SYNTHESIS AND REACTIONS OF LITHIATED MONOCYCLIC AZOLES CONTAINING TWO OR MORE HETERO-ATOMS PART V: ISOTHIAZOLES AND THIAZOLES[1] †

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Abstract *- The metallation and halogen → metal exchange reactions of isothiazoles (1,2-thiazoles) and thiazoles (1,3-thiazoles) and the reactions of the resulting organometallic derivatives, particularly lithiated derivatives, are reviewed comprehensively.*

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

I GENERAL INTRODUCTION

A general introduction to this series of reviews was given in Part I.[2] Parts I-III cover the literature through June 1993 whilst Parts IV and V cover the literature through December 1993.

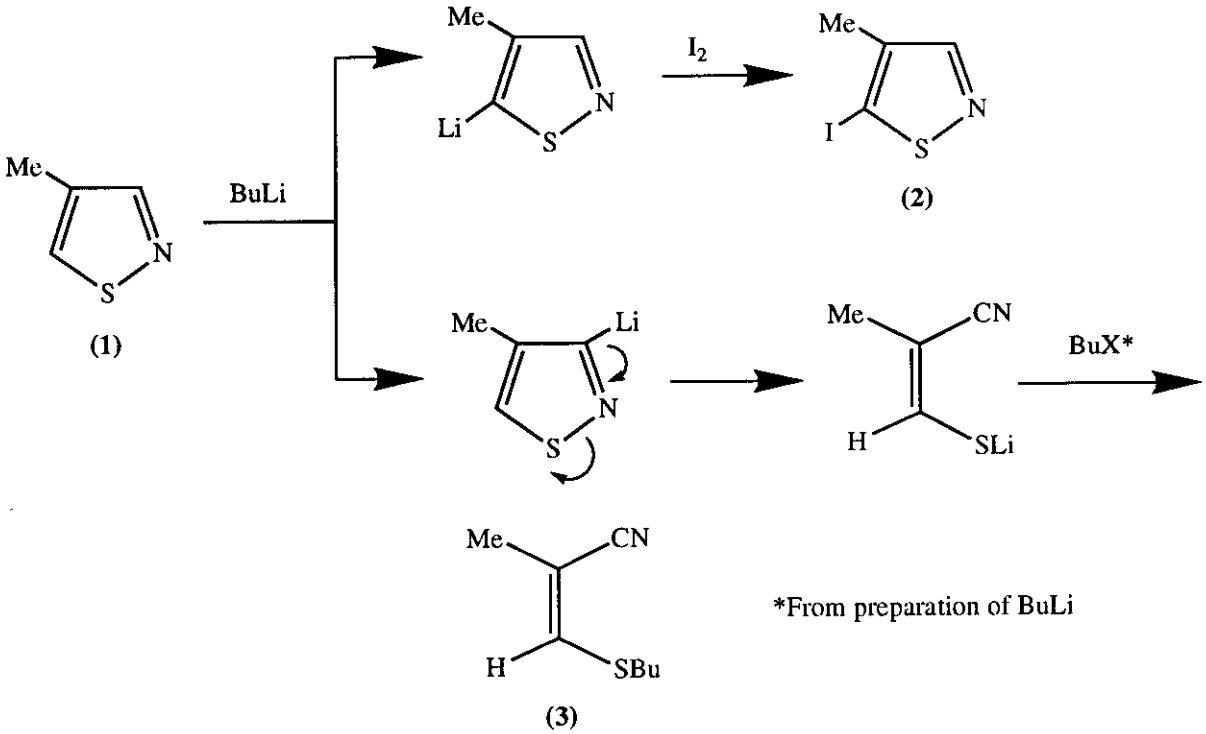
II ISOTHIAZOLES (1,2-THIAZOLES)[3-5]

A Introduction

This is one of the least studied systems covered by this series of reviews, which is probably attributable to the inavailability of many simple isothiazoles. 3(And 4)-lithiated isothiazoles are virtually unknown, and lateral metallation, especially compared with the importance of this topic in the isoxazole area, has been little explored.

B Monometallation in the ring

A minor amount (8% yield) of the ring-opened product (**3**) (Scheme 1) is formed during metallation of 4-methylisothiazole (**1**) with butyllithium[6] (see also ref. 7). Metallation occurs predominantly in position-5, as shown by isolation of 5-iodo-4-methylisothiazole (**2**) (69% yield) following addition of iodine. This (Scheme 1) appears to be the only 3-lithiated isothiazole reported to date.

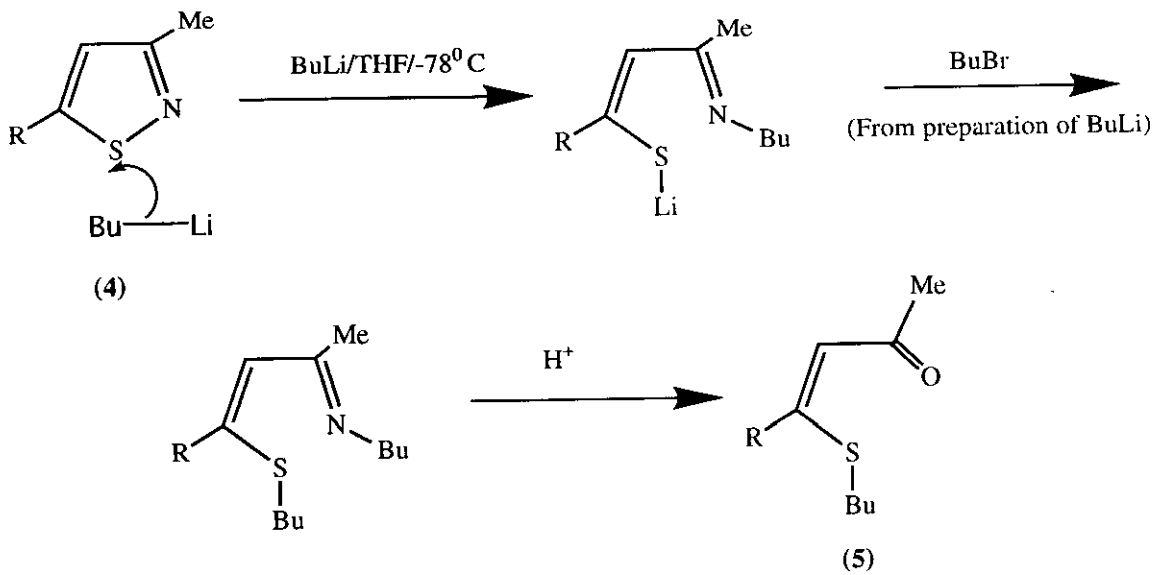


Scheme 1

Likewise, there is only one reference in the literature to metallation of an isothiazole at position-4, namely metallation of 3-methoxy-5-phenylisothiazole with butyllithium [tetrahydrofuran (THF)/-70 °C] and conversion of the 4-lithiated derivative into the corresponding 4-iodo compound (90% yield) with iodine.[8]

Isothiazole and its 3- or 4-mono- and 3,4-disubstituted derivatives are metallated by butyllithium (THF/low temperatures, e.g. -70 °C) in position-5; the resulting 5-lithiated derivatives can be quenched with a range of electrophilic reagents (Table I). At these low temperatures metallation occurs at this position even when substituents are present in other positions which are normally reactive to organolithium reagents, e.g. Br, I,[9-11] CO_2H[9,10,12-15] and CN.[10,11] In view of the low yields reported in some cases, however, it is likely that products arising from attack at the substituent were also present but not characterised. When 4-bromo-3-phenylisothiazole is metallated with butyllithium (THF/-70 °C) and the product trapped with iodomethane, the 5-methyl derivative is the major product (55% yield) but some 3-phenyl- (8.5%) and 5-methyl-3-phenylisothiazoles (4%) (products of Br → Li exchange; see later) are also present in the crude product.[10] Similarly, 4-bromo-3-(4-methoxyphenyl)isothiazole yields mainly its 5-methyl derivative (33%) under these conditions but some 3-(4-methoxyphenyl)-5-methylisothiazole is formed too.[10] Katritzky *et al.*[16] have shown that isothiazole is metallated in position-5 more efficiently with lithium diisopropylamide (LDA) (THF/-70 °C) than with butyllithium.

