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

Brian Iddon

The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT, England

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

CONTENTS

I INTRODUCTION

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

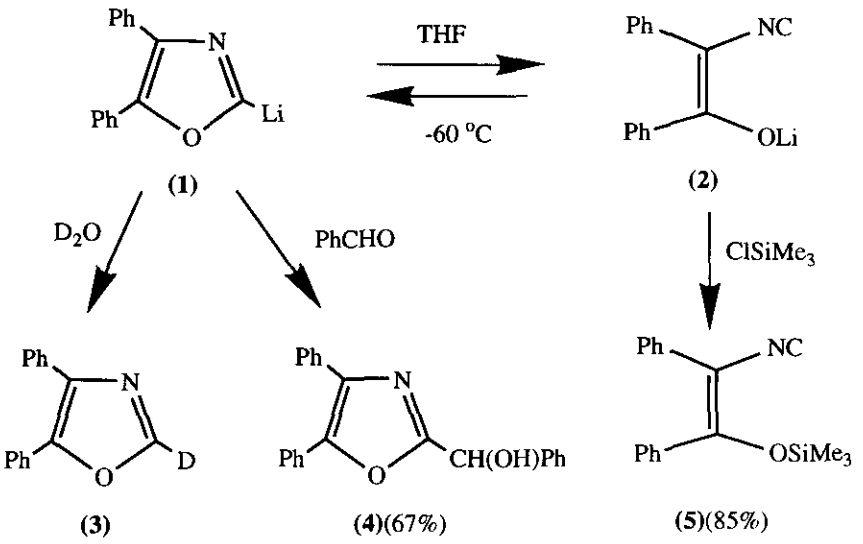
Oxazoles (1,3-oxazoles),[2-6] like isoxazoles, have attracted considerable interest as starting materials for the synthesis of more complex molecules[7-10] (and cross refs. to be found in refs. 11 and 12). This in turn has led to an interest in the introduction of substituents into oxazoles using metallation and halogen → metal exchange methodologies. As with isoxazoles[1] the fragility of the C-O bond gives rise to ring-cleavage processes.

II MONOMETALLATION IN THE RING

Bowie *et al.*, in 1968, first demonstrated that 4-phenyl-,[13] 4-methyl-5-phenyl-,[13] 5-methyl-4-phenyl-,[13] and 4,5-diphenyloxazole[14] could be metallated by butyllithium in position-2; the resulting 2-lithiated derivatives

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

were trapped only with deuterium oxide (Table I). In 1975, however, Schröder *et al.*[15] showed that 4,5-diphenyloxazol-2-yllithium (**1**) exists in equilibrium with the ring-opened lithium enolate (**2**) and that the choice of trapping agent determined the product (**3**)-(**5**) (Scheme 1) (Δ^2-oxazolin-2-yllithium compounds behave analogously[5,12,16-19]). So far isoxazol-2-yllithium[20] and its 4-methyl-,[12,21,22] 4,5-dimethyl-,[23] 4-phenyl-,[10,24] and various other 5-aryl-[12,15] and 4,5-diaryl-derivatives[9] have been shown to behave similarly

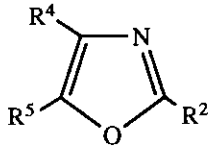


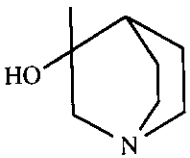
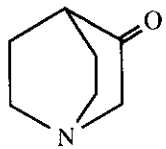
Scheme 1

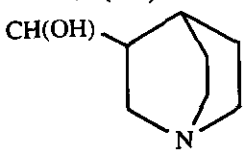
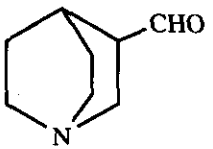
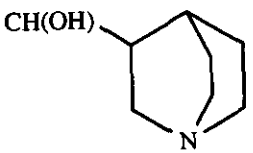
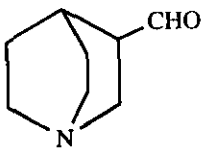
(for a review see ref. 5). However, lithiation of 5-ethoxy-4-methyloxazole [BuLi/tetrahydrofuran (THF)/ -78 °C] and ethyl 4-methyloxazole-5-carboxylate [lithium isopropylcyclohexylamide (LiICA)/THF/-78 °C][25] apparently results in irreversible formation of a ring-opened species corresponding to **2**.[23] Butyllithium, lithium diisopropylamide (LDA), and lithium 2,2,5,5-tetramethylpiperidide (LiTMP) have been used to metallate oxazoles in position-2. Quenching these equilibrium mixtures, e.g. **1** $\rightleftarrows$ **2**, with deuterium oxide or aromatic aldehydes (for 4-unsubstituted oxazoles; see later) invariably leads to the isolation of a 2-substituted oxazole (Table I) whilst quenching with chlorotrimethylsilane[9,15,21] and acetyl[12,21,24] or benzoyl chloride[24] appears to result in trapping of the ring-opened product. However, the reactions are more complicated than they appear from the earlier literature. Noteworthy is the synthesis of 2-aroyloxazoles (Table I) by using *N*-methyl-*N*-(pyrid-2-yl)carboxamides as the quenching agents; a good yield of 5-phenyloxazole-2-carbaldehyde is available *via* this procedure.[11]

Table I

Oxazoles Prepared from Oxazol-2-yllithium Derivatives

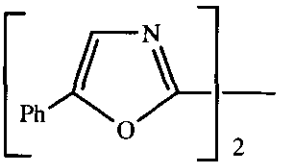


R^2	R^4	R^5	Reagent	Yield (%)	Ref.
D	H	H	D_2O	90	20
CHO	H	H	DMF	50[a]	20
CH(OH)Ph	H	H	PhCHO	–[b]	20
$C(OH)Ph_2$	H	H	Ph_2CO	73	20
	H	H		19	26
$SiMe_3$	H	H	Me_3SiCl	-	27
D	H	Ph	D_2O	90	15
CHO	H	Ph	HCONMe(pyrid-2-yl)	61	11
COPh	H	Ph	PhCONMe(pyrid-2-yl)	18	11
COC_6H_4Me-4	H	Ph	4-MeC_6H_4CONMe(pyrid-2-yl)	67	11
COC_6H_4OMe-4	H	Ph	4-$MeOC_6H_4CONMe$(pyrid-2-yl)	46	11

