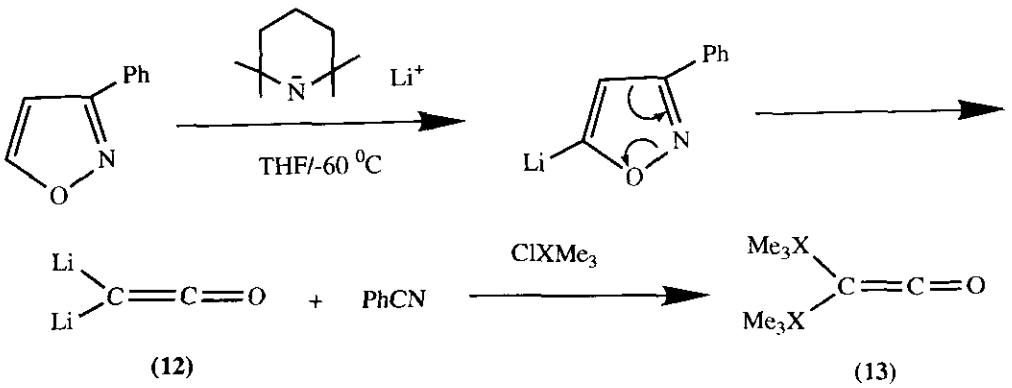
R^3	R^4	R^5	Reagent	Yield (%)	Ref.
Me	Me	Ph	MeI	39, 78[a]	35
Me	Pr	Ph	PrBr	4, 17[a]	35
Me	CH_2Ph	Ph	$PhCH_2Br$	3[a]	35
Me	CH(OH)Et	Ph	EtCHO	22[a]	36
Me	CH(OH)Ph	Ph	PhCHO	3[a]	36
CH_2OMe	Me	Me	MeI	–[a]	37
CH_2NMe_2	Me	Me	MeI	–[a]	37
OMe	I	Ph	I_2	87	38
OMe	CO_2H	Me	CO_2	–	39
OMe	CO_2H	Ph	CO_2	99	38
OMe	CO_2H	C_6H_4Cl-2	CO_2	62	38
OMe	CO_2H	$C_6H_3Cl_2$-2,6	CO_2	75	38
Ph	Me	Cl	MeI	74	38
Ph	CO_2H	Ph	CO_2	10[b]	36
Ph	CH(OH)Et	Ph	EtCHO	9[b]	36
Ph	CO_2H	Cl	CO_2	80	38
Ph	I	Cl	I_2	73	38
Ph	I	OMe	I_2	88	38
Ph	CO_2H	OMe	CO_2	99	38

Ph	CO_2H	OEt	CO_2	81	38
Ph	CO_2H	OPr-*i*	CO_2	77	38
Ph	CO_2H	OBu-*t*	CO_2	75	38
Ph	CO_2H	SEt	CO_2	73	38
Ph	CO_2H	SBu-*t*	CO_2	85	38
C_6H_4Cl-2	CO_2H	OMe	CO_2	97	38
$C_6H_3Cl_2$-2,6	CO_2H	OMe	CO_2	89	38
$C_6H_3Cl_2$-2,6	CO_2H	CH_2NMe_2	CO_2	71	34
$C_6H_3Cl_2$-2,6	Me[c]	CH_2NMe_2	MeI	–	34

[a] Lateral metallation occurs also (see Tables VI and X). [b] Large amounts of starting material recovered. [c] Isolated together with the quaternary ammonium salt - $CH_2\overset{+}{N}H_3$ I^-.[34]

acid (**5**) and the laterally metallated product (**6**) (Scheme 1) (ratio 3:7) (see also Sections IV and V).[40] 3-Methoxy-5-methylisoxazole metallates (BuLi/THF/-75 °C) predominantly in its methyl group but a small amount of 3-methoxy-5-methylisoxazole-4-carboxylic acid is obtained after carbonation.[39] 3,5-Diphenyl- and 3-methyl-5-phenylisoxazole metallate with difficulty at position-4; low yields of trapped products are obtained, the balance being starting material.[36] If alkyl groups are present in either position-3 or -5 (as in the case of 3-methyl-5-phenylisoxazole),[35,36] then lateral metallation may predominate (see Section IV). The best route to isoxazol-4-yllithium compounds is halogen → metal exchange (see Section III).

3,4-Diphenyl- and 3-phenylisoxazole are metallated by butyllithium or lithium 2,2,6,6-tetramethylpiperidide (LiTMP), respectively, in the free position-5, but the resulting 5-lithiated intermediates undergo ring-cleavage,



(12) **(13)**

Scheme 3

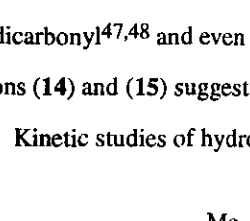
even at -60 °C, to give lithium phenylethynolate (**7**) (Scheme 2) and the dilithiated ketene (**12**) (Scheme 3), respectively.[41-43] Chlorotrimethylsilane traps the former product (**7**), to give ketene (**8**) (41% yield). Successive addition of an aldehyde or ketone, then an alkyl halide, yields a lactone (**9**) (51-79%) (Scheme 2; Table III)[42] whilst addition of an imine ($R^1N{=}CHR^2$) yields a lactam (**11**) through a highly stereoselective addition to the presumed initial intermediate (**10**) (Scheme 2; Table IV).[43] The dilithiated ketene (**12**) is trapped with chlorotrimethylsilane or -stannane, to yield ketenes (**13**; X = Si or Sn) (Scheme 3). 3,4-Dimethylisoxazol-5-yllithium similarly is unstable.[44]

III HALOGEN → LITHIUM EXCHANGE REACTIONS

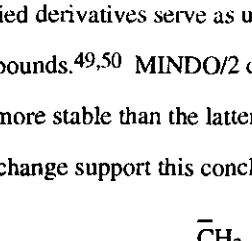
Whilst a number of 4-substituted isoxazoles have been prepared from 4-bromo- or 4-iodoisoxazoles *via* halogen → lithium exchange followed by quenching the reaction mixture with an electrophile (Table V), we are not aware of any examples involving a 3- or 5-halogenoisoxazole. When there are bulky substituents in either position-3 or -5 of the isoxazole (e.g. Ph)[36] or the quenching reagent is bulky,[36,45] steric hindrance reduces yields.

IV LATERAL METALLATION

Following the early work of Micetich[46] lateral metallation, particularly of 3,5-dimethylisoxazole (for reviews see refs. 27, 28, 31), has received considerable attention. Modified derivatives serve as useful precursors for the synthesis of 1,3-dicarbonyl[47,48] and even polycarbonyl compounds.[49,50] MINDO/2 calculations of the heats of formation of anions (**14**) and (**15**) suggest that the former is more stable than the latter by about 7-8 Kcal/mol.[27,31,51] Kinetic studies of hydrogen-deuterium exchange support this conclusion.[27,36,51]



(**14**)



(**15**)

However, the 5-methyl group in 3,5-dimethylisoxazole is less reactive than those in 2-methylpyridine or 2-methylquinoline.[51] The anion (**14**) can be generated with butyllithium (reagent system A in Table VI), LDA (B) or $LiNEt_2$ (E) in THF at -70 °C or with lithium amide (C) or sodium (D) in liquid ammonia. In THF at 0 °C the

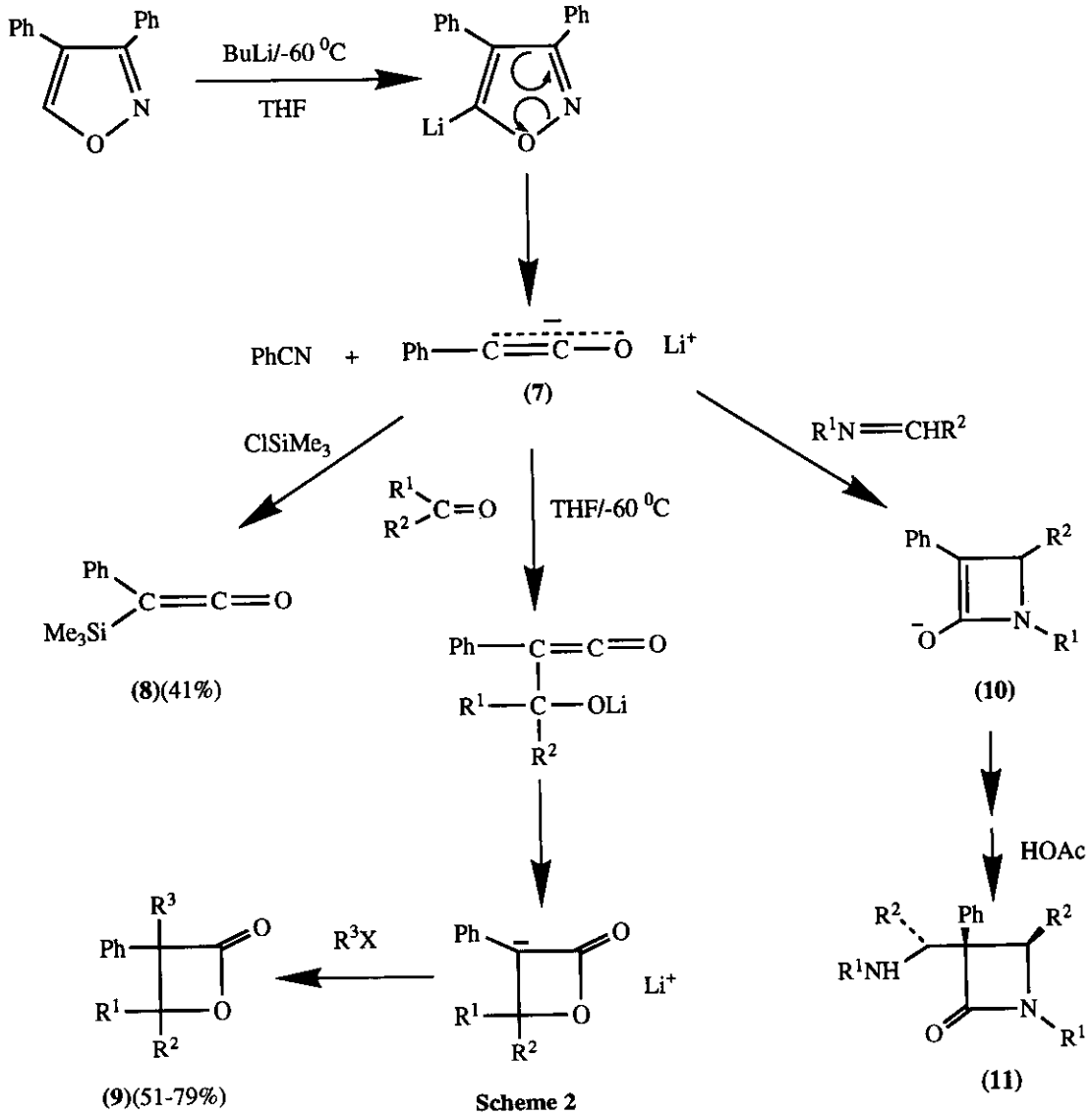

BuLi/-60 °C
THF
PhCN
(7)
ClSiMe3
(8)(41%)
THF/-60 °C
R1N=CHR2
(10)
HOAc
(11)
R3X
(9)(51-79%)
Scheme 2

Table III

β-LACTONES (9) PREPARED FROM 3,4-DIPHENYLISOXAZOLE[42]

R^1	R^2	R^3	Yield (%)
Me	Me	H	59
$-(CH_2)_5-$		H	51
Bu-*t*	H	H	65 (*trans*)
Ph	H	H	60
Ph	H	CH(OH)Ph	79 (mixt. diastereomers)
Me	Me	CH_2Ph	56
Ph	H	CH_2Ph	68

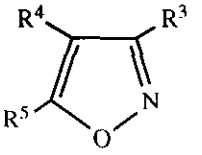
Table IV

β-LACTAMS (11) PREPARED FROM 3,4-DIPHENYLISOXAZOLE[43]

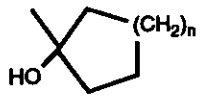
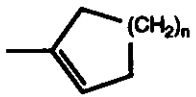
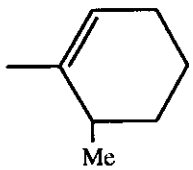
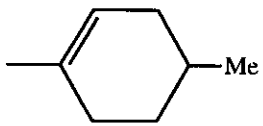
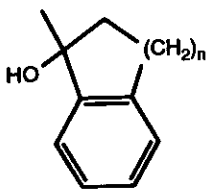
R^1	R^2	Yield (%)
cyclohexyl	H	60
cyclohexyl	Me	64
cyclohexyl	Et	68
cyclohexyl	Pr	54
cyclohexyl	C_7H_{15}	57
$PhCH_2$	Me	51
$PhCH_2$	Et	60
$C_6H_4NO_2$-4	Ph	66
$C_6H_4NO_2$-4	$C_6H_4NO_2$-4	89
$C_6H_4NO_2$-4	C_6H_4Me-3	58
$C_6H_4CO_2Et$-4	$C_6H_4NO_2$-4	79