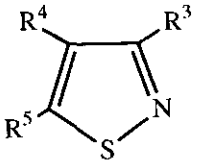
During the synthesis of 3-methylisothiazole-5-carbaldehyde (Table I) from 3-methylisothiazole (**4**; R = H) the ring-opened product (**5**; R = H) is formed, as shown in Scheme 2.[9] An attempt to metallate methyl 3-methyl-

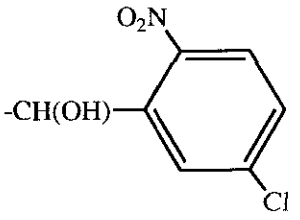
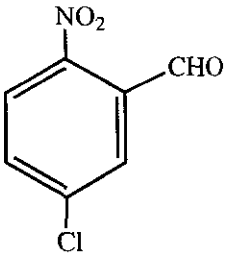


Scheme 2

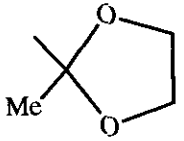
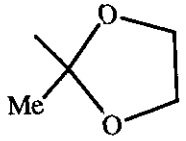
Table I

Isothiazoles Prepared From Isothiazol-5-yllithium Derivatives



R^3	R^4	R^5	Reagent	Yield (%)	Ref.
H	H	Me	MeI	40	9
H	H	CO_2H	CO_2	48, 61	9, 17
H	H	CHO	DMF	75	9
H	H	Br	Br_2	34	9
H	H	CH(OH)Ar	ArCHO[a]	–	18
H	H	$CH(OH)C_6H_4Cl$-4	4-ClC_6H_4CHO	35	19
H	H			46	20
H	H	$C(OH)Me_2$	Me_2CO	20	21
H	H	$C(OH)Ph_2$	Ph_2CO	56, –	16, 22

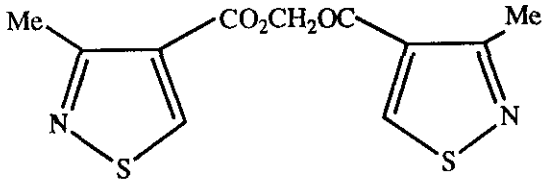
H	H	$C(OH)(C_6H_4Cl\text{-}4)_2$	$(4\text{-}ClC_6H_4)_2CO$	100, –, 66	16, 22, 23
H	H	$CPh(OH)C_6H_4Cl\text{-}4$	$PhCOC_6H_4Cl\text{-}4$	81	16
H	H	$CPh(OH)C_6H_3Cl_2\text{-}3,4$	$PhCOC_6H_3Cl_2\text{-}3,4$	85	16
H	H	$CPh(OH)C_6H_4OMe\text{-}4$	$PhCOC_6H_4OMe\text{-}4$	100	16
H	H	$CPh(OH)C_6H_4CF_3\text{-}4$	$PhCOC_6H_4CF_3\text{-}4$	93	16
H	H	$CPh(OH)C_6H_3F_2\text{-}2,4$	$PhCOC_6H_3F_2\text{-}2,4$	–	22
H	H	$CPh(OH)C_6H_3Cl_2\text{-}2,4$	$PhCOC_6H_3Cl_2\text{-}2,4$	81	16
H	H	$CPh(OH)C_6H_4Cl\text{-}2$	$PhCOC_6H_4Cl\text{-}2$	78	16
H	H	$CO.CO_2Et$	$(CO_2Et)_2$	33.5, 71	24, 25
Me	H	Me	MeI	–	9
Me	H	CO_2H	CO_2	50, –	9, 12
Me	H	CHO	DMF	50	9
Me	H	CH(OH)Ph	PhCHO	32	19
Me	H	$CH(OH)C_6H_4Cl\text{-}4$	$4\text{-}ClC_6H_4CHO$	33	19
Me	H	CH(OH)Ar	ArCHO[a]	–	18
Me	H	CH(OH)pyrid-2-yl	pyrid-2-ylCHO	–	19
Me	H	$CO.CO_2Et$	$(CO_2Et)_2$	45	24
Me	H	SCH_2CO_2Et	S_8, then $BrCH_2CO_2Et$	36[b]	26
H	Me	I	I_2	69	6
H	Me	CO_2H	CO_2	40, –	9, 12
H	Me	CHO	DMF	55	9

H	Me	SCH_2CO_2Et	S_8, then $BrCH_2CO_2Et$	51[b]	26
H	Me	CH(OH)Ar	ArCHO[a]	–	18
Me	Cl	CO_2H	CO_2	75	9
Me	Br	CO_2H	CO_2	56	9
Me	I	CO_2H	CO_2	58	9
Me	Cl	CHO	DMF	47	9
Me	Br	CHO	DMF	51	9
Me	I	CHO	DMF	68	9
Me	Br	Me	MeI	40	9
Me	Br	Et	EtI	34	9
Me	Br	Pr	PrI	28	9
Me	Br	CH_2Ph[c]	$PhCH_2Br$	13[c]	9
Me	CO_2H	Me	MeI	–	15
Me	CO_2H	CO_2H	CO_2	29	9
Me	CO_2H	CHO	DMF	25	9
Me	CO_2H	Br	Br_2	52	9
Me		Me	MeI	–	15
Me		Et	EtI	–	15

H	Cl	CO_2H	CO_2	68	9
H	Cl	CHO	DMF	65	9
H	Br	CO_2H	CO_2	70	9
H	Br	CHO	DMF	75	9
H	I	CHO	DMF	33	9
H	CO_2H	CO_2H	CO_2	15	9
H	CO_2H	Me	Me_2SO_4	–	12
Ph	H	Me	MeI	66, –	10, 27
Ph	H	Br	Br_2	42	27
Ph	H	CO_2H	CO_2	39	27
Ph	CN	Me	MeI	22, –	10, 11
Ph	COOH	Br	Br_2	41, –, 73	10, 13, 14
Ph	Br	Me	MeI	55[d], 41	10, 11
Ph	Br	CHO	DMF	39	10
C_6H_4OMe-4	Br	Me	MeI	33[d], 18	10, 11

[a] A large number of aromatic aldehydes have been reacted with isothiazol-5-yllithium compounds. [b] Yield quoted is that of acid obtained by hydrolysis of ester shown. [c] Isolated together with 10% of $ArCH(CH_2Ph)Ph$, where Ar = 4-bromo-3-methylisothiazol-5-yl. [d] See text (Section II.B) for description of by-products.

isothiazole-4-carboxylate at position-5 with butyllithium followed by attempted carbonation of the product resulted only in formation of compound (**6**) through initial metallation in the ester methyl group followed by self-condensation.[9]



(**6**)

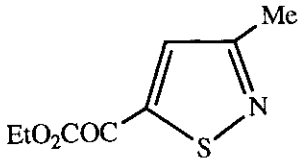
In order to minimise ring-cleavage of an isothiazole ring diethylaminoethyllithium[28] and biphenyl-2-lithium[29] have been used (these systems were not monocyclic isothiazoles).