COC_6H_4Cl-4	H	Ph	4-ClC_6H_4CONMe(pyrid-2-yl)	63	11
COC_6H_4F-4	H	Ph	4-FC_6H_4CONMe(pyrid-2-yl)	63	11
$COC_6H_4NO_2$-4	H	Ph	4-$O_2NC_6H_4CONMe$(pyrid-2-yl)	56	11
COC_6H_4CN-4	H	Ph	4-NCC_6H_4CONMe(pyrid-2-yl)	77	11
$SiMe_3$	H	Ph	Me_3SiCl	50[c]	12
$SiMe_3$	H	C_6H_4Cl-4	Me_3SiCl	50[c]	12
$SiMe_3$	H	C_6H_4OMe-4	Me_3SiCl	35[c]	12
$CH(OH)C_6H_3(OMe)_2$-3,4	H	$C_6H_3(OMe)_2$-3,4	3,4-$(MeO)_2C_6H_3CHO$	50-90	28
$CH(OH)C_6H_3(OCH_2O)$-3,4	H	$C_6H_3(OCH_2O)$-3,4	3,4-$(OCH_2O)C_6H_3CHO$	50-90	28
$CH(OH)C_6H_3(OMe)_2$-3,4	H	$C_6H_3(OCH_2O)$-3,4	3,4-$(MeO)_2C_6H_3CHO$	50-90	28
CHO	Me	H	DMF or *N*-formylmorpholine	–	12
CH(OH)Ph	Me	H	PhCHO	30	21, 12
	Me	H		33	26
	Et	H		10	26
$SiMe_3$	Me	H	Me_3SiCl	60[c]	21
$SnMe_3$	Me	H	Me_3SiCl	60	22, 12

D	Ph	H	D_2O	low, –, –	24, 10, 13
CH(OH)Ph	Ph	H	PhCHO	75	24
$C(OH)Ph_2$	Ph	H	Ph_2CO	96	24
D	Me	Me	D_2O	100	23
Cl	Me	CO_2Et	CCl_4	29	25
Br	Me	CO_2Et	Br_2	21	25
I	Me	CO_2Et	I_2	42	25
D	Me	Ph	D_2O	–	13
D	Ph	Me	D_2O	–	13
D	Ph	Ph	D_2O	–, 95, 100	14, 15, 9
CH(OH)Ph	Ph	Ph	PhCHO	67	15
Et	C_6H_4OMe-4	C_6H_4OMe-4	EtI	21	9
Pr	C_6H_4OMe-4	C_6H_4OMe-4	PrI	23	9
CH_2Ph	C_6H_4OMe-4	C_6H_4OMe-4	$PhCH_2Br$	27	9
$CH(OH)CHMe_2$	C_6H_4OMe-4	C_6H_4OMe-4	Me_2CHCHO	70	9
$CH(OH)CH=CH_2$	C_6H_4OMe-4	C_6H_4OMe-4	$CH_2=CHCHO$	83	9
COPh	C_6H_4OMe-4	C_6H_4OMe-4	PhCN	85	9

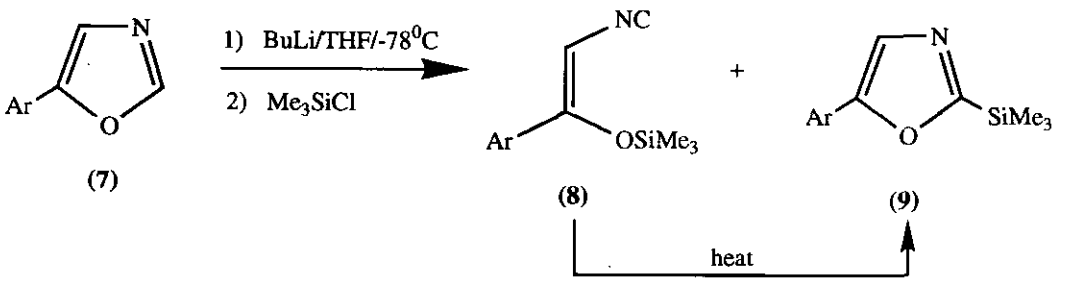
[a] Variable yields after work-up due to volatility of product. [b] Minor product, isolated only at ambient temperature or above; the major product is the 4-substituted isomer (Table II). [c] After distillation of a mixture of compounds (**8**) and (**9**) (Ar = Ph, C_6H_4Cl-4, or C_6H_4OMe-4).



(6)

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

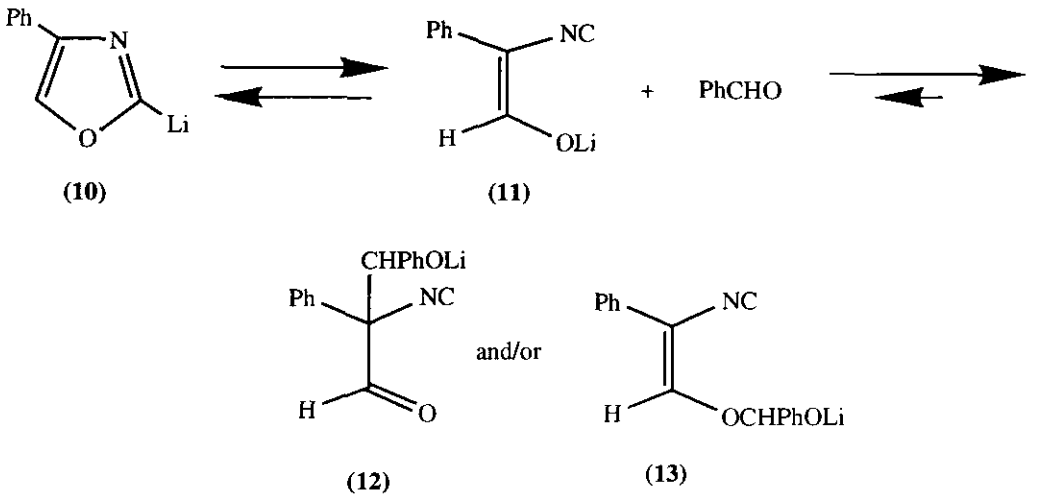
A number of 5-aryloxazol-2-yllithium derivatives (derived from the corresponding 5-aryloxazole; **7**) (Ar = Ph, C_6H_4Cl-4, or C_6H_4OMe-4) react with chlorotrimethylsilane to give comparable amounts of the ring-opened product (**8**) and the corresponding 2-trimethylsilyloxazole (**9**) (Scheme 2).[12] The former compounds are convertible into 2-trimethylsilyloxazoles by heating them in the presence of a base,[5,12,20,21,29] (however, see