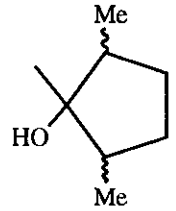
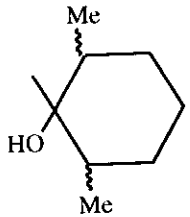
Table V

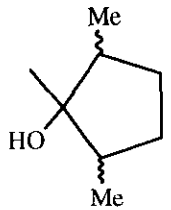
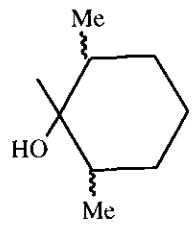
4-SUBSTITUTED ISOXAZOLES PREPARED BY HALOGEN → *LITHIUM* EXCHANGE REACTIONS



R^3	R^4	R^5	Reagent	Yield (%)	Ref.
Me	CHO	Me	$HCONMe_2$	75	36
Me	CO_2H	Me	CO_2	96	36
Me	CO_2Et	Me	$ClCO_2Et$	73	36
Me	CO_2Et	Me	$CO(OEt)_2$	86	36
Me	COMe	Me	$MeCONMe_2$	64	36
Me	COPh	Me	$PhCONMe_2$	41	36
Me	C(=NH)Ph	Me	PhCN	85	36
Me	CH(OH)Me	Me	MeCHO	60	36
Me	CH(OH)Et	Me	EtCHO	59	36
Me	$CH(OH)CH=CH_2$	Me	$CH_2=CHCHO$	50	36
Me	CH(OH)CH=CHPh	Me	PhCH=CHCHO	90	36
Me	C(OH)MeEt	Me	MeCOEt	70	36
Me	C(OH)MePh	Me	MeCOPh	64	36

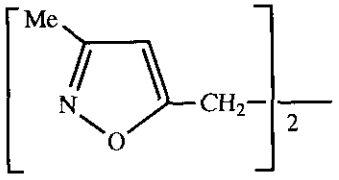
Me	C(OH)PhCH=CHPh	Me	PhCH=CHCOPh	95	36
Me	C(OH)MeCH=CMe_2	Me	Me_2C=CHCOMe	95	36
Me		Me	cyclopentanone	72 (n=1)[a]	36
			cyclohexanone	69, 75 (n=2)[a]	36, 45
Me		Me	cyclo-octanone	65 (n=4)[a]	52
			cyclododecanone	70 (n=8)	52
			cyclopentadecanone	80 (n=11)	52
Me		Me	2-methylcyclohexanone	70	45
Me		Me	4-methylcyclohexanone	75	45
Me		Me	indanone	80 (n=1)	52
			1-tetralone	82 (n=2)	52
			benzocycloheptanone	70 (n=3)[a]	52

Me		Me	2,5-dimethylcyclopentanone	52[b]	53
Me		Me	2,6-dimethylcyclohexanone	35[c], 58[b]	45, 53
Me	CH(OH)Ph	Me	PhCHO	80	36
Me	$CH(OH)C_6H_4Me$-2	Me	2-MeC_6H_4CHO	–	54
Me	$CH(OH)C_6H_4Pr^i$-4	Me	4-$Pr^iC_6H_4CHO$	–	54
Me	$CH(OH)C_6H_4Cl$-2	Me	2-ClC_6H_4CHO	–	54
Me	$CH(OH)C_6H_4NO_2$-2	Me	2-$O_2NC_6H_4CHO$	78	55
Me	[d]	Me	$MeCO_2Et$	38	36
Me	[d]	Me	$PrCO_2Et$	44	36
Me	$SiMe_3$	Me	Me_3SiCl	72	44
Me	$SnMe_3$	Me	Me_3SnCl	69	44
Me	$SnBu_3$	Me	Bu_3SnCl	51	56
Me	CHO	Ph	$HCONMe_2$	45	36
Me	CO_2H	Ph	CO_2	60, 70[e]	36

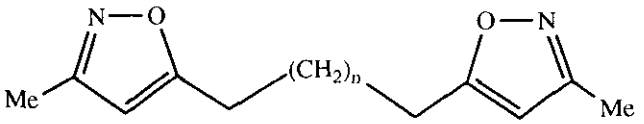
Me	CH(OH)Et	Ph	EtCHO	20	36
Me	CH(OH)Ph	Ph	PhCHO	25	36
Me		Ph	2,5-dimethylcyclopentanone	18[b]	53
Me		Ph	2,6-dimethylcyclohexanone	15[b]	53
Ph	D	Ph	D_2O	45	57
Ph	CHO	Ph	$HCONMe_2$	30	36
Ph	CO_2H	Ph	CO_2	80	36
Ph	CH(OH)Et	Ph	EtCHO	48	36
Ph	CH(OH)Ph	Ph	PhCHO	15	36

[a] Products isolated were alkenes formed by dehydration of carbinols. [b] Products were *meso*-1*S**,2*R**,5(or 6)*S**-2,5(or 6)-dimethyl-1-[3'-methyl-5'-methyl(or phenyl)isoxazol-4'-yl]cycloalkan-1-ols. [c] Reported to be a mixture of stereoisomers; 3-methyl-5-pentylisoxazole is produced also *via* a translithiation process, the amount obtained depending on the length of time between addition of BuLi and quenching. [d] Products were (3,5-dimethylisoxazol-4-yl)$_2$C(OH)R, R = Me or Pr, respectively. [e] 60% when quenched after 15 min, 70% after 75 min.

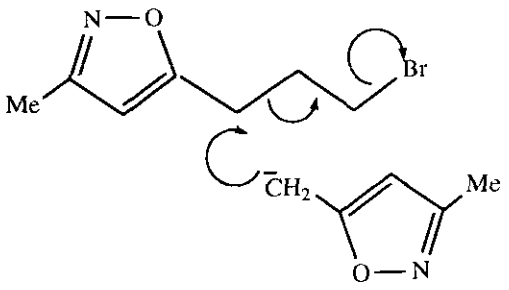
lithium derivative decomposes within 30 min.[48] However, THF is the preferred solvent for generation of the lithium derivative; in ether lower yields of quenched products are obtained. The acidity of protons in a 5-methyl group are decreased by electron-donating substituents at position-4 and increased by electron-withdrawing substituents at this position, as expected.[31,51] Table VI lists some of the products that can be prepared by quenching anion (**14**) with electrophiles. Iodine couples the anion, to give dimer (**16**).[46] 3,5-Dimethylisoxazol-4-yllithium, the kinetic product of halogen → lithium exchange reactions of the 4-bromo and 4-iodo derivatives, has been reported to undergo a transmetallation reaction, yielding anion (**14**).[45]



(**16**)



(**17**)



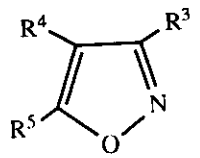
(**18**)

Successive treatment of 3,5-dimethylisoxazole with 1 mol. equiv. of either butyllithium in THF[27] or sodium amide in liquid ammonia (see also later)[27,31,47] and an α,ω-dibromoalkane results in coupling, to give compounds (**17**; n = 3) (84% yield), (**17**; n = 4) (77%), and (**17**; n = 5) (70%) except in the case of 1,2-dibromoethane in which case the reaction proceeds as shown **18**, to give the dimer (**16**) (39%).

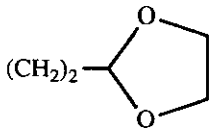
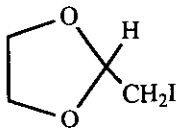
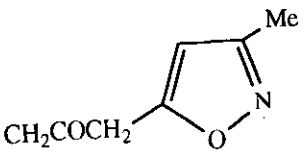
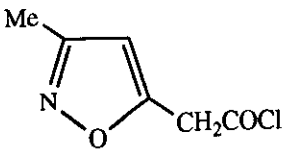
Addition of anion (**14**) (generated with $NaNH_2$/liquid NH_3) to the C=N bond of Schiff's bases occurs, as shown (Scheme 4), to give mixtures of 1:1- (**19**; Ar = Ph, 31% yield: Ar = 4-MeC_6H_4, 13%) and 1:2-adducts (**20**; Ar = Ph, 49%: Ar = 4-MeC_6H_4, 56%).[27,31,95] The yields of (**19**; Ar = Ph) and (**19**; Ar = 4-MeC_6H_4) are 15% and 9%, respectively, when **14** is generated with butyllithium in THF. With *N,N-bis*(4-tolyl)ethylene-diimine only the 2:1 adduct (**21**) (66% yield) is obtained.[95] Addition of anion (**14**) (generated with

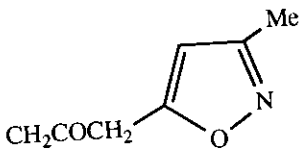
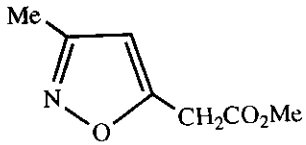
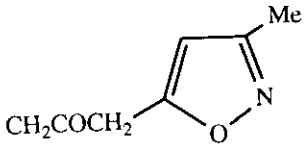
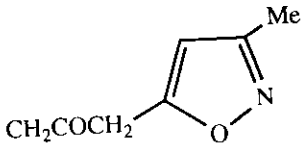
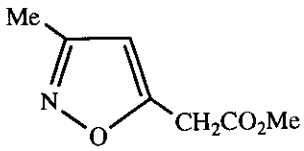
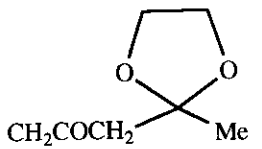
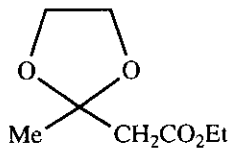
Table VI

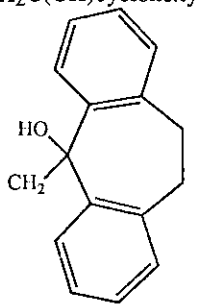
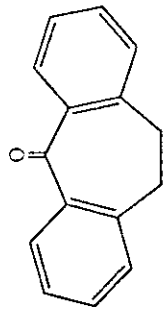
ISOXAZOLES PREPARED BY LATERAL METALLATION OF 5-ALKYLISOXAZOLES[a]



R^3	R^4	R^5	Reagent	Yield (%)	Ref.
Me	H	CH_2D	D_2O	37	31, 57
Me	H	Et	MeI (A, D)	75, 70	27, 31, 47, 48, 58
Me	H	Pr	EtBr (D)	45	31, 47
Me	H	Bu	PrBr (D)	61	31, 47
Me	H	CH_2CHMe_2	Me_2CHBr (A, D)	–	31, 47
Me	H	Bu-*t*	MeI (D)	51	31, 47
Me	H	$(CH_2)_4Me$	BuI (A)	90	48
Me	H	$(CH_2)_2Ph$	$PhCH_2Cl(Br)$ (A, A, D)	62, 98, 70	46, 48, 47, 31
Me	H	$(CH_2)_7OC_6H_3Cl(MeO)$-2,4	2,4-$Cl(MeO)C_6H_3(CH_2)_6Br$	–,59[b]	59, 60
Me	H	$CH_2C_6F_5$	C_6F_6 (A)	20 (see text)	61
Me	H	$CH(C_6F_5)_2$	C_6F_6 (A)	31 (see text)	61
Me	H	$(CH_2)_{11}I$	$I(CH_2)_{10}I$ (A)	78	48

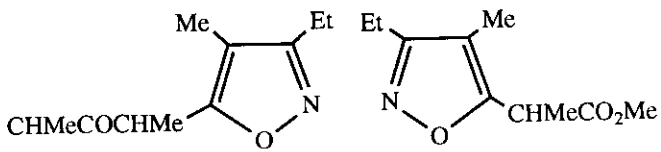
Me	H	$(CH)_2CH{=}CH_2$	$CH_2{=}CHCH_2Br$ (A, D)	97, 44	48, 47, 31
Me	H		 (A)	82	48
Me	H	CH_2SMe	MeSCl (A)	36	62
Me	H	CH_2SMe	Me_2S_2 (A)	87	63, 64
Me	H	CH_2CO_2H	CO_2 (A)	73	46
Me	H	CH_2CO_2Me	CO_2, CHN_2 (A)	–	50
Me	H	$CH(CO_2Me)_2$	$NC{\cdot}CO_2Me$ (D)	–	27, 65
Me	H	CH_2COCl	$COCl_2$ (A)	–	50
Me	H	CH_2COMe	$MeCO_2Et$ (C, D)	40, –	66, 27, 31
Me	H	CH_2COPh	$PhCO_2Me$ (A, C, D)	75, –	46, 66, 27, 31
Me	H	CH_2COPh	PhCN (A, D)	71, 40	46, 66
Me	H	$CH_2COC_6H_2Me(OMe)OH$-2,4,6	2,4,6-Me(MeO)(NaO)-$C_6H_3CO_2Et$ (A)	63	67
Me	H	CH_2CO(3-methylisoxazol-5-yl)	(3-methylisoxazol-5-yl)-CO_2Me (A)	75	46
Me	H	CH_2CO(pyrid-2-yl)	(pyrid-2-yl)CO_2Me (A)	79	68
Me	H		 (A)	25	50