C Halogen → lithium exchange reactions

Hydrolysis of the product of reacting 4-bromo-3-phenylisothiazole with butyllithium (THF/-70 °C) gives 3-phenylisothiazole (39% yield)[10] (see preceding Section). The only other useful preparation of a 4-lithiated isothiazole *via* bromine → lithium exchange is the conversion of 4-bromo-3-(4-methoxyphenyl)-5-methyl-isothiazole into the 4-carboxylic acid (43% yield)[10,11] (see also preceding Section.)

5-Bromo-3-phenylisothiazole can be converted similarly into the corresponding 5-carboxylic acid (88% yield).[27]

3-Methylisoxazol-5-yllithium, prepared similarly, reacts with diethyl oxalate, to give the glyoxalate derivative (**7**) (45%),[24] and with *N,N*-dimethylformamide (DMF), to give 3-methylisothiazole-5-carbaldehyde (29%).[30]



(**7**)

D Lateral metallation

When 3,5-dimethylisothiazole (**4**; R = Me) is allowed to react with butyllithium followed by hydrolysis of the product with acid, the ketone (**5**; R = Me) is formed, as shown in Scheme 2.[6] Lateral metallation can be achieved at position-5, with avoidance of ring-cleavage, with sodium amide or LDA; the latter is preferred[31] (Table II).

Table II

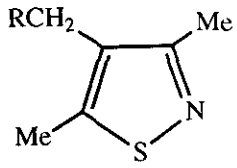
Products Obtained by Metallation of 3,5-Dimethylisothiazole[31]

R	Reagents[a]	Yield (%)	Yield (%)
Me	MeI (A)	21	
Et	EtBr (A)	32	
Bu	BuBr (B)	37	
Bu	BuBr (C)	39	
CH_2Ph	$PhCH_2Cl$ (A)	41	
CH_2Ph	$PhCH_2Cl$ (C)	57	
Me	MeI (D)	53	
Et	EtBr (D)	71	
Bu	BuBr (D)	88	
CH_2Ph	$PhCH_2Cl$ (D)	85	
$CH_2CH=CH_2$	$CH_2=CHCH_2Br$ (D)	83	
$CH_2CH=CHMe$	$MeCH=CHCH_2Cl$ (D)	82	
Et	EtBr (E)	63	27

Bu	BuBr (E)	68	23
CH_2Ph	$PhCH_2Cl$ (E)	65	23
$CH_2CH{=}CH_2$	$CH_2{=}CHCH_2Br$ (E)	73	19
$CH_2CH{=}CHMe$	$MeCH{=}CHCH_2Cl$ (E)	60	25

[a] Reagents: A = $NaNH_2/Et_2O$/-30 °C; B = $NaNH_2/Et_2O$/-78 °C; C = $NaNH_2$/THF/-78 °C; D = LDA/THF/-78 °C (all 1 mol. equiv. with respect to substrate); E = LDA (2 mol. equiv.)/THF/-78 °C.

However, unlike 3,5-dimethylisoxazole,[2] which undergoes dialkylation at position-5, 3,5-dimethylisothiazole undergoes monoalkylation (LDA/THF/-78 °C) at position-5 followed by further alkylation at position-3 (Table I).



(8)

Compounds (**8**) carrying an electron-withdrawing substituent R (CO_2Et, CN, or 4-$MeC_6H_4SO_2$) undergo lateral metallation in the 4-methylene group with sodium amide, LDA, lithium 2,2,6,6-tetramethylpiperidide (LiTMP), lithium cyclohexylisopropylamide (LiCIA), or butyllithium and the resulting anions can be trapped with various electrophiles and they undergo Michael addition to α,β-unsaturated ketones or esters[32] (see Table III for details).

E Other organometallic derivatives

4,5-Dibromoisothiazole may be prepared by treatment of isothiazole with mercuric acetate in aqueous acetic acid followed by addition of bromine.[33] Whereas a nitro group appears to interfere with lithiation of isothiazoles[9] 4-nitroisothiazole may be converted similarly *via* mercuration into its 5-bromo derivative.[33]

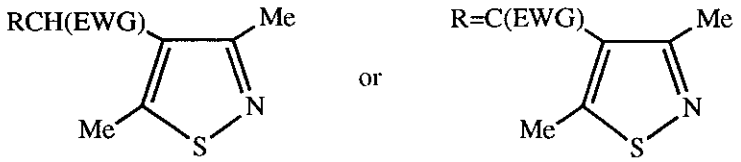
III THIAZOLES (1,3-THIAZOLES)[34-36]

A Introduction

The introduction of substituents into the thiazole ring *via* metallation and halogen → metal exchange methodologies has received growing attention in recent years. The largest contribution to this field has been made by Dondoni's group in Ferrara, Italy.[36-62] They have investigated the synthesis and reactions of thiazol-2-yllithium (Section III.B; see Table IV later for references), 2-trimethylsilylthiazole (2-TMST)[36,37,40,41,44-46,48,49,52-57,60] and various other trimethylsilylthiazoles[36,37,40-43,45] as carbanion equivalents , the synthesis of 2-, 4-, and 5-formylated thiazoles *via* Br → Li exchange strategies (Section III.C),[36,43] and the elongation of amino acids[51,60,61] and carbohydrates[36,39,46-50,54-56,59,62] using thiazol-2-yllithium (Section III.B; Table IV for references), 2-TMST (formyl group equivalent; N.B. we have not attempted in this review to cover all the literature on the **reactions** of this material which is probably more useful as a carbanion equivalent than thiazol-2-yllithium), and various other 2-substituted thiazoles [2-COMe[52-54] and 2-CH=PPh_3[47,48,52-54] for 2-C-atom

Table III

Modification of 4-Substituted 3,5-Dimethylisothiazoles by Lateral Metallation at Position-4[32]



EWG	R	Reagents[a]	Yield (%)
CO_2Et	CO_2Et	$(EtO)_2CO$ (A)	52
CO_2Et	$(CH_2)_3Br$	$Br(CH_2)_3Br$ (B)	23
CO_2Et	$(CH_2)_3Cl$	$I(CH_2)_3Cl$ (B)	46
CO_2Et	$(CH_2)_4Cl$	$I(CH_2)_4Cl$ (B)	49
CO_2Et	$CH_2CH=CH_2$	$CH_2=CHCH_2Br$ (B)	51
CO_2Et	$CHPhCH_2COPh$	PhCH=CHCOPh (B)	64
CO_2Et	=C(OH)Me	MeCOCl (B)	63
CO_2Et	=C(OH)Ph	PhCOCl (B)	60
CO_2Et	$=C(OH)(CH_2)_2Ph$	$Ph(CH_2)_2COCl$ (B)	38
CO_2Et	$=C(OH)(CH_2)_3Ph$	$Ph(CH_2)_3COCl$ (B)	40
CN	CO_2Et	$(EtO)_2CO$ (B)	86
CN	CO_2Et	$ClCO_2Et$ (B)	82
CN	$(CH_2)_3Cl$	$I(CH_2)_3Cl$ (B)	70
CN	$(CH_2)_4Cl$	$I(CH_2)_4Cl$ (B)	63