(7) (8) (9)

Scheme 2

also ref. 24). By contrast, when 4-methyloxazole is treated sequentially with butyllithium [diethyl ether (Et_2O)/ -78 °C] and chlorotrimethylstannane, only 4-methyl-2-trimethylstannane is isolated (Table I)[22] (but see ref. 12). In order to maximise the yields obtained from the reactions of 4-phenyloxazol-2-yllithium (**10**) (Scheme 3) with benzaldehyde or benzophenone it is necessary to allow 18-24 hours to elapse between addition of these reagents and quenching the reaction mixtures with acid prior to work-up.[24] The authors reasoned that addition of e.g. benzaldehyde to the initial equilibrium mixture, **10** $\rightleftarrows$ **11**, creates another equilibrium as shown in Scheme 3, generating either aldol salt (**12**) or hemiacetal salt (**13**). Overall this results in a reduced availability of oxazol-2-yllithium.

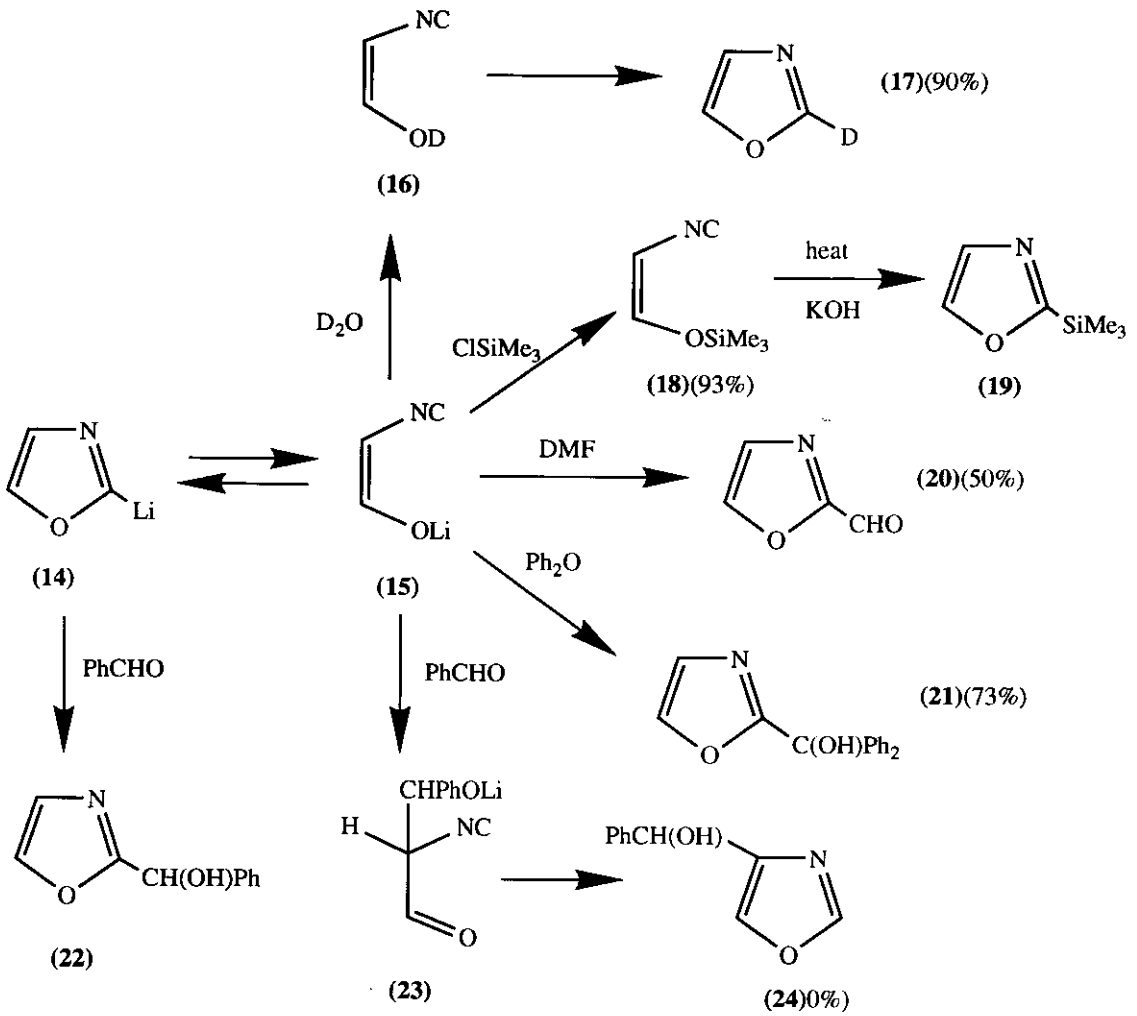


Scheme 3

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

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

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

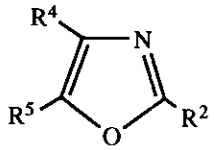


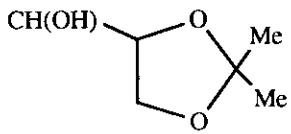
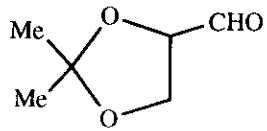
Scheme 4

up, and displacement of the 2-phenyl group by butyl.[30] Use of LDA or potassium diisopropylamide (KDA) at -78 °C[9,30] or *sec.*-butyllithium and a catalytic amount of LiTMP[24] leads to clean metallation at position-4. A number of 4-substituents (Table II) can be introduced by quenching the resulting 2,5-diphenyloxazol-4-yllithium derivative with various electrophiles. We have mentioned already (Section II) that the lithium enolate (**15**) derived by the ring opening of oxazol-2-yllithium (**14**) reacts with aldehydes to give 4-substituted oxazoles, e.g. **24** (Scheme 4) (Table II).[20]