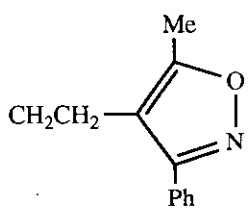
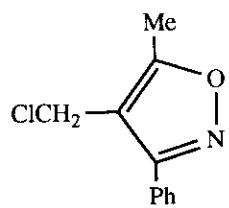
Me	H			(A)	10,36	50, 69, 27, 31
Me	H		$COCl_2$ (A)		50	50
Me	H			(A)	–	27, 49, 69
Me	H			(A,B)	55, –	49, 27, 31
Me	H	$CH_2CO(CH_2)_2CH(OH)Me$	4-pentanolide (D)		18	31, 66
Me	H	$CH_2CH(OH)CH=CH_2$	CH_2=CHCHO (C,D)		5	66
Me	H	$CH_2CH(OH)CH=CHMe$	MeCH=CHCHO (C,D)		43	66
Me	H	$CH_2CH(OH)Ph$	PhCHO (A, D)		96, 22	48, 66, 31,
Me	H	$CH_2CH(OH)C_6H_4Me$-4	4-MeC_6H_4CHO (D)		17	31, 66

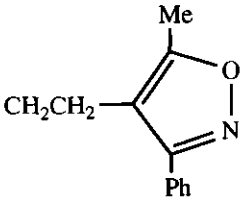
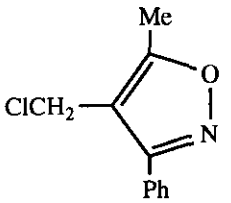
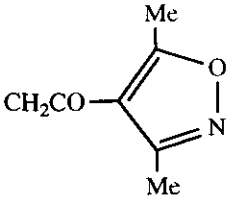
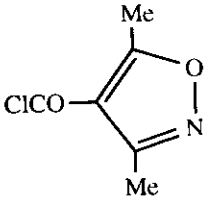
Me	H	$CH_2CH(OH)C_6H_4OMe$-4	4-$MeOC_6H_4CHO$ (D)		41	31, 66
Me	H	$CH_2CH(OH)Ar$	ArCHO		–	27
Me	H	$CH_2C(OH)Me_2$	Me_2CO (A, C)		97, 18	48, 66, 31
Me	H	$CH_2C(OH)Ph_2$	Ph_2CO (A, C)		51, –	46, 66, 31
Me	H	$CH_2C(OH)MePh$	PhCOMe		–	31
Me	H	$CH_2C(OH)$cyclohexyl	cyclohexanone (A, C)		95, 27	48, 66, 31
Me	H			(A)	60	46
Me	H	$(CH_2)_2CH(OH)Et$	2-ethyloxirane	(A, D)	87, 15	48, 47
Me	H	$CH{=}C(SMe)_2$	CS_2, MeI (A)		75	46
Me	H	$CH_2CH(OMe)Ph$	PhCHO, MeI (D)		14	31, 66
Me	H	$CH_2CH(OEt)Ph$	PhCHO, EtBr (D)		10	31, 66
Me	H	$CH_2CH(OCH_2CH{=}CH_2)Ph$	PhCHO, $CH_2{=}CHCH_2Br$ (D)		16	31, 66
Me	H	$CH_2CH(OCH_2Ph)Ph$	PhCHO, $PhCH_2Br$ (D)		23	31, 66
Me	H	$CH_2CH(OMe)C_6H_4Me$-4	4-MeC_6H_4CHO, MeI (D)		28	31, 66
Me	H	$CH_2CH(OMe)C_6H_4OMe$-4	4-$MeOC_6H_4CHO$, MeI (D)		13	31, 66
Me	H	$CH_2(OMe)Ph_2$	Ph_2CO, MeI (D)		13	31, 66

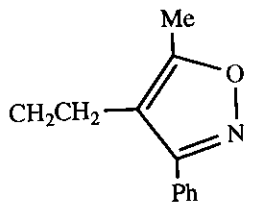
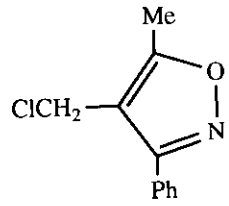
Me	H	CH_2SiMe_3	Me_3SiCl (A)	70, 80	44, 48
Me	H	$CH(OMe)CO_2H$	CO_2 (A)	50	34
Me	H	CHMeSMe	Me_2S_2 (A)	65	34
Me	H	$CH(SMe)CO_2H$	CO_2 (A)	60	34
Me	H	CH(SMe)CH(OH)Ph	PhCHO (A)	95	62
Me	H	$CH(SMe)_2$	Me_2S_2 (A)	62	34
Me	H	$CH(C_6F_5)CO_2Me$	C_6F_6 (A)	18	61
Cl	H	$CH=CHC_6H_4OH$-2	2-$OHCC_6H_4OCHMeOMe$	51	70
Me	H	CH=NOH	$C_5H_{11}ONO$ (D)	19	71
Me	H	$CH=\overset{+}{N}(O^-)Ph$	PhNO (A)	17	71
Me	H	$CH=\overset{+}{N}(O^-)C_6H_4NMe_2$-4	4-$Me_2NC_6H_4NO$ (A)	2	71
OMe	H	CH_2CO_2H	CO_2 (A)	–,[c]	39
OMe	H	$CHMeCO_2H$	CO_2 (B)	61	72
CH_2OH	H	Et	MeI (A)	90	37
CH_2OMe	H	Et	MeI (B)	90	37
CH_2NMe_2	H	Et	MeI (B)	84	37
OH	H	CH_2CO_2H	CO_2 (B)	51	40
OH	H	CH_2CO_2Me	$CO(OMe)_2$ (B)	24	40
OH	H	CH_2CH_2Ph	$PhCH_2Cl$ (B)	72	40
OH	H	$CH_2C(OH)Ph$	Ph_2CO (B)	53[d]	40

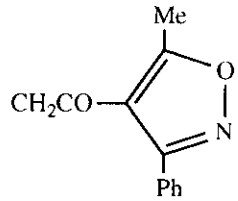
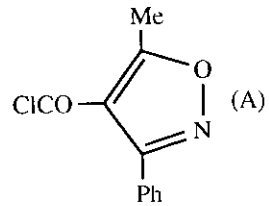
OH	H	CH_2COMe	$MeCO_2Me$ (B)	35	40
OH	H	CH_2COMe	$MeCONMe_2$ (B)	19	40
OH	H	CH_2COMe	MeCON(OMe)Me (B)	45	40
OH	H	CH_2COPh	$PhCO_2Et$ (B)	82	40
OH	H	CH_2COCH_2COPh	$PhC(ONa)=CHCO_2Et$ (B)	68	40
OH	H	CH=NOH	$C_5H_{11}ONO$	68	31, 40
Ph	H	CH_2CO_2H	CO_2 (A)	81	46
Ph	H	CH_2SMe	MeSCl (A)	90	62
Ph	H	CH_2SMe	Me_2S_2 (A)	91.5	63
Ph	H	$CHMeSO_2Ph$	MeI (A)	47	73
Ph	H	$CH(CH_2CH=CH_2)SO_2Ph$	$CH_2=CHCH_2Br$ (A)	51	73
Ph	H	$CH(CH_2Ph)SO_2Ph$	$PhCH_2Br$ (A)	57	73
$C_6H_3Cl_2$-2,6	H	CH_2SMe	Me_2S_2 (A)	94	63
$C_6H_2Cl_3$-2,6	H	CHMeOPh	MeI (A)	76	34
$C_6H_3Cl_2$-2,6	H	CHMeSMe	MeI (A)	91	34
$C_6H_3Cl_2$-2,6	H	$CHSMeCH_2Ph$	$PhCH_2Cl$ (A)	84	34
$C_6H_3Cl_2$-2,6	H	CH(OMe)SMe	Me_2S_2 (A)	92	34
$C_6H_3Cl_2$-2,6	H	$CH(OPh)CO_2H$	CO_2 (A)	85	34
$C_6H_3Cl_2$-2,6	H	$CH(SMe)CO_2H$	CO_2 (A)	88	34
$C_6H_3Cl_2$-2,6	H	$CH(SMe)_2$	Me_2S_2 (A)	65	34
Me	Cl	$CH=CHC_6H_4OH$-2	2-$HOC_6H_4OCHMeOMe$ (A)	51	70

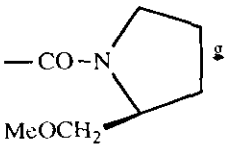
Me	Me	$CH{=}CHC_6H_4OH$-2	2-$OHCC_6H_4OCHMeOMe$ (A)	–	70
Me	Me	CH_2SiMe_3	Me_3SiCl (A)	60	44
Me	Me	CH_2SnMe_3	Me_3SnCl (A)	75	44
Me	Me	CH_2SMe	Me_2S_2 (A)	37	63
Me	CH_2OH	Et	MeI (A)	30	37
Me	$(CH_2)_3OMe$	$CH_2C_6F_5$	C_6F_6 (A)	9 (see text)	61
Me	$(CH_2)_3OMe$	$CH(C_6F_5)_2$	C_6F_6 (A)	7 (see text)	61
Me	CH_2ONH_2	Et	MeI (A)	68	37
Me	CH_2NMe_2	Et	MeI (A)	90	37
Me	CH_2NHCO_2Bu-*t*	Et	MeI (A)	85	37
Me	CH_2NEtCO_2Bu-*t*	Et	MeI (A)	86	37
Et	Me	$CHMeCO_2Me$	CO_2, CH_2N_2 (A, B, E)	–	49
Et	Me		(B, E)	–	49, 69
OH	CO_2Me	CH_2CO_2H	CO_2 (B)	–	74
OMe	Me	CH_2CO_2H	CO_2 (A)	–	39
OMe	Et	CH_2CO_2H	CO_2 (A)	–	39
OMe	Me	$CHMeCO_2H$	CO_2 (B)	84	72
C_6H_4OTHP-4	C_6H_4OMe-4	CH_2CO_2H	CO_2 (A)	35	75

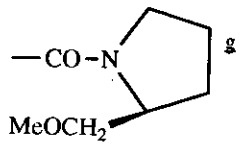
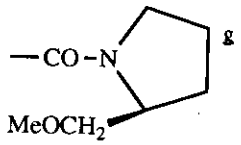
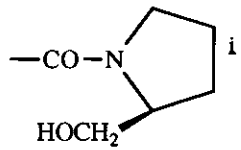
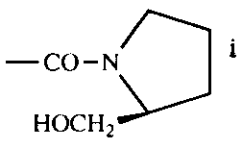
C_6H_4OMe-4	C_6H_4OTHP-4	CH_2CO_2H	CO_2 (A)	39	75
C_6H_4OTHP-4	C_6H_4OTHP-4	CH_2CO_2H	CO_2 (A)	20	75
C_6H_4OMe-4	C_6H_4OMe-4	CH_2CO_2H	CO_2 (A)	–	76
OH	CO_2Me	CH_2CO_2H	CO_2 (B)	–	74
Me	CO_2H	CH_2D	MeOD (A)	83	77
Me	CO_2H	Et	MeI (A)	91	77
Me	CO_2H	$CHMe_2$	MeI (A)	92	77
Me	CO_2H	$(CH_2)_2Ph$	$PhCH_2Br$ (A)	88	77
Me	CO_2H	$(CH_2)_8Me$	$C_8H_{17}Br$ (A)	69	77
Ph	CO_2H	CH_2D	MeOD (A)	99	77
Ph	CO_2H	Et	MeI (A)	81	77
Ph	CO_2H	$CHMe_2$	MeI (A)	89, –	77, 78,
Ph	CO_2H			(A) 53	77
Me	ox.[e]	CH_2D	MeOD (A)	82-89	77, 79
Me	ox.	Et	MeI (A, B)	78-86, 92	77, 79
Me	ox.	CH_2Ph	$PhCH_2Br$ (A, B)	91, 49	77, 79
Me	ox.	$(CH_2)_8Me$	$C_8H_{17}Br$ (A, B)	82	77, 79