CN	$CH_2CH{=}CH_2$	$CH_2{=}CHCH_2Br$ (B)	89
CN	CH_2Ph	$PhCH_2Cl$ (B)	75
CN	$CH(OH)CHMe_2$	Me_2CHCHO (B)	17
CN	CH(OH)Ph	PhCHO (B)	44
CN	$CH(OH)C_6H_4Cl$-4	4-ClC_6H_4CHO (B)	51
CN	$CH(OH)C_6H_4OMe$-4	4-$MeOC_6H_4CHO$ (B)	24
CN	$CHPhCH_2COPh$	$PhCH{=}CHCOPh$ (B)	83
CN	$CHPhCH_2CO_2Et$	$PhCH{=}CHCO_2Et$ (B)	41
CN	$CHMeCH_2CN$	$MeCH{=}CHCN$ (B)	76
CN	=CH(OH)	HCO_2Et (B)	81
CN	=C(OH)Me	$MeCO_2Et$ (B)	31
CN	=C(OH)Me	MeCOCl (B)	75
CN	=C(OH)Ph	$PhCO_2Et$ (B)	23
CN	=C(OH)Ph	PhCOCl (B)	72
CN	$=C(OH)CO_2Et$	$(CO_2Et)_2$ (B)	50
CN	$=C(OH)(CH_2)_2Ph$	$Ph(CH_2)_2COCl$ (B)	70
4-$MeC_6H_4SO_2$	Me	MeI (C)	71
4-$MeC_6H_4SO_2$	Bu	BuBr (C)	43
4-$MeC_6H_4SO_2$	$(CH_2)_4Cl$	$I(CH_2)_4Cl$ (C)	48
4-$MeC_6H_4SO_2$	$CH_2CH{=}CH_2$	$CH_2{=}CHCH_2Br$ (C)	69

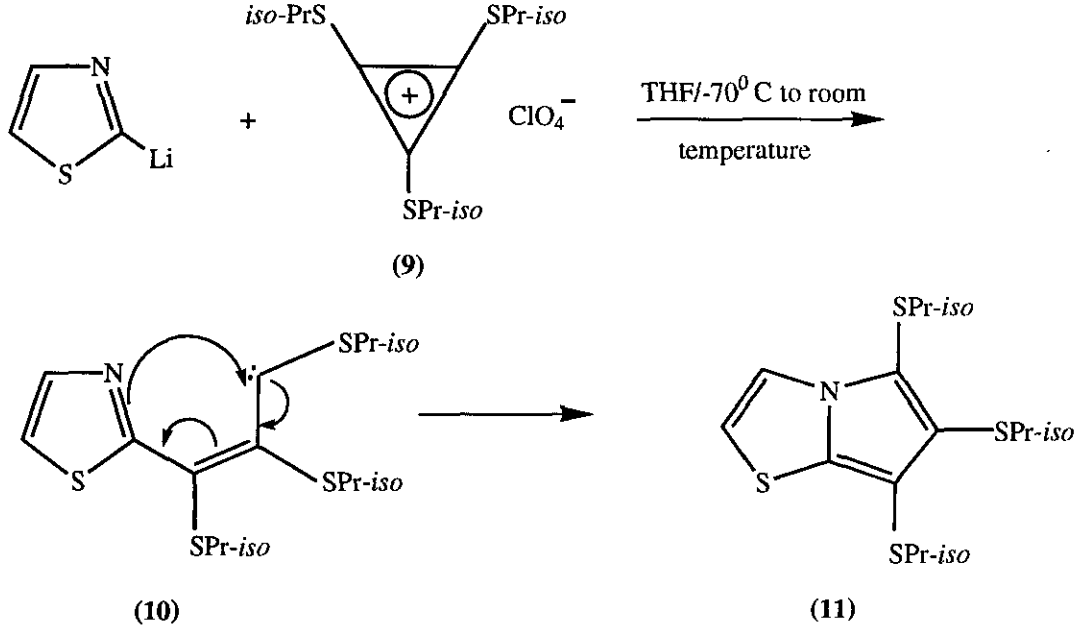
[a] Metallating reagent: A = $NaNH_2/Et_2O$/35 °C; B = lithium cyclohexylisopropylamide (LiCIA)/THF/-78 °C; C = BuLi/THF/-78 °C.

extensions, and 2-COCH=PPh_3[52-54] for 3-C-atom extensions]. The thiazole ring is one of the most convenient formyl group equivalents. It can be incorporated into the different types of reagents and easily installed in a variety of substrates. It is stable to various reaction conditions and can be cleaved to release a formyl group (thiazole C-2 atom) under mild and neutral conditions, recently improved.[63] Dondoni has reviewed the work of his group several times[36,40,41,44,48,49,52-54] and we refer the reader to the literature for further details. Few fragmentation reactions of metallated thiazoles have been reported.

B Monometallation in the ring

Metallation of thiazoles with organolithium reagents [THF or ether (Et_2O)] occurs readily in position-2, if vacant, and the resulting 2-lithiated derivatives have been used extensively to introduce other substituents into this position (Table IV). Butyllithium is the reagent usually used for the metallation step but other reagents have been employed. Thiazol-2-yllithium is reported to be stable only at low temperatures (< -40 °C)[64,65] but its substitution by alkyl groups at position-4 and/or -5 increases the stability of the corresponding 2-lithiated derivative.[65,66] A study has been made of the relative reactivities of 4-ethyl- and 4,5-dimethylthiazol-2-yllithiums towards the C=N bonds in pyridine, quinoline, pyridine-4-carbonitrile, and benzylideneaniline;[66] both of these 2-lithiated thiazoles are less reactive in this respect than butyl- or phenyllithium (BuLi > PhLi).

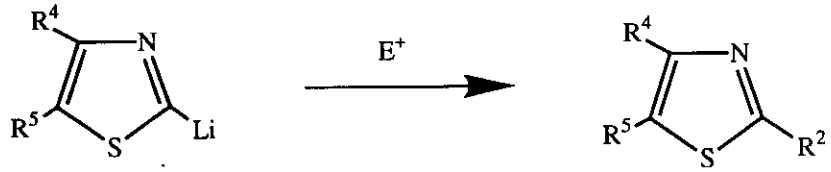
Thiazol-2-yllithium reacts with 1,2,3-*tris*(isopropylthio)cyclopropylium perchlorate (**9**), to give the pyrrolo[2,1-*b*]thiazole (**11**) (71% yield) *via* formation of the intermediate vinyl carbene (**10**) (Scheme 3).[67]

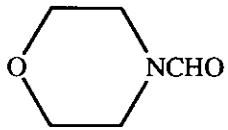


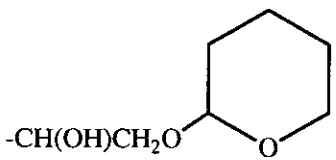
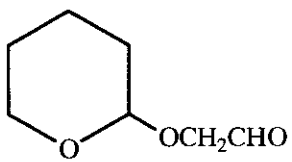
Scheme 3