Table II

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



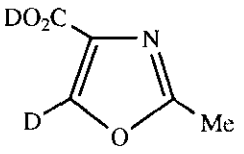
R^2	R^4	R^5	Reagent	Yield (%)	Ref.
H	$CH(OH)C_4H_9$	H	C_4H_9CHO	28[a]	20
H		H		65[a]	20
H	CH(OH)Ph	H	PhCHO	20[a,b]	20
H	CH(OH)thiazol-2-yl	H	thiazol-2-ylCHO	65[a]	20
H	CH(OH)thiazol-4-yl	H	thiazol-4-ylCHO	62[a]	20
Ph	Br	Ph	Br_2	58	24
Ph	Me	Ph	MeI	85	24
Ph	$(CH_2)_6OTMS$[c]	Ph	$TMSO(CH_2)_6I$	45	30
Ph	$(CH_2)_8OTBDMS$[d]	Ph	$TBDMSO(CH_2)_8Br$	60	30
Ph	CHO	Ph	DMF	50	9
Ph	COPh	Ph	PhCOCl	73	24

Ph	$CH(OH)C_5H_{11}$	Ph	$C_5H_{11}CHO$	82	9
Ph	$CH(OH)(CH_2)_3OTBDMS$[d]	Ph	$TBDMSO(CH_2)_3CHO$	47	30
Ph	CH(OH)Ph	Ph	PhCHO	94, 70	24, 9
Ph	$C(OH)Me_2$	Ph	Me_2CO	80	9
Ph	$SiMe_3$	Ph	Me_3SiCl	83, 92	24, 9
Ph	$SiEt_3$	Ph	Et_3SiCl	71	24
C_6H_4OMe-4	D	C_6H_4OMe-4	D_2O	50	9
C_6H_4OMe-4	Me	C_6H_4OMe-4	MeI	30	9
C_6H_4OMe-4	Et	C_6H_4OMe-4	EtI	20	9
C_6H_4OMe-4	CH_2Ph	C_6H_4OMe-4	$PhCH_2Br$	26	9
C_6H_4OMe-4	$CH(OH)CHMe_2$	C_6H_4OMe-4	Me_2CHCHO	35	9

[a] These aldehydes react, as shown for PhCHO, in **Scheme 4** (i.e. *via* initial generation of oxazol-2-yllithium, **14**⇌**15**). [b] At ambient temperature $PhCH_2OH$ is formed also in 34% yield along with a trace amount (2%) of the corresponding 2-isomer (amount dependent on temperature). [c] TMS = trimethylsilyl. [d] TBDMS = *tert*-butyldimethylsilyl.

2,4-Diphenyloxazole is metallated at position-5 with butyllithium (THF/-60 °C) in the presence of hexamethylphosphoric triamide (HMPA)[31] or with *sec.*-butyllithium and a catalytic amount of LiTMP[24] and the resulting 5-lithiated derivative can be trapped with various electrophiles (Table III). 2-Phenyloxazole is deprotonated similarly and exclusively at position-5[7] as shown by isolation of the 5-deuteriated derivative on addition of deuterium oxide. The **same** 5-deuteriated derivative is obtained following sequential treatment of 2-(2-bromophenyl)oxazole with butyllithium and deuterium oxide, showing that the C-5 proton is thermodynamically more acidic than the *ortho*-proton of the phenyl ring.[7]

Oxazole-4-carboxylic acid is metallated with butyllithium (2 mol. equiv. required: THF/-78 °C) in position-5 as shown by isolation of its 5-deuteriated derivative after addition of MeOD.[8,32] Similarly, 2-methyloxazole-4-carboxylic acid[8,32,33] and its methyl,[32] ethyl[34] and *tert.*-butyl esters[35] were not metallated by butyl- (THF/-78 °C) or *tert.*-butyllithium (THF/-40 °C) or LDA in their methyl groups (Section IV) but in position-5 instead. The resulting oxazol-5-yllithium derivatives can be trapped with various electrophiles (Table III). Even more surprising perhaps is the fact that compound (**25**), prepared in the manner just described, reacts with 2 mol. equiv. of *tert.*-butyllithium (butyllithium is reported not to react) at -78 °C only by deuterium extraction; addition



(**25**)

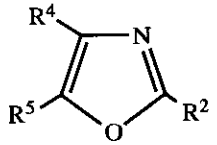
of iodomethane gives 2,5-dimethyloxazole-4-carboxylic acid together with 2-methyloxazole-4-carboxylic acid (ratio 10:90, which suggests that the dilithiated derivative of 2-methyloxazole-4-carboxylic is a very poor nucleophile).[8,32]

III HALOGEN → LITHIUM EXCHANGE REACTIONS

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

Table III

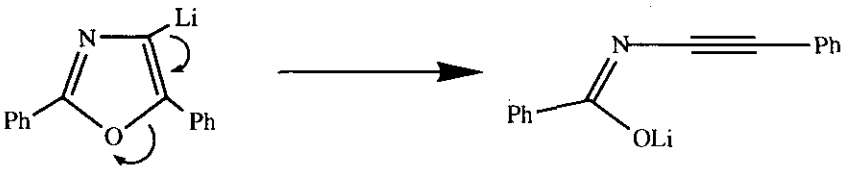
5-Substituted Oxazoles Prepared from Oxazol-5-yllithium Derivatives