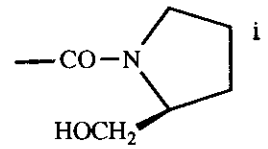
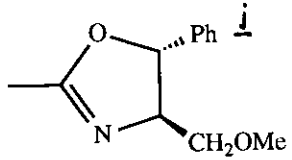
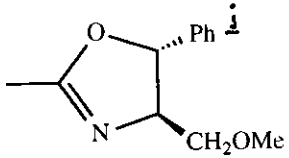
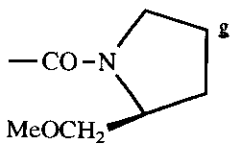
Me	ox.			(A)	72	77, 79
Me	ox.	CH_2OH	MOOPH[f] (A)		32-53	77, 79
Me	ox.	$CH_2CH(OH)Ph$	PhCHO (A)		97	77, 79
Me	ox.	CH_2COPh	PhCOCl (A)		70	80
Me	ox.	CH_2CO(2-furyl)	2-furylCO (A)		65	80
Me	ox.			(A)	53	80
Me	ox.	CH_2SPh	Ph_2S_2 (A)		50	81
Me	ox.	CH_2S(pyrid-2-yl)	(pyrid-2-yl)$_2S_2$ (A)		55	81
Me	ox.	$CH_2N(CO_2Et)NHCO_2Et$	$EtO_2CN{=}NCO_2Et$ (A)		75	82
Me	ox.	CH_2SiPh_2Bu-*t*	*t*-$BuPh_2SiCl$ (A)		34	83
Et	ox.	Et	MeI (A)		74	77, 79
Ph	ox.	CH_2D	MeOD (A)		72	77, 79

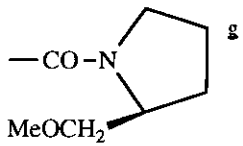
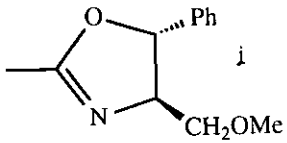
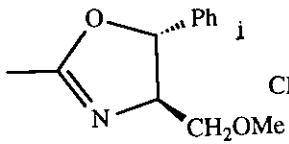
Ph	ox.	Et	MeI (A, B, D)	86-92, 36, 89	77, 79
Ph	ox.	$(CH_2)_4Cl$	$Cl(CH_2)_3Br$ (A)	81, 61	77, 79
Ph	ox.	$(CH_2)_2C_6H_4Br$-2	2-$BrC_6H_4CH_2Br$ (A)	98	77, 79
Ph	ox.	$(CH_2)_2C_6H_3Cl_2$-2,6	2,6-$Cl_2C_6H_3CH_2Cl$ (A)	89	77, 79
Ph	ox.		 (A)	67	77, 79
Ph	ox.	$CH_2CH(OH)Ph$	PhCHO (A)	81	77
Ph	ox.	$CH_2CH(OH)C_6H_4Cl$-2	2-ClC_6H_4CHO (A)	50	77
Ph	ox.	$CH_2CH(OH)C_6H_3(OMe)_2$-2,5	2,5-$(MeO)_2C_6H_3CHO$ (A)	77	77
Ph	ox.	$CH_2CH(OH)C_6H_4CN$-4	4-NCC_6H_4CHO (A)	40	77
Ph	ox.	$CH_2CH(OH)C_6H_4Br$-4	4-BrC_6H_4CHO (A)	66	77
Ph	ox.	$CH_2CH(OH)C_6H_4NO_2$-4	4-$O_2NC_6H_4CHO$ (A)	50	77
Ph	ox.	$CH_2CH(OH)$(pyrid-3-yl)	pyrid-3-ylCHO (A)	66	77
Ph	ox.	CH_2COPh	PhCOCl (A)	67	80
Ph	ox.	$CH_2COC_6H_4CN$-4	4-NCC_6H_4COCl (A)	60	80

Ph	ox.		 (A)	61	80
Ph	ox.	CH_2SMe	Me_2S_2 (A)	60-65	81
Ph	ox.	CH_2SPh	Ph_2S_2 (A)	55-60	81
Ph	ox.	CMe_2SPh	Ph_2S_2 (A)	73	81
Ph	ox.	CHDSPh	D_2O (A)	77	81
Ph	ox.	$CH_2N(CO_2Et)NHCO_2Et$	$EtO_2CN{=}NCO_2Et$ (A)	80	82
Ph	ox.	CH_2SiMe_3	Me_3SiCl (A)	97	77, 79
Ph	ox.	CH_2SiMe_2Bu-*t*	*t*-$BuMe_2SiCl$ (A)	78	83
Me	CONHMe	$CH_2CH(OH)Ph$	PhCHO (A)	–	84
Et	CONHMe	$CH_2CH(OH)Ph$	PhCHO (A)	–	85, 86
Me	$CONPr^i_2$	CH_2D	MeOD (A)	86	87
Me	$CONPr^i_2$	Et	MeI (A)	55	87
Me	$CONPr^i_2$	$CH_2C_6F_5$	C_6F_6 (A)	42 (see text)	61
Me	$CONPr^i_2$	$CH(C_6F_5)_2$	C_6F_6 (A)	7 (see text)	61
Me	$CONPr^i_2$	$CH_2CH(OH)C_6H_4Br$-4	4-BrC_6H_4CHO (A)	43	87
Me	$CONPr^i_2$	$CH_2CH(OH)C_6H_4CN$-4	4-NCC_6H_4CHO (A)	48	87

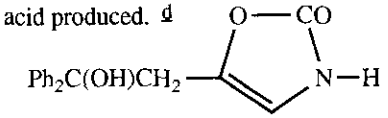
Me	$CONPr^i_2$	$CH_2CH(OH)C_6H_4NO_2$-4	4-$O_2NC_6H_4CHO$ (A)	37	87
Me	$CONPr^i_2$	$CH_2CH(OH)$(2-furyl)	2-furylCHO (A)	70	87
Me	$CONPr^i_2$	$CH_2CH(OH)$(pyrid-3-yl)	pyrid-3-ylCHO (A)	62	87
Me	$CONPr^i_2$	CH_2COPh	PhCOCl (A)	50	80
Me	$CONPr^i_2$	CH_2SPh	Ph_2S_2 (A)	65	81
Me	$CONPr^i_2$	CHMeSMe	Me_2S_2 (A)	82	81
Me	$CONPr^i_2$	$CH_2N(CO_2Et)NHCO_2Et$	$EtO_2CN{=}NCO_2Et$ (A)	96	82
Me	$CONPr_2$	$CH_2N(CO_2Bu$-$t)NHCO_2Bu$-t	t-$BuO_2CN{=}NCO_2Bu$-t (A)	81	82
Ph	CONHMe	$CH_2CH(OH)Ph$	PhCHO (A)	–	88, 89, 90,
Ph	CONHMe	CH_2COPh	PhCN (A)	–	91
Ph	CONHMe	CH_2CO(pyrid-2-yl)	pyrid-2-ylCO_2Et (A)	–	92
Ph	$CONPr^i_2$	CH_2D	MeOD (A)	88	87
Ph	$CONPr^i_2$	Et	MeI (A)	70	87
Ph	$CONPr^i_2$	$CH_2C_6F_5$	C_6F_6 (A)	39 (see text)	61
Ph	$CONPr^i_2$	$CH(C_6F_5)_2$	C_6F_6 (A)	24 (see text)	61
Ph	$CONPr^i_2$	$CH_2CH(OH)C_6H_4Br$-4	4-BrC_6H_4CHO (A)	40	87
Ph	$CONPr^i_2$	CH_2SiMe_2Bu-t	t-$BuMe_2SiCl$ (A)	41	83
Ph	$CON(CH_2Ph)_2$	CH_2SiMe_2Bu-t	t-$BuMe_2SiCl$ (A)	63	83
Me		CH_2SiMe_2Bu-t	t-$BuMe_2SiCl$ (A)	32	83

Me	 g	CH_2D	D_2O (A)	55,95[h]	93
CH_2D	 g	Me	D_2O (A)	93[h]	93
Me	 i	CH_2D	D_2O (A)	> 95	93
Me	 i	$CH(SPh)_2$	Ph_2S_2 (A)	66	81

Me		$CH_2N(CO_2Et)NHCO_2Et$	$EtO_2CN{=}NCO_2Et$ (A)	78	82
Me		CH_2SPh + $CH(SPh)_2$	Ph_2S_2 (A)	60, 10	81
Me		$CH_2N(CO_2Et)NHCO_2Et$	$EtO_2CN{=}NCO_2Et$ (A)	74	82
Ph	CO(piperidino)	CH_2D	MeOD (A)	90	87
Ph	CO(piperidino)	Et	MeI (A)	66	87
Ph	CO(piperidino)	$CH_2CH(OH)C_6H_4Br$-4	4-BrC_6H_4CHO (A)	48	87
Ph	CO(morpholino)	CH_2D	MeOD (A)	91	87
Ph	CO(morpholino)	Et	MeI (A)	72	87
Ph	CO(morpholino)	$CH_2CH(OH)C_6H_4Br$-4	4-BrC_6H_4CHO (A)	60	87
Ph	$CON(CH_2Ph)_2$	Et	MeI (A)	62	87
Ph		CH_2D	MeOD (A)	97	87

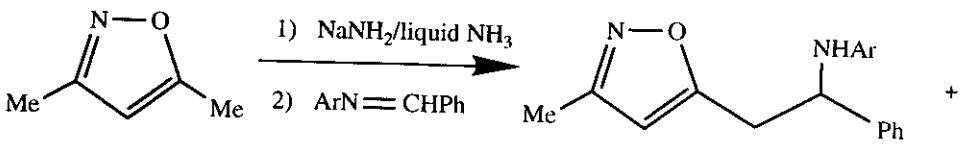
Ph	 g	$(CH)_2Ph$	$PhCH_2Br$ (A)	56	87
Ph	 i	CH_2SPh + $CH(SPh)_2$	Ph_2S_2 (A)	55, 15	81
Ph	 i	$CH_2N(CO_2Et)NHCO_2Et$	$EtO_2CN{=}NCO_2Et$ (A)	95	82
Me	DHP[k]	$CH(CH_2Ph)SO_2Me$	$PhCH_2Br$ (B)	56	94
Me	DHP[k]	$CH(Me)SO_2Ph$	MeI (B)	62	94
Me	DHP[k]	$CH(CH_2Ph)SO_2Ph$	$PhCH_2Br$ (B)	75	94
Me	DHP[k]	$CH(CH_2C_6H_4Br\text{-}3)SO_2Ph$	$3\text{-}BrC_6H_4CH_2Br$ (B)	72	94
Me	DHP[k]	$CH(CH_2C_6H_4OMe\text{-}3)SO_2Ph$	$3\text{-}MeOC_6H_4CH_2Br$ (B)	83	94
Me	DHP[k]	$CH(SO_2Ph)N(CO_2Bu\text{-}t)NLiCO_2Bu\text{-}t)$	$t\text{-}BuO_2CN{=}NCO_2Bu\text{-}t$	—[l]	94

[a] Reagents in parentheses: A = BuLi/THF/low temperature; B = LDA/THF/low temperature; C = $LiNH_2$/liquid NH_3; D = $NaNH_2$/liquid NH_3; E = $LiNEt_2$/THF/-70 °C. [b] Several other compounds with $R^5 = (CH_2)_nOAr$ prepared similarly. [c] Major product: some 3-methoxy-5-methylisoxazole-4-carboxylic acid produced. [d]

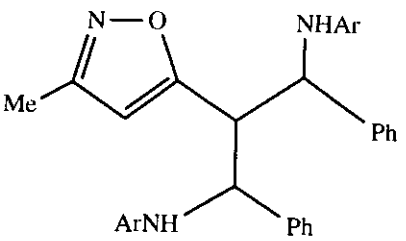


produced also by rearrangement. [e] ox. = 4,4-dimethyl-Δ^2-oxazolin-2-yl. [f] MOOPH = molybdenumoxodiperoxy pyridine HMPA complex [*N*-phenylsulfonyloxaziridene gives similar results]. [g] The (*S*)-2'-methoxymethylpyrrolidinyl carboxamide. [h] Kinetic control (BuLi/THF/TMEDA/-78°C) favors (93:7) deuteriation in the C-3 methyl group whilst thermodynamic control (BuLi/THF/-78°C) favours deuteriation in the C-5 methyl group; ratio 55:45 after 1 h and 95:5 after 2 h. [i] Tertiary amide of (*S*)-prolinol. [j] The 4-substituent is 4'-(*S*)-methoxymethyl-5'-(*S*)-phenyl-Δ^2-oxazolin-2-yl. [k] DHP = 3,5-diethoxycarbonyl-1,4-dihydro-2,6-dimethylpyridin-4-yl [see compound (**80**), the precursor]. [l] Initial product reacts further.