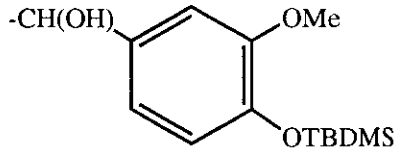
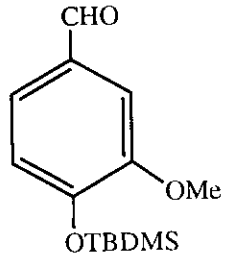
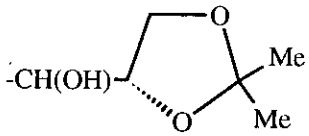
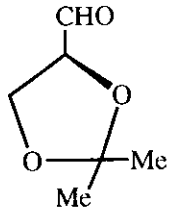
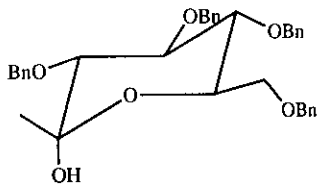
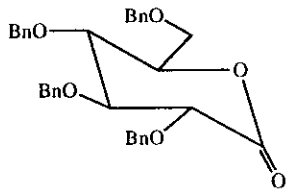
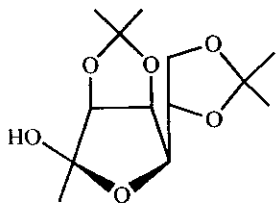
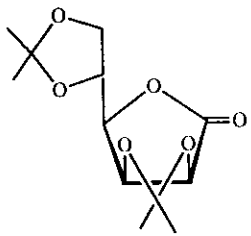
Table IV

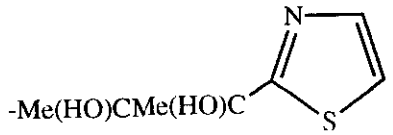
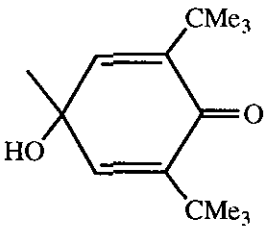
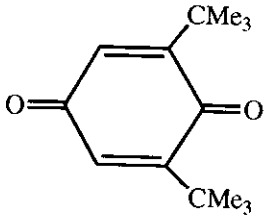
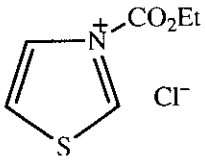
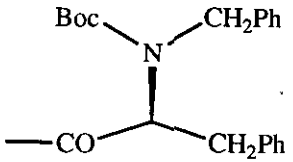
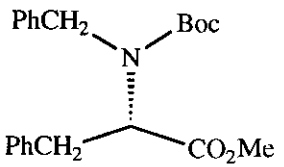
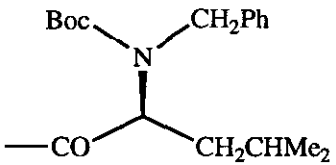
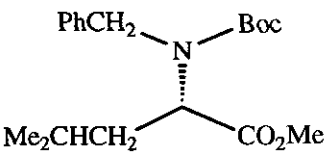
2-Substituted Thiazoles Prepared from Thiazol-2-yllithium Compounds

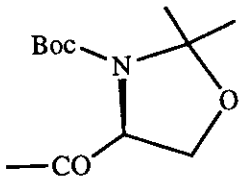
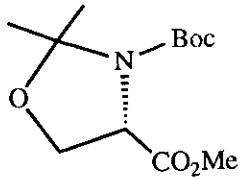
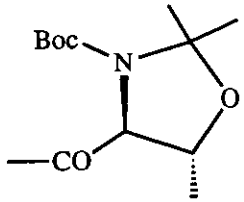
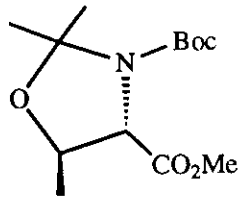
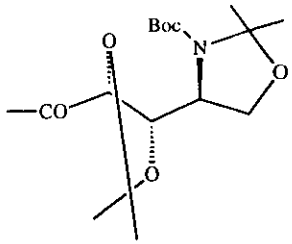
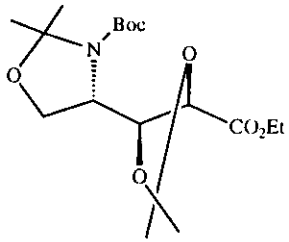


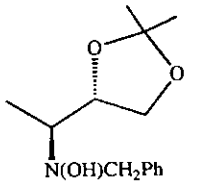
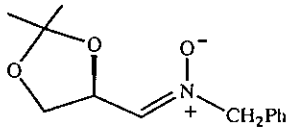
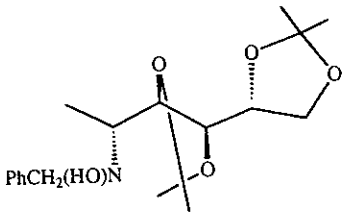
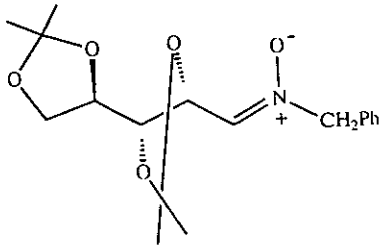
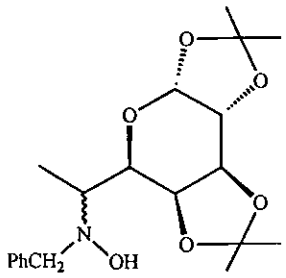
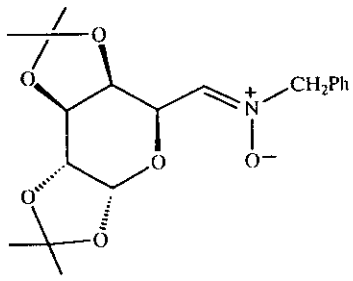
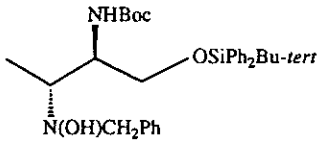
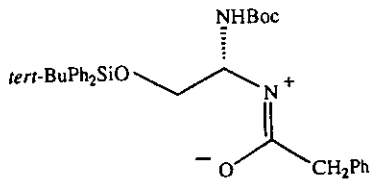
R^4	R^5	R^2	Reagent	Yield (%)	Ref.
H	H	D	$DOAc/D_2O$	40[a]	68
H	H	I	I_2	90[b]	69
H	H	CHO	DMF	78[b], 80[b], 61[b]	43, 53, 70
H	H	CHO	PhNMeCHO	–	71
H	H	CHO		80[b]	43
H	H	CO_2H	CO_2	40, 94[b], 62[b], 75-90[b]	64, 72-74
H	H	COMe	$MeCO_2Et$	92	53
H	H	$COCH_2Br$	$BrCH_2CO_2Et$	45	62
H	H	$COCH_2Ph$	$PhCH_2CONMeOMe$	98[b]	75, 76

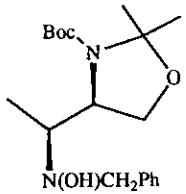
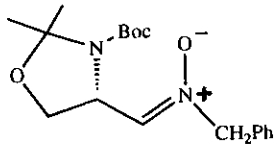
H	H	$CO.CO_2Et$	$(CO_2Et)_2$[c]	72	25
H	H	CH(OH)Me	MeCHO	30, 51[b]	65, 77
H	H	CH(OH)Et	EtCHO	50	65
H	H	CH(OH)Pr	PrCHO	90	65
H	H	CH(OH)Pr-*iso*	*iso*-PrCHO	85	65
H	H	$CH(OH)(CH_2)_5Me$	$Me(CH_2)_5CHO$	90	65
H	H	CH_2CH_2OH	oxirane	30	65
H	H	$CH(OH)CH(CH_2Ph)N(CH_2Ph)_2$	$(PhCH_2)_2NCH(CH_2Ph)CHO$	79	78
H	H	$CH(OH)CH(CH_2OTBDMS)N(CH_2Ph)_2$	$(PhCH_2)NCH$-$(CH_2OTBDMS)CHO$	67	78
H	H	CH(OH)Ph	PhCHO	91[b], –[b]	79, 80
H	H	$CH(OH)C_6H_4NO_2$-2	2-$O_2NC_6H_4CHO$	77[b]	20
H	H	$CH(OH)C_6H_3NO_2Cl$-2,5	5,2-$ClO_2NC_6H_3CHO$	69[b]	20
H	H	$CH(OH)CH_2OCPh_3$	$Ph_3CCH_2CH_2CHO$	50[b]	81
H	H			39[b,d]	81