R^2	R^4	R^5	Reagent	Yield (%)	Ref.
H	CO_2H	D	MeOD	–	32, 8
Ph	H	D	D_2O	–	7
Me	CO_2H	D	D_2O	92, 77	32, 8
Me	CO_2H	D → Me	MeI	~ 10%[a]	32, 8
Me	CO_2H	$SiMe_3$	Me_3SiCl	86	33
Me	CO_2Me	D	D_2O	99,92	32, 8
Me	CO_2Et	D	D_2O	–	34
Me	CO_2Bu-*t*	$SiMe_3$	Me_3SiCl	62	35
Me	Ph	D	D_2O	–	13[b]
Ph	H	H	H_2O	88	36[b]
Ph	H	D	D_2O	84	36[b]
Ph	H	Me	MeI	73	36[b]
Ph	H	Et	EtI	70	36[b]

Ph	H	CH_2Ph	$PhCH_2Br$	72	36[b]
C_6H_4Cl-4	H	H	H_2O	84	36[b]
C_6H_4Cl-4	H	D	D_2O	80	36[b]
$C_6H_4Bu^t$-4	H	H	H_2O	85	36[b]
$C_6H_4Bu^t$-4	H	D	D_2O	86	36[b]
Ph	Ph	Me	MeI	85	31
Ph	Ph	CH(OH)Ph	PhCHO	–	31
Ph	Ph	$SiMe_3$	Me_3SiCl	88	24

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



(26) (27)

Scheme 5

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

Similarly, with butyllithium (Et_2O/-65 °C) 5-bromo-2-methyl-4-phenyloxazole yields the corresponding oxazol-5-yllithium derivative which has been trapped with deuterium oxide.[13] Formation of 2-aryloxazol-5-yllithium (THF/-18 °C) compounds is reported[36] to require 5 mol. equiv. of butyllithium for good conversion; the resulting 5-lithiated derivatives have been treated with water, deuterium oxide, iodomethane and -ethane, and benzyl bromide (Table III).

IV LATERAL METALLATION

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

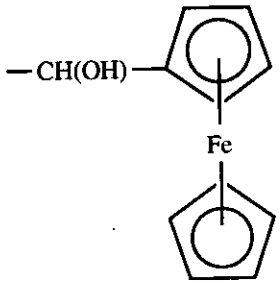
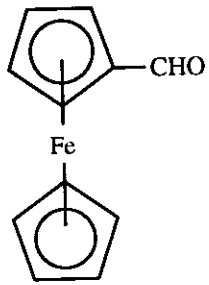
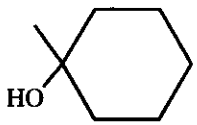
The first reported lateral metallation of an oxazole was the 2-α-deuteriation of 2-methyl-4-phenyloxazole through its sequential treatment with butyllithium (Et_2O/-65 °C) and deuterium oxide.[13] The same anion can be trapped also with 5-bromopent-1-ene (see Table IV).[24]

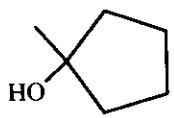
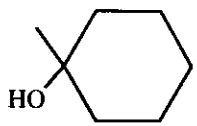
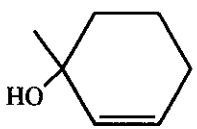
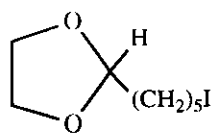
Kashima *et al.*[38] has generated anion (**28**) through treatment of the 2-methyl compound with LDA (THF/-78 °C) and trapped it with 4-methylbenzaldehyde, methyl 4-methylbenzoate and with varying amounts of iodomethane, iodoethane, and benzyl bromide (Table IV). The products obtained on alkylation depend upon the ratio of 2-methyl compound : LDA : RI; one, two, or three alkyl groups can be introduced successively. More than one mol. equiv. of LDA is required due to the formation of $RNPr^i_2$ on addition of the alkylating reagent; attempted

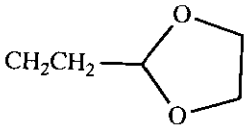
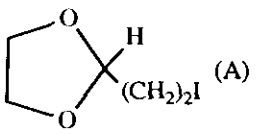
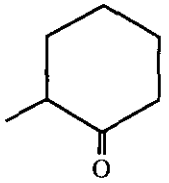
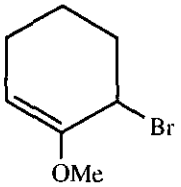
Table IV

2-Substituted Oxazoles Prepared by Lateral Metallation of 2-Methyloxazoles[a]

R^4	R^5	E	Quenching Reagent	Yield (%)	Ref.
Ph	H	D	D_2O (A)	–	13
Ph	H	$(CH_2)_3CH=CH_2$	$CH_2=CH(CH_2)_3Br$ (A)	65	24
Ph	H	$CH_2E \equiv CPh(OMOM)COMe$	MeCOCl	30	24
H	Ph	Me	MeI (B)	68[b]	38
H	Ph	Et	EtI (B)	60[b]	38
H	Ph	$CHMe_2$	MeI (B)	70[c]	38
H	Ph	$CHEt_2$	EtI (B)	58[d]	38
H	Ph	CH_2Ph	$PhCH_2Br$ (B)	62[b]	38
H	Ph	$CH(CH_2Ph)_2$	$PhCH_2Br$ (B)	65	38
H	Ph	$CH(OH)C_6H_4Me$-4	4-MeC_6H_4CHO (B)	63	38
H	Ph	$CH(OH)C_6H_4Me$-4	4-$MeC_6H_4CO_2Me$ (B)	58	38
Me	Me	CH_2Ph	$PhCH_2Cl$ (B)	92	39
Me	Me	CH_2(naphth-2-yl)	naphth-2-ylCH_2Br (B)	70	39

Me	Me	CH(OH)Ph	PhCHO (B)	89	39
Me	Me	CH(OH)(2-furyl)	2-furylCHO (B)	73	39
Me	Me			57	39
Me	Me		cyclohexanone (B)	95	39, 9
Me	Me	$CH_2CH(OH)Ph$	2-phenyloxirane (B)	72	39, 9
Ph	Me	$CH_2CH{=}CH_2$	$CH_2{=}CHCH_2Br$ (A, B)	80, 80	39, 9
Ph	Me	$SiMe_3$	Me_3SiCl (A)	75	39
Me	Ph	$CH(OH)C_6H_{13}$	$C_6H_{13}CHO$ (A, B)	80, 80	39, 9
Me	Ph	$CHMe_2$	Me_2CHI (A)	86	39
Ph	Ph	Me	MeI (A, B)	84, 73	39-41, 9
Ph	Ph	Pr	PrI (B)	82	40, 41, 9
Ph	Ph	Bu	BuI (A)	93	42