$NaNH_2$/liquid NH_3) to benzonitrile yields adduct (**22**) (49% yield) which is hydrolysed readily to ketone (**23**) (95%) (Scheme 5).[27,31,95]

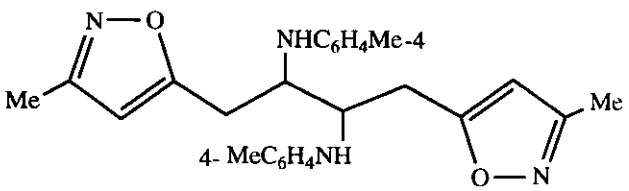


(19)

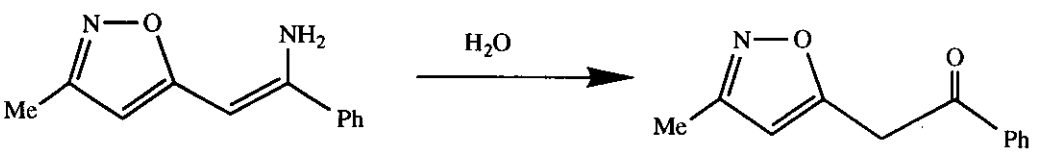


(20)

Scheme 4



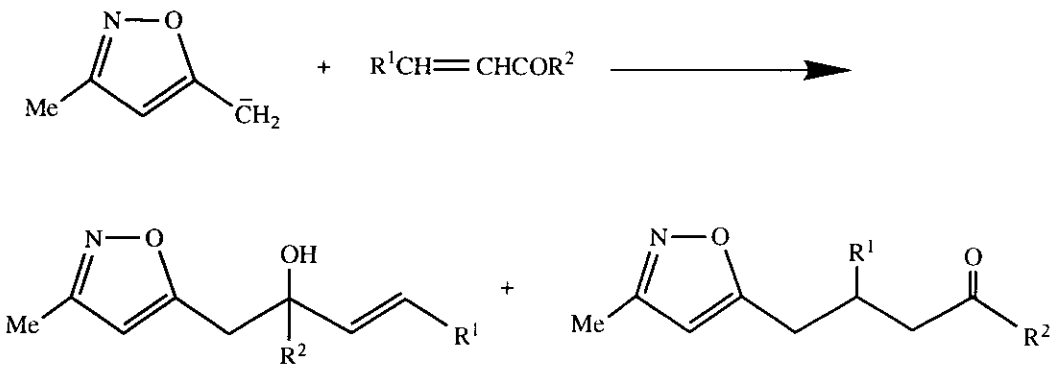
(21)



(22) **(23)**

Scheme 5

When anion (**14**) is generated using either lithium amide or sodium amide in liquid ammonia and reacted with α,β-unsaturated ketones, both Michael addition and addition to the carbonyl group can occur to give mixtures of the 1:1-adducts (**24**) and (**25**) (Scheme 6) ($R^1 = R^2 = Ph$; 35 and 11% : $R^1 = H$, $R^2 = Me$; 6 and 8% : and $R^1 = Ph$, $R^2 = H$; 38% and a trace, respectively).[31,66]



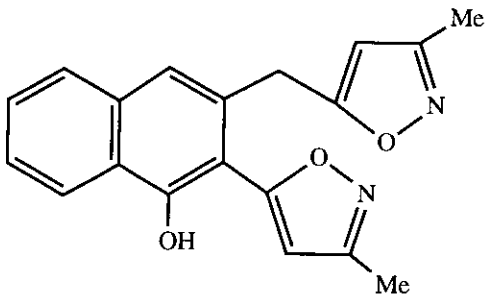
(**24**) (**25**)

Scheme 6

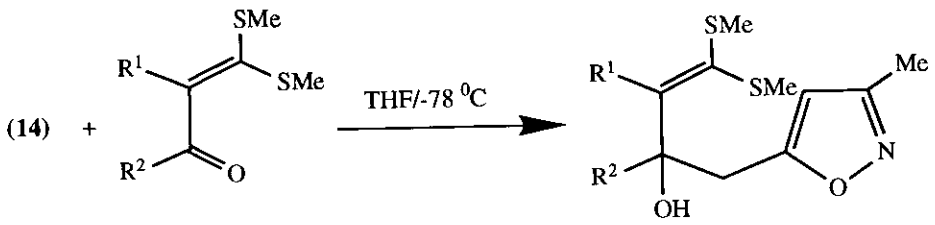
Acrylaldehyde and crotonaldehyde give only **24** ($R^1 = R^2 = H$; 5% : and $R^1 = Me$, $R^2 = H$; 43%, respectively) whilst methyl cinnamate gives only **25** ($R^1 = Ph$, $R^2 = OMe$; 10%). With 2 mol. equiv. of lithium amide even cinnamic acid reacts to give a low yield (4%) of adduct (**25**) ($R^1 = Ph$, $R^2 = OH$).[66]

In addition to recovered starting material (40%) and 3-methylisoxazole-5-carboxamide (15%), the oxime of 3-methylisoxazole-5-carbaldehyde (19%) is obtained when 3,5-dimethylisoxazole (in Et_2O) is treated successively with sodamide (liquid NH_3) and amyl nitrite.[27,71] After treatment of 3,5-dimethylisoxazole with either sodamide or butyllithium, the derived anion forms nitrones with nitrosobenzene (17% yield) or 4-dimethylaminonitroso-benzene (only 2% yield).

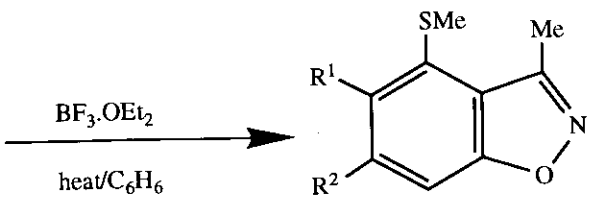
Anion (**14**) reacts with $2\text{-}MeO_2CC_6H_4CH_2CO_2Me$ to give naphthalene derivative (**26**)[96] and with α-oxoketene dithioacetals with the general structure (**27**) (20 examples) to give 1:1-adducts (**28**) which cyclise in hot benzene in the presence of boron trifluoride diethyl etherate, yielding the benzisoxazoles (**29**) (Scheme 7).[97,98] Dethiomethylation of these products with Raney nickel proved not to be possible. However, the corresponding 4-unsubstituted products were synthesised similarly by reacting anion (**14**) with β-methylthio-α,β-unsaturated ketones (**27**) (one SMe = H).[98]



(26)



(27) (28)



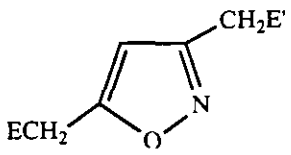
(29)

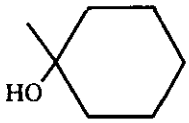
Scheme 7

Following the introduction of one substituent into the 5-methyl group of 3,5-dimethylisoxazole *via* lateral metallation with butyllithium (THF/-78 °C) Brunelle reported that a second substituent could be introduced into the 3-methyl group, providing that the second lateral metallation was carried out under kinetic control with *t*- or *sec*-butyllithium (Et_2O or THF) (Table VII).[48]

Table VII

3,5-DISUBSTITUTED ISOXAZOLES PREPARED *VIA* DIMETALLATION OF 3,5-DIMETHYLISOXAZOLE[48]

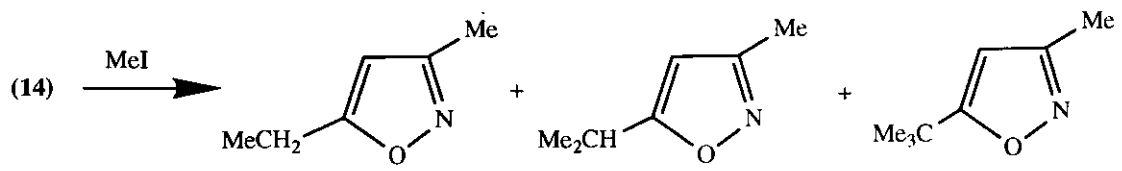


CH_2E	E'	Reagent (for E')	Yield (%)
Et	Me	MeI (BuLi)	4[35]
Bu	Pr	PrBr (BuLi)	8[35]
n-C_5H_{11}	Me	MeI (*t*-BuLi, *sec*-BuLi)	50, 92
n-C_5H_{11}	$CH_2CH{=}CH_2$	$CH_2{=}CHCH_2Br$ (*sec*-BuLi)	80
n-C_5H_{11}	CH(OH)Ph	PhCHO (*t*-BuLi)	93
n-C_5H_{11}		cyclohexanone (*sec*-BuLi)	80
n-C_5H_{11}	$SiMe_3$	Me_3SiCl (*sec*-BuLi)	83
CH_2CH_2Ph	Bu	BuI (*sec*-BuLi)	85
CH_2CH_2Ph	CH_2Ph	$PhCH_2Cl$ (*sec*-BuLi)	85
CH_2CH_2Ph	$SiMe_3$	$MeSi_3Cl$ (*sec*-BuLi)	90

However, other evidence presented by Micetich[46] and Kashima's group[27,47]suggests that the second substituent preferentially enters the 5-methyl group (under thermodynamic control). Table VIII summarises the results obtained when increasing amounts of sodium amide (liquid NH_3) are used followed by quenching with equivalent

Table VIII

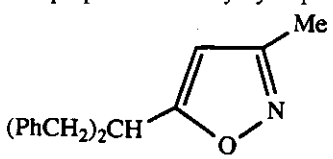
PRODUCTS OF LATERAL METALLATION OF 3,5-DIMETHYLISOXAZOLE WITH $NaNH_2$/LIQUID NH_3 FOLLOWED BY ADDITION OF MeI[27,31,47,58]



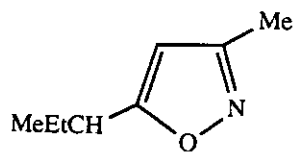
(30) (31) (32)

$NaNH_2$ (mol. equiv.)	MeI (mol. equiv.)	Yield (%)	Product ratio (30 : 31 : 32)
1	1	58	100 : 0 : 0
2	2	68	33 : 57 : 10
3	3	59	9 : 62 : 29
4	4	51	0 : 0 : 100

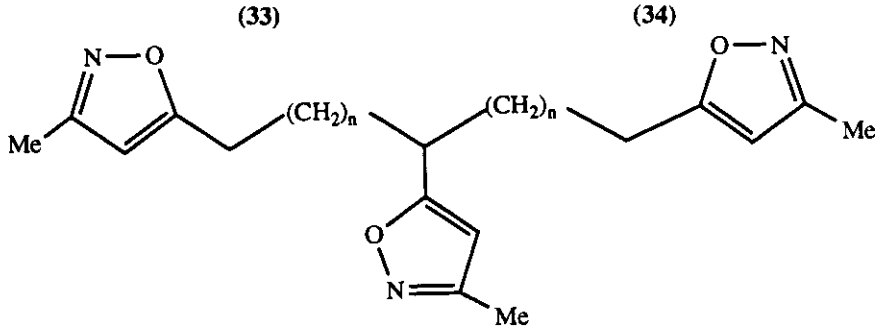
amounts of iodomethane.[27,31,47,58] Compounds such as **33** (35% yield) and **34** (12% together with other products) can be prepared similarly by stepwise introduction of substituents. When 3,5-dimethylisoxazole is



(33)



(34)

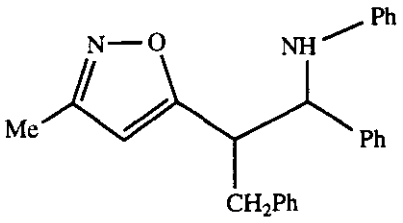


(35)

treated with 2 mol. equiv. of sodium amide in liquid ammonia, then 1,3-dibromopropane is added, the trimer (**35**; n = 3) (12% yield) is obtained together with the dimer (**17**; n = 3) (25%).[31,47] A similar result is achieved with

1,4-dibromobutane, to give trimer (**35**; n = 4) (15%) and dimer (**17**; n = 4) (19%). In the same way a benzyl group can be introduced by coupling anion (**14**) with benzyl bromide, then the second anion can be reacted with the Schiff's base PhN=CHPh, to give compound (**36**) (25% yield).[95] Stepwise reaction with benzonitrile and an alkyl halide gives compounds (**37**) which are hydrolysed readily to ketones (**38**) (Scheme 8) (R = Me, 7%; R = Et, 24%).[95]

Other 5-alkylisoxazoles are similarly metallated in the α-position (Table VI summarises the results) but metallation appears to become more difficult with increasing size of the 5-substituent. Thus, e.g., 3-methyl-5-pentyl-isoxazole does not react either with butyllithium or LDA (THF/-78°C).[48] The phenylsulphonyl group in compound (**39**) activates the α-position to metallation and, after alkylation at this position, it can be removed with sodium amalgam (see also Section V).[73] Several patents[76,99-101] claim lateral metallation of a series of 3,4-disubstituted 5-methylisoxazoles [e.g. 3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxylic acid] with butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as a route to the corresponding

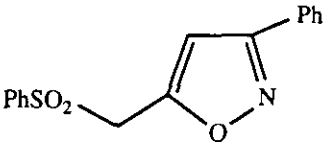


(**36**)

(**37**) (**38**)

Scheme 8

acetic acid derivatives (compounds claimed **not** listed in Table VI). Attempts to introduce a trimethylsilyl group into the 5-methyl group of 3,5-dimethyl-4-nitroisoxazole (**40**) *via* lateral metallation resulted in addition of the reagent to the 4,5-double bond, e.g. to give adduct (**41**) (50% yield) with butyllithium (Scheme 9).[102]