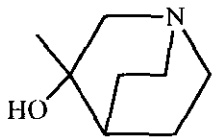
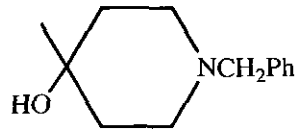
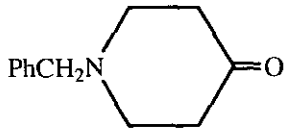
H	H			95	82
H	H			–[c]	39,46 (see also ref. 50)
H	H	$C(OH)MeCH(OMe)_2$	$(MeO)_2CHCOMe$	–[b]	81
H	H	$C(OH)MeCH(OEt)_2$	$(EtO)_2CHCOMe$	–[b]	81
H	H	$C(OH)MeCMe(OMe)_2$	$MeCOCMe(OMe)_2$	–[b]	81
H	H	$C(OH)MeCO_2Me$	$MeCOCO_2Me$	3[b]	81, 83
H	H			80[b]	59
H	H			76[b]	59

H	H		MeCOCOMe	b,f	81
H	H			b	84
H	H	$COCHMeOCH_2OCH_2Ph$	$PhCH_2OCH_2OCHMeCO_2Et$	b	47
H	H	CO(thiazol-2-yl)		18g	38
H	H			91b,h	51, 60
H	H			93b,i	60

H	H			90[b,i]	60
H	H			89[b,k]	60
H	H			80[b,i]	55
H	H	$C(OH)Ph_2$	Ph_2CO	22	65
H	H	$C(OH)(C_6H_4Cl\text{-}4)_2$	$(4\text{-}ClC_6H_4)_2CO$	29	23
H	H	CSNHMe	MeNCS	96	85
H	H	CSNHPh	PhNCS	45.5	85
H	H	CSNH(naphth-1-yl)	(naphth-1-yl)NCS	24	85

H	H			62[b,l]	50
H	H			61[b,m]	50
H	H			good[b,n]	56
H	H			86[b,o]	61

H	H			89[b,p]	61
H	H	$SiMe_3$	$ClSiMe_3$	55[b], 93[q], 85[b], 85[b], –	37, 45, 53, 57, 86
H	$SiMe_3$	$SiMe_3$	$ClSiMe_3$	40[q]	37 (see ref. 45)
H	H	$SnMe_3$	$ClSnMe_3$	96, 85[b]	42, 87
H	H	(thiazol-2-yl)$_2$P-	PCl_3	47[b], 64	88
Me[r]	H	Me	MeI	–	65
Me	H	CO_2H	CO_2	86	72
Me	H	CHO	DMF	61	70
Me	H	CH_2CH_2OH	oxirane	42	65
Me	H	$CH_2CH(OH)Me$	2-methyloxirane	51	65
Me	H	CH(OH)Me	MeCHO	48, –	90, 91
Me	H	CH(OH)Et	EtCHO	–	91
Me	H	CH(OH)Pr	PrCHO	93	65
Me	H	CH(OH)Bu-*iso*	*iso*-BuCHO	–	91
Me	H	$CH(OH)CH=CH_2$	CH_2=CHCHO	–	91

Me	H		quinuclidin-3-one	51	92
tert-Bu	H			–	93
Br	H	CO_2H	CO_2	50	94
Br	H	CH(OH)Et	EtCHO	56	95
Br	H	$SiMe_3$	$ClSiMe_3$	86[b], 95[a]	42, 43, 45, 95
H	Me	CHO	DMF	54	70
H	Me	CH(OH)Me	MeCHO	49	96
H	SMe	CH(OH)Me	MeCHO	79	96
H	$R^1C_6H_4C(OH)$-$C_6H_4R^2$	H	H_2O	71-81[a]	16
H	CPh(OH)-($C_6H_3Cl_2$-3,4)	Me	MeI	100	16
CF_3	Br	CO_2H	CO_2	–[d]	97
Me	Br	CO_2H	CO_2	–	97
Me	Me	CO(pyrid-4-yl)	pyrid-4-ylCN	–	66

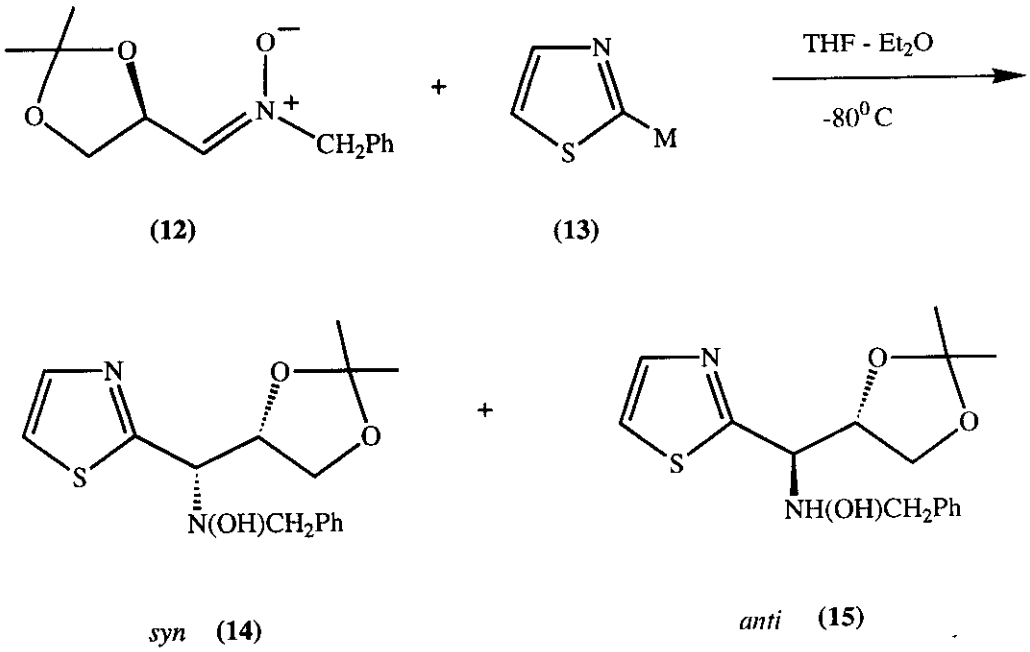
Me	Me	CH_2OH	HCHO	58	98
Me	Me	CH_2OMe	$ClCH_2OMe$	42	98
Me	Me	CH(OH)Ph	PhCHO	55	98
Et	Me	$CH_2CH(OH)Me$	2-methyloxirane	–	65
Me	$CH_2CH_2OCPh_3$	$C(OH)MeCMe(OMe)_2$	$MeCOCMe(OMe)_2$	–[b]	81