Ph	Ph	$(CH_2)_{11}OH$	$THPO(CH_2)_{11}I$ (B)	57[a]	40, 41, 9
Ph	Ph	$(CH_2)_{12}OH$	$THPO(CH_2)_{12}I$ (B)	43[a]	40, 41, 9
Ph	Ph	$(CH_2)_{11}CH(OH)Me$	$THPOCHMe(CH_2)_{11}I$ (B)	40[a]	40, 41, 9
Ph	Ph	$(CH_2)_5CH{=}CHCH_2CH(OH)Me$	$THPOCHMeCH_2CH{=}CH(CH_2)_5I$ (B)	43[a]	40, 41, 9
Ph	Ph	CH_2CH_2OH	oxirane (B)	85	43
Ph	Ph	$CH_2CH(OH)Me$	2-methyloxirane (B)	45	40
Ph	Ph	CH(OH)Ph	PhCHO (C)	–	44
Ph	Ph	$C(OH)Ph_2$	Ph_2CO (C)	–	44
Ph	Ph		cyclopentanone (A, B)	90, 90	39, 9
Ph	Ph		cyclohexanone (C)	–	44
Ph	Ph		cyclohexenone (A)	–	39
Ph	Ph	$(CH_2)_5CHO$	 (B)	62	41

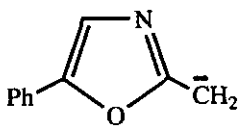
Ph	Ph	CH_2CH_2OH	$Me_3SiOCH_2CH_2I$ (A)	77[d]	45
Ph	Ph		 (A)	84	45
Ph	Ph	CH_2SnMe_3	Me_3SnCH_2I (B)	70	46
Ph	Ph	CH_2COMe	$CH_2=C(OMe)CH_2Br$ (A)	59	47
Ph	Ph			96	47
CO_2H	$SiMe_3$	D	MeOD (A)	77	33
CO_2H	$SiMe_3$	Me	MeI (A)	86	33
CO_2H	$SiMe_3$	$CH(OH)CHMe_2$	Me_2CHCHO (A)	88	33
CO_2H	$SiMe_3$	$C(OH)Me_2$	Me_2CO (A)	90	33
Me	CO_2H	Me	MeI (A, B)	87	48, 49
Me	CO_2H	Et	EtI (A, B)	66	49
Me	CO_2H	$CH_2CH=CH_2$	$CH_2=CHCH_2Br$ (A, B)	79	49
Me	CO_2H	CH(OH)Ph	PhCHO (A, B)	87	48, 49
Me	CO_2H	$CH(OH)C_6H_{13}$	$C_6H_{13}CHO$ (A, B)	80	48, 49

Me	CO_2H	$CH(OH)C_6H_4OMe$-4	4-$MeOC_6H_4CHO$ (A, B)	50	48
Me	CO_2H	$C(OH)Ph_2$	Ph_2CO (A, B)	78	48, 49

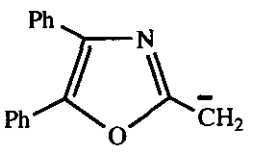
[a] Metallation reagents: A = BuLi/Et_2O or THF/low temperatures (e.g. -78 °C); B = LDA/THF/-78 °C; C = $LiNH_2$/liquid NH_3; D = *tert*-BuLi (2 mol. equiv. in THF/-78 °C). [b] The product obtained depends on the ratio of starting material : LDA : RX; polyalkylation occurs under certain conditions. [c] Yield of alcohol after hydrolysis of THP ether. [d] Yield of alcohol after hydrolysis during work-up of TMS-protected alcohol.

use of butyllithium resulted in failed reactions. Noteworthy is a comment by Meyers and Walker[34] that it is difficult to deprotonate (some) 2-methyloxazoles.

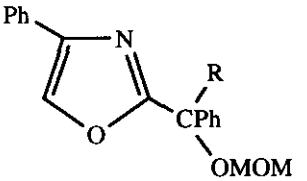
The most studied anion (**29**) (see ref. 50) is generated from the corresponding 2-methyl compound using either butyllithium (THF/-78 °C or -90 °C),[42,45,47] LDA (THF/-78 °C or -50 °C),[9,39-41,46] LDA in the presence of HMPA,[43] or sodamide in liquid ammonia.[44] This anion (**29**) has been trapped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



(**28**)



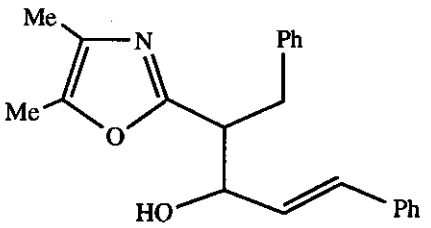
(**29**)



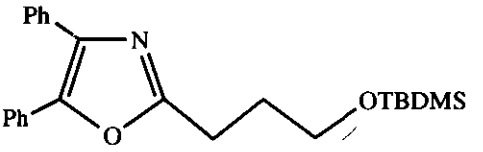
(**30**)

Noteworthy is the fact that the methoxymethyl (MOM) protected ether (**30**; R = H) undergoes α-deprotonation with butyllithium (THF/-78 °C) rather than metallation at position-5 and the resulting anion can be trapped with acetyl chloride to give compound (**30**; R = $COCH_3$) (Table IV).[24]