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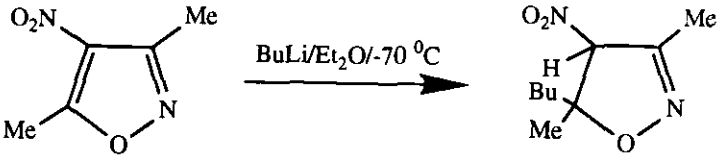
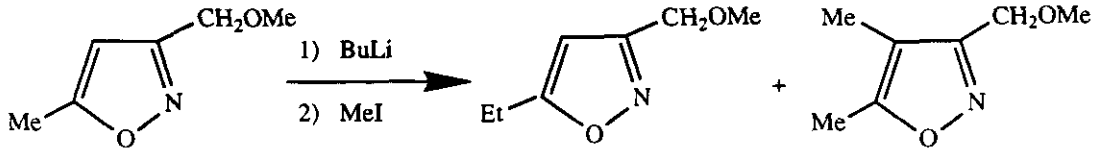


(40) (41)

Scheme 9

The role of substituents which can co-ordinate with organolithium reagents in competition with co-ordination at the ring *O*-atom in directing the position of metallation has received considerable attention, particularly from Natale's group. As long ago as 1968 Bowden *et al.*[39]reported that lithiation of 3-methoxy-5-methylisoxazole with butyllithium (THF/-75 °C) gave a mixture of the 4- and 5-α-lithiated derivatives (ratio 17:83) then, in 1976, Gainer *et al.*[37] reported that the 3-methoxymethyl group in 5-methyl-3-methoxymethylisoxazole (**42**) directed metallation into the free position-4 in competition with lateral metallation in the 5-methyl group; a mixture of

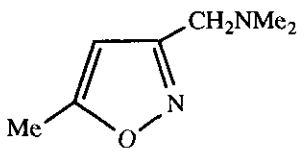


(42) (43) (44)

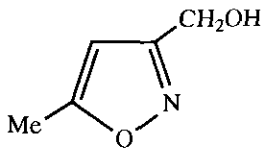
Scheme 10

compounds (**43**) and (**44**) (82% yield) (ratio 4:1) was obtained (Scheme 10). A similar result was achieved with the corresponding *N,N*-dimethylaminomethyl compound (**45**) but, in this case, the increased *ortho*-directing power of the 3-substituent was reflected in a 1:1-ratio of the two quenched products. In both cases, **42** (90% yield) and **45** (84%), use of LDA resulted in exclusive lateral metallation.

Likewise, the 3-hydroxymethyl compound (**46**) reacted successively with butyllithium (2 mol. equiv.) and iodomethane, to give exclusively its 5-ethyl derivative (90% yield).[37] Compounds (**47**) (R = NMe_2, $NHCO_2Bu$-*t*, $NEtCO_2Bu$-*t*, OH, ONH_2) all metallate exclusively in the 5-methyl group.[37]

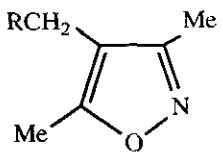


(45)

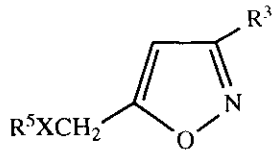


(46)

5-Alkoxymethyl- (**48**; R^3 = Me, $C_6H_3Cl_2$-2,6; XR^5 = OMe, OPh) or 5-alkylthiomethylisoxazoles (**48**; R^3 = Me, $C_6H_3Cl_2$-2,6; XR^5 = SMe) are metallated with butyllithium (THF/-65 °C) exclusively in the α-methylene group and the products can be trapped with iodomethane, benzyl chloride, benzaldehyde, dimethyl disulfide, or



(47)



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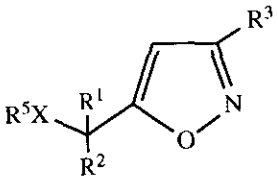


(49)

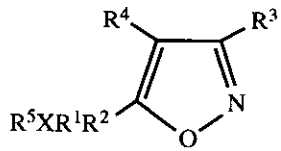
carbon dioxide (Table VI).[34,62] The process of lithiation followed by reaction with iodomethane, dimethyl disulfide, or carbon dioxide can be repeated to give compounds (**49**; XR^5 = OMe or SMe; R^1 = Me, OMe or SMe; R^2 = Me, SMe, or CO_2H)[34] (see also ref. 62) (Table IX). A mixture of 3-methoxymethyl-5-methyl-isoxazole and 5-methoxymethyl-3-methylisoxazole (**48**; R^3 = Me, XR^5 = OMe) can be separated by virtue of the fact that only the latter compound is laterally metallated by addition of an equivalent amount of butyllithium (THF/-65 °C): conversion of the α-lithiated product into a carboxylic acid allows separation of the resulting acidic product from the other, neutral starting material.[63]

When position-5 is blocked by an unreactive substituent, lateral metallation can occur in a 3-alkyl group. Thus, when 3-methyl-5-phenylisoxazole (**50**) is lithiated with butyllithium, mixtures of products (**51**) and (**52**) (Scheme 11) (Tables II and X) are obtained following addition of a suitable electrophile.[35,36]

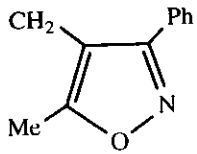
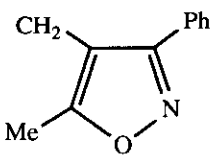
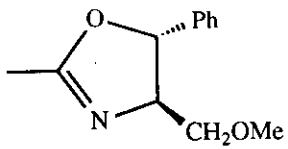
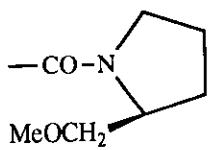
When the isoxazole is added to the butyllithium some dialkylated product (alkylated both at position-4 and in the 3-methyl group) may be formed.[35] Lithium isopropylcyclohexylamide-*N,N,N',N'*-tetramethylethylenediamine (LiICA-TMEDA) is the most effective reagent system for achieving deprotonation of the 3-methyl group in 3-

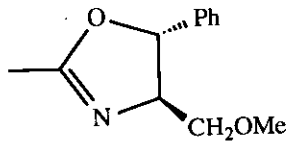
Table IX

ISOXAZOLES PREPARED BY TWO SUCCESSIVE LATERAL METALLATIONS OF 3-SUBSTITUTED 5-ALKYL-, 5-ALKOXYMETHYL-, OR 5-ALKYLTHIOMETHYLISOXAZOLES[a]



R^3	R^4	XR^5	R^1	R^2	Yield (%)	Ref.
Me	H	H	Me	Et	12[b]	47
Me	H	H	CH_2Ph	CH_2Ph	35	47
Me	H	H	Me	CO_2H	70	46
Me	H	H	CO_2Et	CO_2Et	–	31, 65
Me	H	SMe	Me	Me	70	34
Me	H	SMe	SMe	SMe	78	34
Me	H	SMe	SMe	CO_2H	65	34
$C_6H_3Cl_2$-2,6	H	OMe	SMe	SMe	77	34
$C_6H_3Cl_2$-2,6	H	SMe	Me	CO_2H	95	34
$C_6H_3Cl_2$-2,6	H	SMe	OMe	CO_2H	89	34

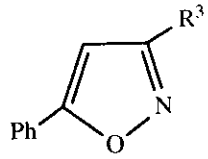
$C_6H_3Cl_2$-2,6	H	SMe	SMe	SMe	84	34
$C_6H_3Cl_2$-2,6	H	SMe	SMe	CO_2H	92	34
Me	ox.[c]	H	Me	D	85[d]	77, 79
Me	ox.[c]	H	Me	Me	73	77, 79
Me	ox.[c]	H	CH_2Ph	Me	70	77
Me	ox.[c]	H	$SiPh_2Bu$-*t*	D	73	83
Ph	H	H	SMe	CH(OH)Ph	95	62
Ph	ox.[c]	H	Me	D	97	77, 79
Ph	ox.[c]	H	Me	Me	93[e]	77, 79
Ph	ox.[c]	H	Me	CH_2Ph	74	77, 79
Ph	ox.[c]	H			89	77, 79
Ph	ox.[c]	H	$SiMe_2Bu$-*t*	D	72-86	83
Me		H	SPh	SPh	10[f,g]	81
Me		H	SPh	SPh	66[g]	81

Ph		H	SPh	SPh	15[f,g]	81

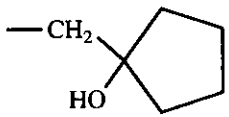
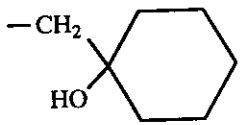
[a] R^1 introduced first, then R^2. [b] 5-Ethyl- (47%), 5-propyl- (7%), and 5-*i*-propylisoxazole (8%) produced also. [c] ox. is 4,4-dimethyl-Δ^2-oxazolin-2-yl. [d] Deuterium also incorporated into 3-methyl group (ratio 5:95 in favour of 5-methyl group). [e] The deprotonation reagent was $NaNH_2$ (MeI added). [f] Produced as a by-product in monothioalkyl formation. [g] See also Table VI.

Table X

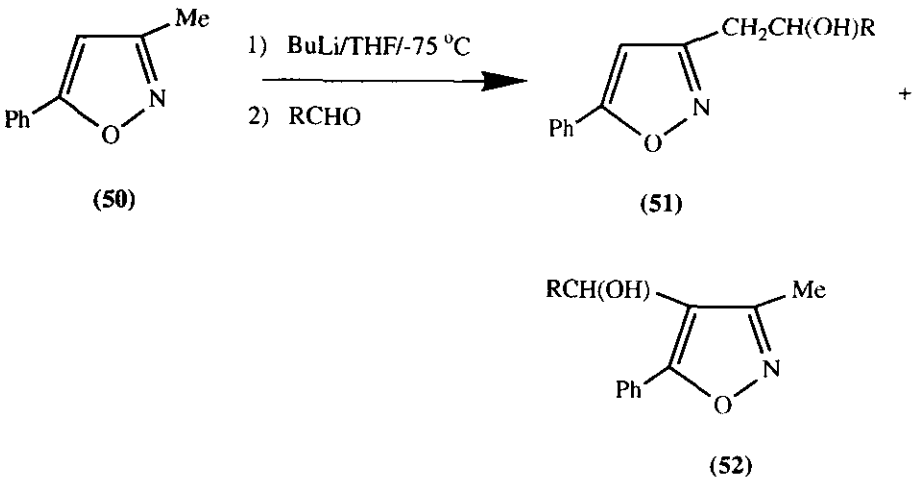
ISOXAZOLES PREPARED BY LATERAL METALLATION OF 3-METHYL-5-PHENYLISOXAZOLE[35]



R^3	Reagents[a]	Yield (%)[b]
Et	MeI (BuLi)	20 (39)
Et	MeI (BuLi)[c]	12 (78, 4)
Et	MeI (LiICA)	33 (8)
Et	MeI (LiICA-TMEDA)	27
Bu	PrBr (BuLi)	12 (4)
Bu	PrBr (BuLi)[c]	16 (17, 8)
Bu	PrBr (LiICA)	13
Bu	PrBr (LiICA-TMEDA)	27
$(CH_2)_2Ph$	$PhCH_2Br$ (BuLi)	9 (3)
$(CH_2)_2Ph$	$PhCH_2Br$ (BuLi)[c]	7 (3)
$(CH_2)_2Ph$	$PhCH_2Br$ (LiICA)	31
$(CH_2)_2Ph$	$PhCH_2Br$ (LiICA-TMEDA)	23

$CH_2CH(OH)Et$	EtCHO (BuLi)	11 (22)[36]
$CH_2CH(OH)Ph$	PhCHO (BuLi)	3 (29)[36]
$CH_2CH(OH)Ph$	PhCHO (LiICA)	30
$CH_2CH(OH)Ph$	PhCHO (LiICA-TMEDA)	70
$CH_2CH(OH)CH{=}CHPh$	PhCH=CHCHO (LiICA-TMEDA)	39
$CH_2C(OH)MePh$	PhCOMe (LiICA-TMEDA)	87
$CH_2C(OH)MeCH{=}CHPh$	PhCH=CHCOMe (LiICA-TMEDA)	64
	cyclopentanone (LiICA-TMEDA)	80
	cyclohexanone (LiICA-TMEDA)	58
CH_2COMe	$MeCO_2Et$ (LiICA-TMEDA)	49
CH_2COPr	$PrCO_2Et$ (LiICA-TMEDA)	24[d]
CH_2COMe	MeCN (LiICA-TMEDA)	30
CH_2COPh	PhCN (LiICA-TMEDA)	33

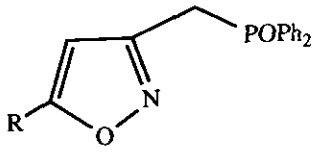
[a] In THF at -78 °C. [b] The yields in parentheses are the yields of the 4-substituted 3-methyl-5-phenylisoxazole and the yields of products formed by disubstitution both in position-4 and the 3-methyl group. [c] Isoxazole added to the base. [d] $(pyCH_2)_2C(OH)Pr$ formed too (21% yield) where py = 5-phenylisoxazol-3-yl.