[a] Some *bis*(thiazol-2-yl)methylcarbinol formed as a by-product. [b] Thiazol-2-yllithium compound prepared from the 2-bromothiazole by halogen-metal exchange with BuLi (THF or Et_2O/-78 °C). [c] By reverse addition. [d] Yield given is that obtained after hydrolysis to the glycol. [e] 2,3-*O*-Isopropylidene-D-glyceraldehyde was the starting material - 50:50 mixture of enantiomers. [f] A trace of thiazol-2-ylC(OH)MeCOMe produced also. [g] Ethyl thiazole-2-carboxylate proposed as an intermediate. [h] Starting material prepared from L-phenylalanine. [i] Starting material prepared from L-leucine. [j] Starting material prepared from L-serine. [k] Starting material prepared from L-threonine. [l] Starting material prepared from D-glyceraldehyde acetonide. [m] Starting material prepared from D-arabinose aetonide. [n] Starting material prepared from 1,2:3,4-di-*O*-isopropylidene-α-D-galactohexodialdo-1,5-pyranose. [o] Starting material prepared from L-serinal as a single Z-isomer; high *anti*-selectivity. [p] Starting material prepared from L-serinal as Z-isomer; high d.s., *syn*-isomer ≥ 95%. [q] Thiazol-2-yllithium compound prepared by direct metallation with BuLi (Et_2O/-78 °C). [r] 4-Methylthiazol-2-yllithium has been reacted also with various chlorogold(I) complexes (Section III.F). [s] Various compounds debrominated in 71-81% yields ($R^1 = R^2 = H$/79%; $R^1 = R^2 = Cl$/71%; $R^1 = Cl$, $R^2 = H$/71%; $R^1 = 3,4\text{-}Cl_2$, $R^2 = H$/78%; $R^1 = 4\text{-}OMe$, $R^2 = H$/72%; $R^1 = 4\text{-}CF_3$, $R^2 = H$/81%). [t] As well as the 2-carboxylic acid the 5-mono- and 2,5-dicarboxylic acids were major products.

Unlike 2-TMST (Section III.A) thiazol-2-yllithium and the corresponding Grignard compounds react with D-glyceraldehyde acetonide with a complete lack of stereoselectivity.[36,39,48]

Formylation of the anomeric carbon of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose can be achieved by addition of thiazol-2-yllithium to the corresponding lactones (see Table IV for formulae and for other uses of this lithium compound in carbohydrate syntheses) followed by reductive dehydroxylation of the product and release of C-2 of the thiazole ring as the formyl group.[59]

The nitrone (**12**) derived from D-glyceraldehyde acetonide reacts diastereoselectively with the organometallic derivatives (**13**, M = Li, MgBr, $AlEt_2$) to give predominantly, the *syn*-hydroxylamine adduct (**14**) (Scheme 4).[58] The sense of diastereoselective addition can be reversed by addition of Lewis acids ($TiCl_4$ and Et_2AlCl). The highest yields of adducts are obtained with thiazol-2-yllithium [82% in the absence of Lewis acids;



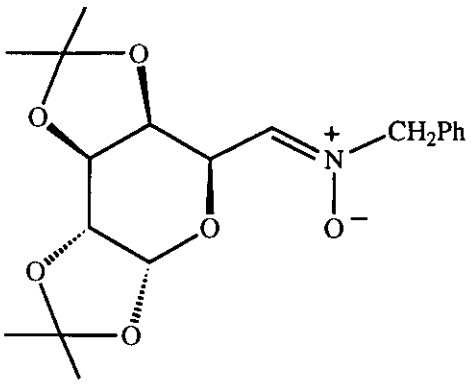
(**12**) (**13**)

syn (**14**) *anti* (**15**)

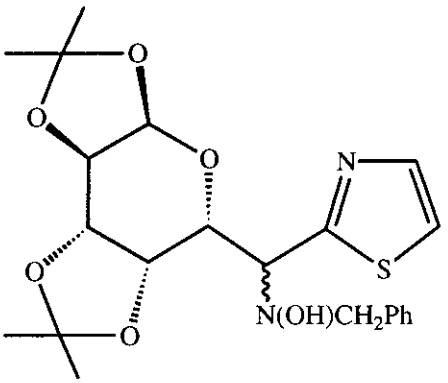
Scheme 4

ratio *syn* (**14**):*anti* (**15**) = 92:8 - 84% in the presence of Et_2AlCl; ratio *syn* (**14**):*anti* (**15**) = 3:97 - 69% in the presence of $TiCl_4$; ratio *syn* (**14**):*anti* (**15**) = 5:95].[58]

Likewise, the nitrone (**16**) derived from 1,2:3,4-di-*O*-isopropylidene-α-D-galactohexodialdo-1,5-pyranose reacts with thiazol-2-yllithium (prepared from 2-bromothiazole in Et_2O/-80°C), to give the *syn*- and *anti*-hydroxylamine adducts (**17**) in approximately equal amounts.[56] The *syn*-adduct predominates when the nitrone (**16**) is precomplexed with zinc or magnesium bromide. By contrast, a reversed diasteroeselectivity is observed



(16)

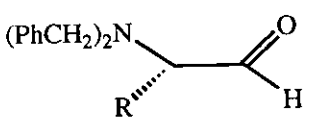


(17)

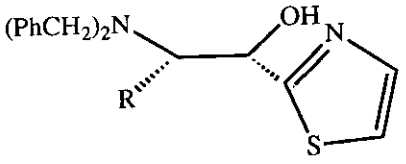
following precomplexation with diethylaluminium chloride or titanium tetrachloride. Other nitrones behave similarly.[50] Recently, however, the assignments of structures shown in Table IV have been shown to be incorrect.[58]

By contrast, the *N*-benzyl nitrone derived from *N-tert*-butoxycarbonyl-L-serinal acetonide reacts with thiazol-2-yllithium (or similar compounds, Li = MgBr or $AlEt_2$) with a high level of *syn*-diastereoselectivity (ds ≥ 95% by nmr), which is not affected by precomplexation of the nitrone with Lewis acids (Et_2AlCl, $MgBr_2$, or $ZnBr_2$), whereas a reversed *anti*-diastereoselectivity is observed with the *N*-benzyl nitrone prepared from *O-tert*-butyldiphenylsilyl-*N-tert*-butoxycarbonyl-L-serinal (structures in Table IV).[61]

The optically active β-amino aldehydes (**18**) react with thiazol-2-yllithium (Et_2O/-78°C), with 80-95% nonchelation control, to give predominantly diastereoisomers (**19**) (R = CH_2Ph, 79% isolated yield;



(18)

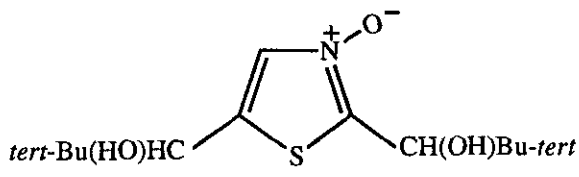


(19)

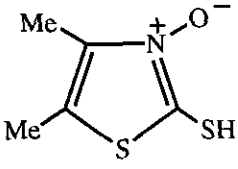
R = $CH_2OTBDMS$, 67%).[78] Addition of zinc or magnesium chloride has no beneficial effect in this case.