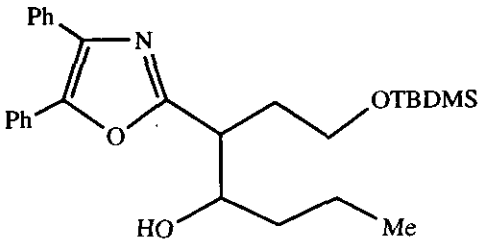
Sequential treatment of 4,5-dimethyl-2-phenethyloxazole with LDA (THF/-78 °C) and cinnamaldehyde yields compound (**31**) (60% yield) as a mixture of diastereoisomers[39] whilst similar reactions between the TBDMS-protected ether (**32**) and butyraldehyde[43] and between 2-pentyl-4,5-diphenyloxazole and *S*-2-methoxymethyl-oxypropanal[42] yield compound (**33**) (75% yield) and compound (**34**) (58%), respectively, also as mixtures of diastereoisomers. (+)-(1*R*,2*R*,3*S*)-**34** was obtained pure from the mixture by flash chromatography. Likewise, 5-methyl-4-phenyl-2-trimethylsilylmethyloxazole is α-metallated at position-2 and the α-lithiated product has been treated with benzaldehyde.[39]



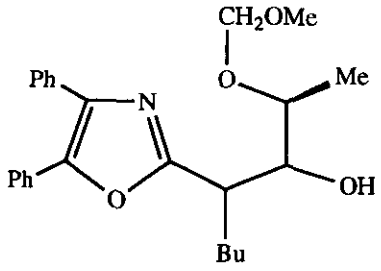
(**31**)



(**32**)

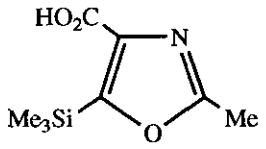


(33)

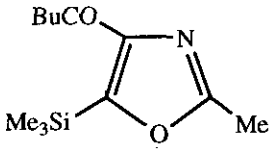


(34)

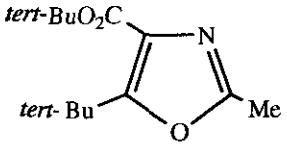
In order to substitute the methyl group in 2-methyloxazole-4-carboxylic acid it is necessary first to protect position-5 with a trimethylsilyl group (Section II; Table III). The product (**35**) can be metallated with *tert.*-butyllithium (2 mol. equiv. in THF/-78 °C); after 2 min the appropriate trapping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



(35)



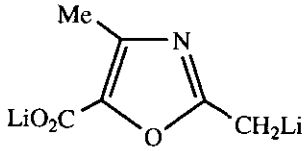
(36)



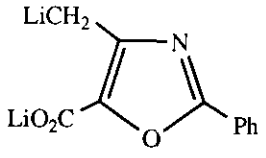
(37)

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

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

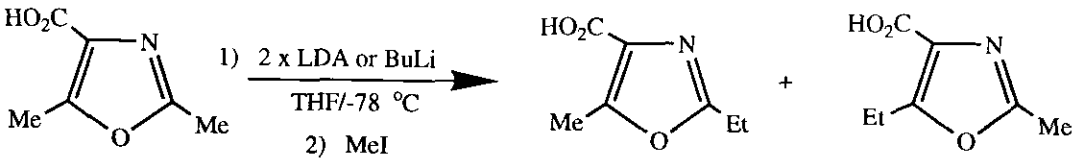


(38)



(39)

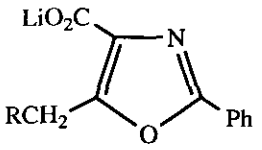
yields (68%) of 4-ethyl-2-phenyloxazole-5-carboxylic acid are to be obtained following addition of iodomethane. 2,5-Dimethyloxazole-4-carboxylic acid (**40**) reacts at both methyl groups. Comparable amounts of compounds (**41**) and (**42**) (Scheme 6) are produced with LDA but, with butyllithium, the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



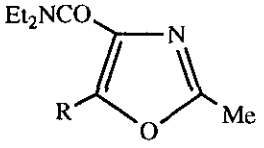
(**40**) (**41**) (**42**)

Scheme 6

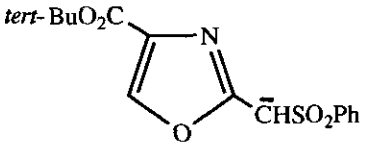
(BuLi/THF/- 78 °C), which can be quenched with iodomethane, to give 5-ethyl-2-phenyloxazole-4-carboxylic acid (**43**; R = Me, Li = H) (86% yield).[48,49] Compounds [**43**; R = $CH_2CH{=}CH_2$, Li = H (75%) and R = $CH_2CH(OH)Et$, Li = H (60%)] can be prepared similarly.[48] Ethyl 4-methyloxazole-5-carboxylate is metallated with LiICA exclusively in position-2.[25] The amide group in compound (**44**) is a much more powerful *ortho*-directing group which allows selective introduction of substituents into the 5-methyl group; compounds (**45**)-(**49**) can be synthesised in this way (using BuLi/THF/-78 °C).[48,49]



(**43**)



(**44**) R = Me
(**45**) R = Et (98%)
(**46**) R = Pr (91%)
(**47**) R = $(CH_2)_2CH{=}CH_2$ (90%)
(**48**) R = $CH_2CH(OH)Ph$ (98%)
(**49**) R = $CH_2CH(OH)Pr$ (15%)



(**50**)

Noteworthy is the generation of anion (**50**) *via* treatment of the corresponding 2-phenylsulfonylmethyl compound with sodium hydride in THF at -15 → -10 °C[35]; it has been allowed to react with various acylating electrophiles.

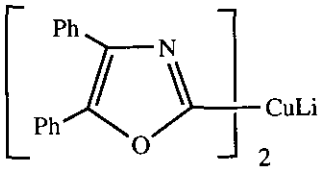
V POLYLITHIATED DERIVATIVES

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

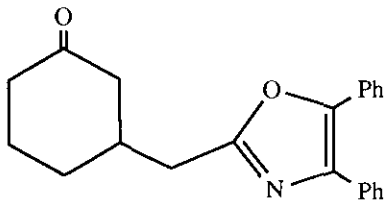
VI OTHER ORGANOMETALLIC DERIVATIVES

2-Methyl-4,5-diphenyloxazole reacts sequentially with butyllithium (THF/-100 °C) and cuprous iodide (Et_2O/ -45 °C) in the presence of dimethyl sulfide to give organocopper derivative (**51**) which undergoes conjugate addition with 2-cyclohexenone, to give adduct (**52**) (> 80% yield).[39]