(50) (51) (52)

Scheme 11

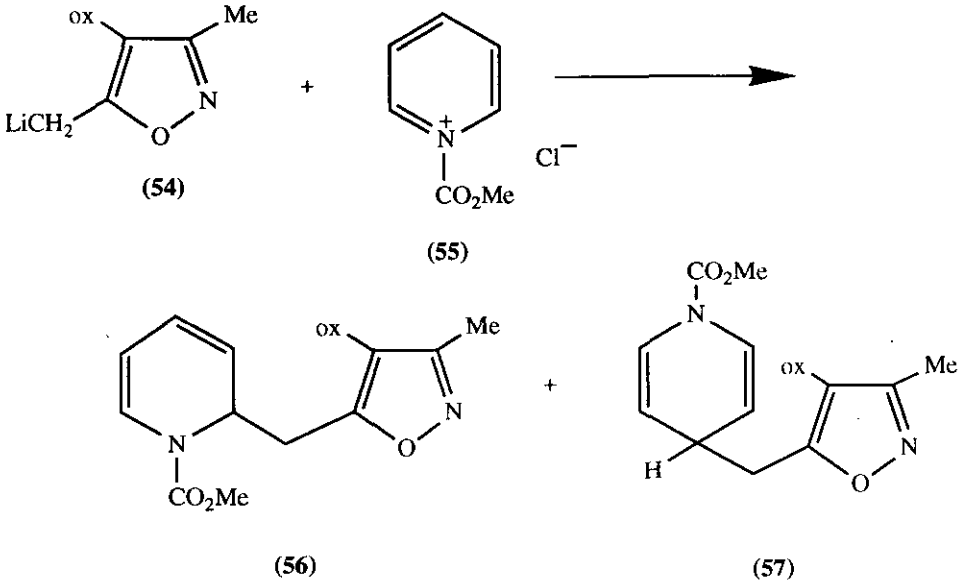
methyl-5-phenylisoxazole (Table X).[35] When 3,4,5-trimethylisoxazole is lithiated with butyllithium, lateral metallation in the 5-methyl group is preferred, but a small amount of lithiation occurs also in the 3-methyl group, as shown by quenching with dimethyl disulfide (yields of quenched products are 37% and 7%, respectively).[63] Deprotonation of compounds [**53**; R = Et, $(CH_2)_{10}Me$, or $(CH_2)_2CO_2Et$] with butyllithium or LDA occurs



(53)

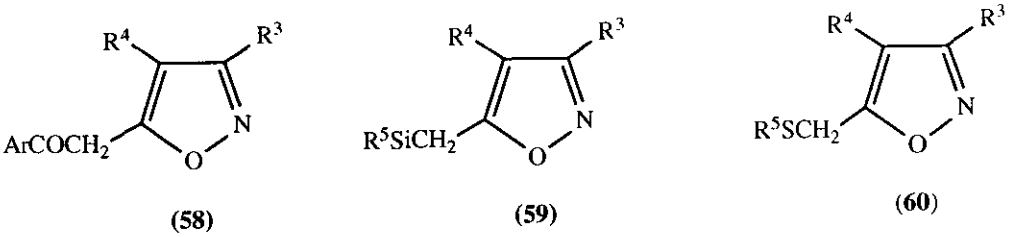
exclusively in the 3-position and the anions have been employed to generate several *E*-alkenes in Wittig reactions.[103]

Natale's group have examined metallations of 3,5-disubstituted 4,4-dimethyl-2-(isoxazol-4-yl)-Δ^2-oxazolines.[77] 5-Alkyl groups are readily deprotonated with butyllithium (THF/-78 °C) (A) (Table VI), LDA (THF/-5 °C) (B), or sodium amide (THF/-78 °C) (D). The products obtained by quenching the resulting anion with electrophiles are listed in Table VI. Anion (**54**) reacts with acylpyridinium salt (**55**) to give a mixture of the 1,2- (**56**) and 1,4-adducts (**57**) (Scheme 12) which can be oxidised to the respective pyridines with tetrachloro-*p*-benzoquinone.[77] A repetition of these processes allows the introduction of a second substituent (Table IX: introduction of R^1 followed by R^2).[77,79] Similar results have been achieved with *N,N*-disubstituted 5-alkylisoxazole-4-



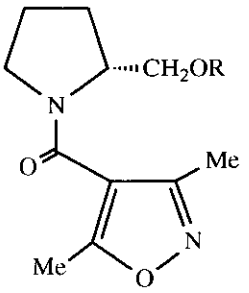
Scheme 12

carboxamides (Table VI).[87] Anions (**54**), their 3-phenyl counterparts, and the corresponding *N,N*-disubstituted isoxazole-4-carboxamides couple with aroyl chlorides in the presence of cerium trichloride, to give compounds with the general structure (**58**) (Table VI),[80] with chlorotrialkylsilanes, to give compounds with the general



structure (**59**) (Table VI),[83] and with dialkyl and diaryl disulfides, to give compounds with the general structure (**60**) (Table VI).[81] The silyl compounds (**59**) form a second anion with butyllithium (THF/-78 °C) and these have been quenched with deuteriomethanol (MeOD) (56-86% incorporation, depending on time allowed for metallation step).[83] A similar process can occur with compounds (**60**) where the methylene group of the product is more acidic than the methyl group of the starting material (see Table IX).[81]

The dianion derived from 3,5-dimethylisoxazole-4-(*S*-2'-hydroxymethyl-*N*-pyrrolidino)carboxamide (**61**; R = H) by treatment with butyllithium under kinetic (THF-TMEDA) or thermodynamic (THF) conditions is quenched with deuterium oxide to reveal almost exclusive (> 95%) deuteriation at the C-5 methyl group.[93] However, when

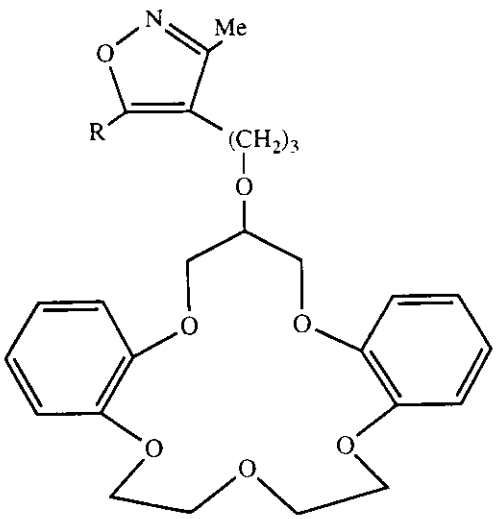


(61)

its methyl ether (**61**; R = Me) is treated similarly, predominant (> 93% incorporation of D) C-3 lateral metallation occurs under kinetic conditions and C-5 metallation after equilibration.

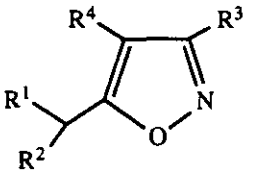
Anion (**54**) and analogous anions derived from 4-substituted 3,5-dimethylisoxazole and 5-methyl-3-phenyl-isoxazoles in which the 4-substituent is 4-(*N*,*N*-diisopropyl)carboxamido (the carboxamide derived from *S*-prolinol behaves similarly), 4-(4,4'-dimethyl-Δ^2-oxazolin-2-yl), or 4-(4'-*S*-methoxymethyl-5'-*S*-phenyl-Δ^2-oxazolin-2-yl) react with dialkyl azodicarboxylates [$RO_2CN{=}NCO_2R$ (R = Et or *t*-Bu)], to give the corresponding hydrazine derivatives, $EtO_2CNHN(CO_2R^2)CH_2$(isoxazole) (74-96% yields) (Table VI).[82]

Likewise, metallation of 4-[3'-{*sym*-dibenzo-16-crown-5-oxy}-prop-1'-yl]-3,5-dimethylisoxazole (**62**; R = H) (BuLi/THF/-78°C) followed by carbonation yields the corresponding carboxylic acid (**62**; R = CH_2CO_2H) (52% yield) (**not** listed in Table VI).[104]

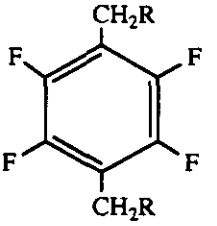


(62)

Anion (**63**; R^1 = Li, R^2 = R^4 = H, R^3 = Me) reacts with hexafluorobenzene by displacement of fluorine, to give compound (**63**; R^1 = C_6F_5, R^2 = R^4 = H, R^3 = Me) (20% yield). The pentafluorophenyl substituent in this product renders it more prone to lateral metallation than the starting material and the major product isolated (31%) is the disubstituted compound (**63**; R^1 = R^2 = C_6F_5, R^3 = Me, R^4 = H).[61] Two minor products are obtained also, one (**64**; R = 3-methylisoxazol-5-yl) (3%) through displacement of two fluorine atoms in hexafluorobenzene by anion (**54**) and the other (**65**; R = 3-methylisoxazol-5-yl) (10%) through displacement of a fluorine atom in the major product (**63**; R^1 = R^2 = C_6F_5, R^3 = Me, R^4 = H) by anion (**63**; R^1 = Li, R^2 = R^4 = H, R^3 = Me). Anion (**63**; R^1 = Li, R^2 = CO_2Me, R^3 = Me, R^4 = H) reacts with hexafluorobenzene to give only a monosubstituted product (**63**; R^1 = C_6F_5, R^2 = CO_2Me, R^3 = Me, R^4 = H) (18% yield).[61] The efficiency of the



(63)



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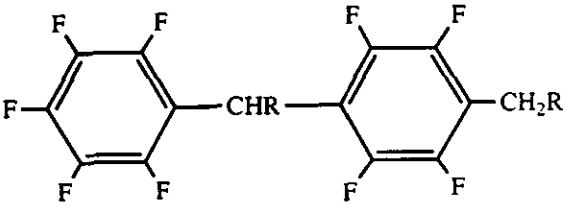
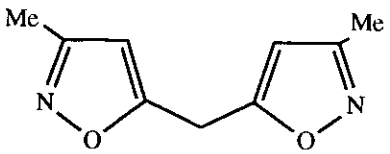


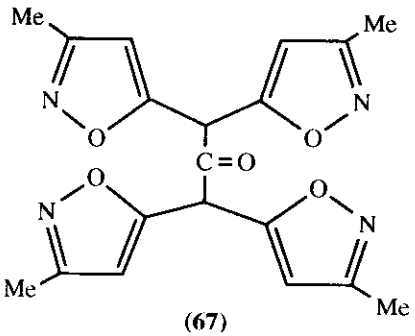
(65)

process is improved when an electron-withdrawing group is present at position-4 and *vice-versa*. Thus, the anion (**63**; R^1 = Li, R^2 = H, R^3 = Me, R^4 = $CONPr^i_2$) reacts with hexafluorobenzene to yield the monosubstituted compound (**63**; R^1 = C_6F_5, R^2 = H, R^3 = Me, R^4 = $CONPr^i_2$) (42% yield) together with the disubstituted product (**63**; R^1 = R^2 = C_6F_5, R^3 = Me, R^4 = $CONPr^i_2$) (7%). Anion (**63**; R^1 = Li, R^2 = H, R^3 = Ph, R^4 = $CONPr^i_2$) similarly yields the mono- (39%) and disubstituted products (24%).[61] By contrast, anion [**63**; R^1 = Li, R^2 = H, R^3 = Me, R^4 = $(CH_2)_3OMe$] gives only poor yields of the mono- (9%) and disubstituted products (7%).

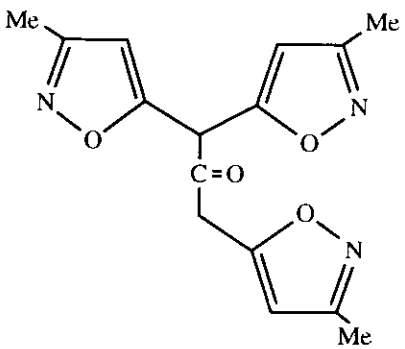
Compound (**66**) is deprotonated (BuLi/THF/-78 °C) exclusively in the bridge methylene group and the derived monoanion is coupled, on addition of iodine, to give the dimer (100% yield). It gives the related dimeric ketone (**67**) (40%) with phosgene, and gives ketone (**68**) (35%) with 2-(3-methyl-oxazol-5-yl)acetyl chloride.[50] Compound (**69**) is deprotonated similarly with butyllithium preferentially in its bridge methylene group (see also Section V) and the resulting monoanion can be deuteriated (100% yield) and condensed with benzoyl chloride, which gives a ketone (50%) analogous to **68** .[50] LDA, however (see also Section V), deprotonates compound



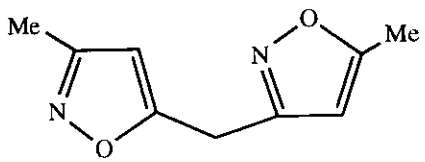
(66)



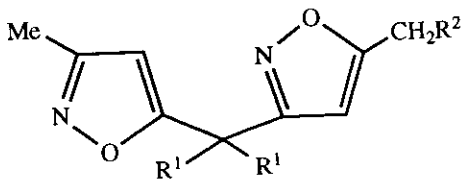
(67)



(68)

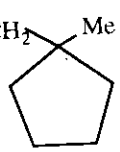


(69)



(70) $R^1 = H$, $R^2 = COPh$

(71) $R^1 = H$, $R^2 = COCH_2$



(72) $R^1 = H$, $R^2 = CONPr^i_2$

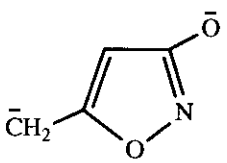
(73) $R^1 = COPh$, $R^2 = H$

(**69**) mainly in the methyl group adjacent to oxygen and the resulting monoanion gives ketone (**70**) with methyl benzoate and compound (**71**) (52%) with the ethylene acetal of acetoacetic ester.[49,105]

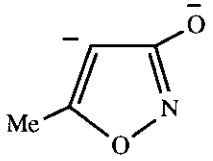
V POLYLITHIATED DERIVATIVES

We referred to the formation of dianions (**3**; R = H, Me) in Section II and, in Section IV, we mentioned the formation of dianions from the treatment of 3-hydroxymethyl-5-methyl- (**46**) and 4-hydroxymethyl-3,5-dimethyl-isoxazole (**47**; R = OH) with butyllithium.[37]

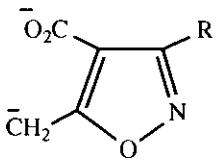
When 3-hydroxy-5-methylisoxazole is reacted with 2 mol. equiv. of butyllithium (THF/–10 °C), it gives a mixture of dianions (**74**) and (**75**) (ratio 7:3) (Section II).[40] With 2 mol. equiv. of LDA in THF at low temperatures, however, only lateral metallation occurs[40] (see also ref. 74) and the resulting dianion can be quenched by various electrophiles, resulting in substitution in the 5-methyl group (Table VI). Similarly, dianions (**76**; R = Me, Ph) can be generated from the corresponding 5-methylisoxazole-4-carboxylic acid using 2 mol. equiv. of butyllithium (THF/-78 °C) and quenched at position-5 with various electrophiles (Table VI).[77] This method allows entry into functionally complex isoxazole-4-carboxylic acids without the need for protecting group strategies. When base in excess of 2 mol. equiv. is used products arising from incorporation of more than one



(**74**)



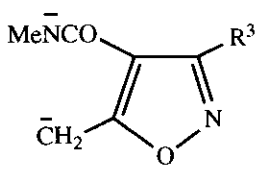
(**75**)



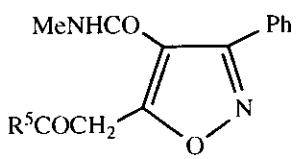
(**76**)

electrophile are observed (Table VI).[77] 5-Ethyl-3-phenylisoxazole-4-carboxylic acid is converted similarly into the 5-isopropyl derivative.[78]

Dianion (**77**; R^3 = Ph), similarly prepared, reacts with benzonitrile, to give ketone (**78**; R^5 = Ph, after hydrolysis of the intermediate imine),[91] and with ethyl pyrid-2-ylcarboxylate, to give ketone (**78**; R^5 = pyrid-2-



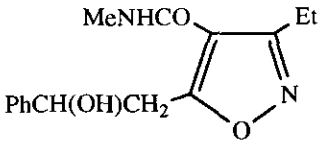
(**77**)



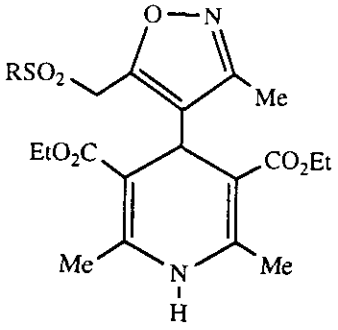
(**78**)

yl) (Table VI),[92] whilst dianion (**77**; R^3 = Et) reacts with benzaldehyde to give carbinol (**79**)[85] (see also refs. 84, 86, 88-90) (Table VI).

The Hantzsch esters (**80**; R = Me or Ph) form dianions with LDA (THF/-78°C) which are quenched with electrophiles, to give products of lateral substitution adjacent to the sulfonyl group (Table VI).[94] These esters form dianions also with potassium *t*-butoxide but addition of an electrophile, such as iodomethane, results in a mixture of the *C*- and *N*-alkylated product; addition of an excess of the electrophile results in disubstitution (> 60% yield).[94]



(79)



(80)

Compound (**69**) reacts with 2 mol. equiv. of LDA in THF both at the bridge methylene group and in the methyl group adjacent to oxygen and the resulting dianion has been trapped with deuterium oxide (100% yield) and phosgene [which yields compound (**72**) (40%)].[50] However, with 2 mol. equiv. of butyllithium, compound (**69**) produces diketone (**73**) following addition of benzoyl chloride.[50]

VI GRIGNARD DERIVATIVES

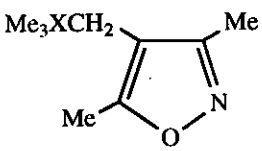
In 1969, 3-bromo-5-phenylisoxazole was converted into its Grignard derivative (Mg/THF/0 °C) which was hydrolysed by water to 5-phenylisoxazole (20% yield) and reacted with carbon dioxide, formaldehyde, and acetone, to give the acid (12%), hydroxymethyl derivative (15%), and 5-phenylisoxazol-3-yldimethyl carbinol (11%).[106] The low yields are attributable to a ring-cleavage reaction, giving rise to $PhCOCH_2CN$ (*cf.* the corresponding instability of isoxazol-3-yllithium derivatives: Section II).

As far as we are aware, there are no reports of isoxazol-5-ylmagnesium halides but, by contrast, isoxazol-4-ylmagnesium halides are well-known. These were first prepared in 1960 when Kochetkov *et al.*[107] reacted 4-

bromo(and iodo)-3,5-dimethylisoxazole with magnesium (Et_2O or THF) in the presence of bromoethane as an entrainer. The iodide gives significantly better results than the bromide and, in some cases, the use of dibromoethane as the entrainer increases yields.[108] 4-Bromo(and iodo)-3,5-dimethylisoxazole yields a Grignard derivative also with ethylmagnesium bromide.[109,110] Prolonged heating of 4-bromo-3,5-dimethylisoxazole with ethylmagnesium bromide yields 3,3',5,5'-tetramethyl-4,4'-diisoxazole.[111] Attempts to prepare the Grignard reagent from 4-chloro-3,5-diphenylisoxazole result in ring-cleavage, to give the monoimine of dibenzoylchloromethane (64% yield).[107,109] A transmetallation reaction between ethylmagnesium bromide and this chloroisoxazole gives a similar result.[109] Likewise, when 3,5-dimethylisoxazole, 4-iodo-5-phenylisoxazole,[108] 4-chloro-3,5-dimethylisoxazole, 4-chloro-3-methyl-5-phenylisoxazole,[109] or 3-methyl-5-phenyl-isoxazole,[112] are allowed to react with ethylmagnesium bromide a similar ring-cleavage reaction occurs. The structures of 3,5-diacylisoxazoles have been confirmed by examining the ring-cleaved products arising from their reactions with ethylmagnesium iodide.[113]

4-Substituted 3,5-dimethyl- and 3-methyl-5-phenylisoxazoles prepared from isoxazol-4-ylmagnesium halides, are listed in Table XI.

A Grignard reagent can be prepared from 4-chloromethyl-3,5-dimethylisoxazole but its treatment with carbon dioxide[108] or chlorotrimethylsilane[44] in ether results mainly in a Wurtz-type coupling reaction. When THF is used as the solvent, however, compounds (**81**) (60% yield) and (**82**) (49%) can be obtained.[44] 3-Chloromethyl-5-methylisoxazole also forms a Grignard derivative which reacts similarly with chlorotrimethylsilane(and stannane). 4-Chloro(and iodo)methyl-3,5-dimethylisoxazole react with Grignard reagents and aluminium



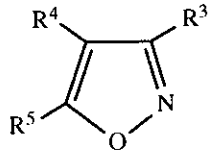
(81) X = Si

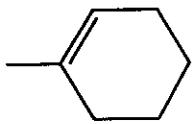
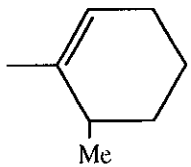
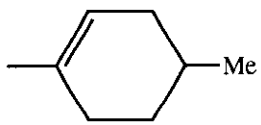
(82) X = Sn

trialkyls to give *C*-α-alkylated products. Particularly good yields are obtained with allyl-, benzyl-, and phenylmagnesium halides; in other cases 3,4,5-trimethylisoxazole and the product of coupling of the isoxazole are obtained also. 4-(α-Chlorobenzyl)-3,5-dimethylisoxazole reacts similarly but is more reactive.[114]

Table XI

4-SUBSTITUTED ISOXAZOLES PREPARED FROM ISOXAZOL-4-YLMAGNESIUM HALIDES



R^3	R^4	R^5	Reagent	Yield (%)	Reference
Me	CH_2Ph	Me	$PhCH_2Cl$	20[a]	111
Me	$CHPh_2$	Me	Ph_2CHCl	72[a]	111
Me	$CH_2CH=CH_2$	Me	$CH_2=CHCH_2Br$	75-85	111
Me	$CH_2CMe=CH_2$	Me	$CH_2=CMeCH_2Br$	93	111
Me		Me	cyclohexanone	75	45
Me		Me	2-methylcyclohexanone	10(60)[b]	45
Me		Me	4-methycyclohexanone	75	45

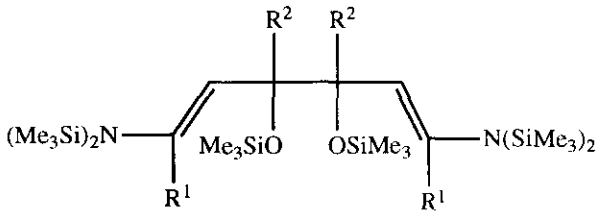
Me	CO_2H	Me	CO_2	53-57, 65	107, 108
Me	CH(OH)Me	Me	MeCHO[c]	–	110, 118
Me	CH(OH)Ph	Me	PhCHO	17, 36	107, 108
Me	$C(OH)Ph_2$	Me	Ph_2CO	43	107
Me	$SiMe_3$	Me	Me_3SiCl[d]	27	44
Me	$B(OH)_2$	Me	$(MeO)_3B$	–	119
Me	CO_2H	Ph	CO_2	45	108
Me	$B(OH)_2$	Ph	$(MeO)_3B$	–	119
Ph	H	Ph	H_2O	78, 36	108, 109
Ph	CO_2H	Ph	CO_2	10	108

[a] 3,5-Dimethylisoxazole (25%) produced also by hydrolysis. [b] 4-(2-Methylcyclohexen-1-yl)-3,5-dimethylisoxazole (60%) produced too. [c] (3,5-Dimethylisoxazol-4-ylCHMe)$_2$O produced too. [d] *Bis*(3,5-dimethylisoxazol-4-yl) obtained as a by-product.

2-Ethyl-3,4,5-triphenylisoxazolium salts are cleaved by methylmagnesium iodide or phenylmagnesium bromide, to give PhCOCPh=CPhNHEt.[115] 2,3-, 2,5-, and 4,5-Dihydroisoxazoles have been selectively synthesised through addition of organolithium, -magnesium, and -aluminium reagents to isoxazoles carrying electron-withdrawing groups (e.g. CN, NO_2).[116] Noteworthy is the displacement of a methoxy group in 3-phenyl-5-methoxyisoxazole-4-carbonitrile with phenylmagnesium bromide.[117]

VII OTHER ORGANOMETALLIC DERIVATIVES

Variously substituted isoxazoles, but not isoxazole itself,[120] react with mercuric acetate under milder conditions than required for mercuration of benzene and the resulting 4-mercuracetates react with potassium bromide to give the corresponding mercurbromides. These mercurated derivatives are particularly useful for introduction of halogen into the isoxazole ring at position-4.[120,121] Isoxazole-boronic acids yield the corresponding mercuracetates when they are treated with mercuric acetate.[119] Isoxazole and its 3(and 5)-methyl- and 3,5-dimethylderivatives are cleaved in a homolytic process by *bis*(trimethylsilyl)mercury, to give high yields of highly substituted hexadienes with the general structure (**83**).[122]



(**83**)

ACKNOWLEDGEMENTS

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