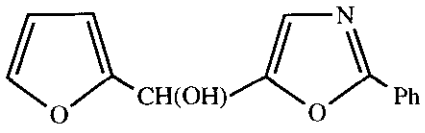
2,4-, 2,5-, and 4,5-Diphenyloxazole and 2-methyl-5-phenyloxazole are mercurated by mercuric acetate in the vacant ring-position[51,52] and the resulting mercurated derivatives react with bromine or iodine[51,53] to give *moderate (55%) to high (85%) yields of the corresponding halogen derivative* (see also ref. 54). The mercurated derivatives derived from 2,4- or 2,5-diphenyloxazole give the corresponding [oxazol-5(or 4)-yl]$_2$Hg derivative with sodium stannite.[51,52] Each of the mercurated derivatives is hydrolysed back to the corresponding oxazole with dilute mineral acid.[51,52]



(**51**)



(**52**)



(**53**)

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

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

ACKNOWLEDGEMENTS

We thank Sandra Fahy for her help in preparing this article.

REFERENCES

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

18. D. Hoppe and U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 300.

19. U. Schöllkopf, F. Gerhart, I. Hoppe, R. Harms, K. Hantke, K.H. Scheunemann, E. Eilers, and E. Blume, *Liebigs Ann. Chem.*, 1976, 183.

20. J.C. Hodges, W.C. Patt, and C.J. Connolly, *J. Org. Chem.*, 1991, **56**, 449.

21. A. Dondoni, T. Dall'Occo, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, *J. Chem. Soc., Chem. Commun.*, 1984, 258.

22. A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, *Synthesis*, 1987, 693.

23. P.A. Jacobi, S. Ueng, and D. Carr, *J. Org. Chem.*, 1979, **44**, 2042.

24. S.E. Whitney and B. Rickborn, *J. Org. Chem.*, 1991, **56**, 3058.

25. R.K. Howe and L.F. Lee, U.S. Patent 4,360,678/1982.

26. R. Baker, R.J. Snow, J. Saunders, and G.A. Showell, Europ. Pat. Appl. 0-307-141-A2/1988 (*Chem. Abstr.*, 1989, **111**, 153786).

27. P.D. Edwards, J.J. Lewis, C.W. Perkins, D.A. Trainor, and R.A. Wildonger, Europ. Pat. Appl. 0-291 234-A2/1988 (*Chem. Abstr.*, 1989, **110**, 232092).

28. A.P. Kozikowski and A. Ames, *J. Org. Chem.*, 1980, **45**, 2548.

29. A. Dondoni, *Phosphorus, Sulfur, Silica*, 1989, **43**, 25.

30. H.H. Wasserman, R.W. DeSimone, W.-B. Ho, K.E. McCarthy, K.S.Prouse, and A.P. Spada, *Tetrahedron Lett.*, 1992, **33**, 7207.

31. I. Hoppe and U. Schöllkopf, *Liebigs Ann. Chem.*, 1979, 219.

32. A.I. Meyers and J.P. Lawson, *Tetrahedron Lett.*, 1981, **22**, 3163.

33. R.D. Wood and B. Ganem, *Tetrahedron Lett.*, 1983, **24**, 4391.

34. A.I. Meyers and D.G. Walker, *J. Org. Chem.*, 1982, **47**, 2999.

35. Y. Nagao, S. Yamada, and E. Fujita, *Tetrahedron Lett.*, 1983, **24**, 2287.

36. C. Kashima and H. Arao, *Synthesis*, 1989, 873.

37. T.L. Gilchrist and D.P.J. Pearson, *J.C.S., Perkin Trans. 1*, 1976, 989.

38. C. Kashima, H. Arao, and R. Okada, *Heterocycles*, 1990, **30**, 487.

39. B.H. Lipshutz and R.W. Hungate, *J. Org. Chem.*, 1981, **46**, 1410.

40. H.H. Wasserman, R.J. Gambale, and M.J. Pulwer, *Tetrahedron Lett.*, 1981, **22**, 1737.

41. H.H. Wasserman, R.J. Gambale, and M.J. Pulwer, *Tetrahedron*, 1981, **37**, 4059.

42. H.H. Wasserman and R.J. Gambale, *Tetrahedron*, 1992, **48**, 7059.

43. H.H. Wasserman and T-J. Lu, *Recl. Trav. Chim. Pays-Bas*, 1986, **105**, 345.

44. V. Dryanska and K. Ivanov, *God. Sofii. Univ. Khim. Fak.*, **63**, 105 [1968-1969 (Publ. 1971)] (*Chem. Abstr.*, 1972, **76**, 126844).

45. L.N. Pridgen, S.C. Shilcrat, and I. Lantos, *Tetrahedron Lett.*, 1984, **25**, 2835.

46. W.R. Baker, *J. Org. Chem.*, 1985, **50**, 3942.

47. T. Sasaki, M. Ohno, and E. Ito, *J. Chem. Soc., Perkin Trans. 1*, 1983, 3027.

48. P. Cornwall, C.P. Dell, and D.W. Knight, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2417.

49. P. Cornwall, C.P. Dell, and D.W. Knight, *Tetrahedron Lett.*, 1987, **28**, 3585.

50. H.H. Wasserman and K.S. Prowse, *Tetrahedron*, 1992, **48**, 8199.

51. O.P. Shvaika and G.P. Klimisha, *Dopovidi Akad. Nauk. Ukr. RSR*, 1965, 1479 (*Chem. Abstr.*, 1966, **65**, 7159).

52. O.P. Shvaika and G.P. Klimisha, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1966, **2**, 14.

53. O.P. Shvaika and G.P. Klimisha, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1966, **2**, 517.

54. W.J. Hammar and M.A. Rustad, *J. Heterocycl. Chem.*, 1981, **18**, 885.

55. A.I. Meyers and E.D. Mihelich, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 270.

56. J. ApSimon and A. Holmes, *Heterocycles*, 1977, **6**, 731.

57. B.E. Marynoff, *Chem. Heterocycl. Compd.*, 1986, **45**, 963.

Received, 20th September, 1993