In general, thiazoles are activated towards deprotonation with bases by *N*-oxidation, *N*-oxidation followed by *O*-methylation or *O*-acylation of the resulting *N*-oxide, or quaternization at *N*-3.[99] Starting with thiazole 3-oxide,

groups can be introduced successively at positions-2, -5, and -4 (in that order). Thiazole 3-oxide is deprotonated by sodium hydride in DMF and the resulting anion is trapped with 2,2-dimethylpropanal, to give the 2,5-disubstituted product (**20**) (80% yield) as a mixture of four stereoisomers.[100] The initially generated lithium alkoxide presumably deprotonates position-5, thus allowing a second substituent to be introduced. The anion generated similarly from 4,5-dimethylthiazole 3-oxide reacts with dimethyl disulfide to give the 2-thiol (**21**) (78%).[100]



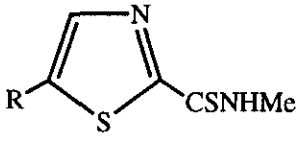
(20)



(21)

Better yields of 2-substituted thiazoles (Table IV) are obtained in some cases when the thiazol-2-yllithium derivative is prepared from the corresponding 2-bromo compound by halogen → metal exchange (2-bromothiazole is more readily available than the parent heterocycle[35]). Thus, e.g., when thiazol-2-yllithium is prepared in this way and quenched with chlorotrimethylsilane, it gives only 2-trimethylsilylthiazole[37,45] whereas metallation of thiazole with butyllithium (Et_2O/–78 °C) followed by addition of chlorotrimethylsilane is reported to give comparable amounts of 2-trimethylsilyl- and 2,5-*bis*(trimethylsilyl)thiazoles (isolable in 40% yield)[37] (see also ref. 45). Similarly, when thiazole is metallated with butyllithium in THF and the product(s) quenched with methyl thiocyanate, a mixture of the mono- (**22**) (45.5% yield) (Table IV) and disubstituted products (**23**) (6%) is reported to be formed.[85]

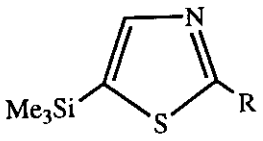
2-Bromothiazole is deprotonated at position-5 with LDA.[16,101] After suitable substitution at position-5 the 2-bromine atom is removable *via* treatment with butyllithium followed by hydrolysis, thus providing a route to 5-substituted thiazoles (see Section III.C).[16]



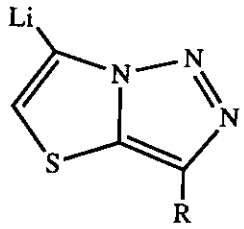
(22) R = H
(23) R = CSNHMe

Whereas 5-bromothiazole undergoes bromine → lithium exchange with butyllithium the 4-bromo isomer is metallated exclusively in position-2.[45]

2-Chloro-5-methylthiazole fails to metallate in position-4 with LDA or butyllithium (Et_2O/-78 °C).[101] Likewise, we[102] have failed to metallate 2,5-dibromothiazole in position-4 with LDA or potassium diisopropylamide (KDA) (THF/-78 °C). When 2,5-*bis*(trimethylsilyl)thiazole is treated with an excess of butyllithium in THF, the 2-trimethylsilyl group is replaced by lithium instead, as shown by quenching the product with deuterium oxide or



(24) **R = D**
(25) **R = $SnMe_3$**



(26)

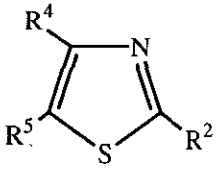
chlorotrimethylstannane, which gives the corresponding 2-substituted 5-trimethylsilylthiazole, (**24**) (95% yield) or (**25**) (65%), respectively.[45]

Noteworthy is the metallation of 1,2,3-triazolo[1,5-*b*]thiazoles in position-6 (equivalent to position-4 of thiazole),[103] to give the lithiated derivatives (**26**, R = H, Me, Ph) which can be quenched with various electrophiles. The products can be converted into 2,4-disubstituted thiazoles using one of four reagent systems. 2-Bromo-,[16,101] 2-chloro-,[16,77,96,101,104] 2-methyl-,[96] 2-*tert*-butyl-,[105] 2-methoxy-,[96] 2-methylthio-,[96] 2-trimethylsilyl-,[16,42,43,45,86] 2-phenyl-,[106] 2-*N,N-bis*(trimethylsilyl)amino-,[16] 2,4-dibromo-,[102] 2,4-dichloro,[102,104] 2-chloro-4-methyl-,[104] (but see also ref. 101), 2-chloro-4-phenyl-,[104] 2,4-dimethyl-,[65,79] 2,4-*bis*(trimethylsilyl)-,[45] 2-phenyl-4-trifluoromethyl-,[107] and 2-trifluoroacetamido-4-trifluoromethylthiazoles[108] are all reported to metallate under various conditions in position-5 and the resulting 5-lithiated derivatives have been used to introduce a number of other substituents at this position (Table V). 2-Chlorothiazole is deprotonated more readily at position-5 than 2-bromothiazole.[100] Lateral metallation is also possible in the case of 2-alkylthiazoles (Section III.D).

2-Methylthiothiazole is deprotonated at position-5 also with sodium amide, as shown by addition of bromoethane, which yields 5-ethyl-2-methylthiothiazole (90% yield).[109]

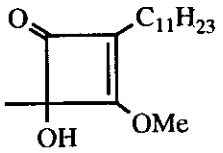
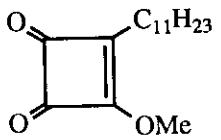
Table V

5-Substituted Thiazoles Prepared from Thiazol-5-yllithium Compounds



R^2	R^4	R^5	Reagent	Reaction Conditions[a]	Yield (%)	Ref.
H	H	$SiMe_3$	$ClSiMe_3$	A	36[b]	45
H	H	CO_2H	CO_2	A	31[b]	73
H	H	$C(OH)(C_6H_4Cl\text{-}4)_2$	$(4\text{-}ClC_6H_4)_2CO$	A	29[b]	23
Me	H	D	$DOAc/D_2O$	A	–	105
Me	H	CO_2H	CO_2	A	42	105
Me	H	COPh	PhCN	A	50	105
Me	H	CH(OH)Me	MeCHO	A	97	96
Br	H	$C(OH)Ph_2$	Ph_2CO	B	62, 35	16, 101
Br	H	$C(OH)(C_6H_4Cl\text{-}4)_2$	$(4\text{-}ClC_6H_4)_2CO$	B	79	16
Br	H	$CPh(OH)C_6H_4Cl\text{-}4$	$4\text{-}ClC_6H_4COPh$	B	66	16
Br	H	$CPh(OH)C_6H_3Cl_2\text{-}3,4$	$3,4\text{-}Cl_2C_6H_3COPh$	B	72	16
Br	H	$CPh(OH)C_6H_4OMe\text{-}4$	$4\text{-}MeOC_6H_4COPh$	B	71	16

Br	H	$CPh(OH)C_6H_4CF_3$-4	4-$F_3CC_6H_4COPh$	B	72	16
Cl	H	D	D_2O	B	70	101
Cl	H	Me	MeI	E	–	96
Cl	H	Me	MeI	B	52	101
Cl	H	CHO	DMF	C	95[c]	104
Cl	H	COPh	$PhCONMe_2$	C	88[c]	104
Cl	H	CH(OH)Me	MeCHO	A	88	77
Cl	H	$C(OH)Ph_2$	Ph_2CO	D	66	101
Cl	H	$C(OH)Ph_2$	Ph_2CO	B	100	101
Cl	H	$C(OH)Ph_2$	Ph_2CO	C	45[d]	101
Cl	H	CMe(OH)Bu-*tert*	MeCOBu-*tert*	C	33	101
Cl	H	$C(OH)(C_6H_4Cl\text{-}4)_2$	$(4\text{-}ClC_6H_4)_2CO$	A	52	16
Me	H	CH(OH)Me	MeCHO	E	97	96
$SiMe_3$	H	$SiMe_3$	$ClSiMe_3$	A	96	45
$SiMe_3$	H	$SnMe_3$	$ClSnMe_3$	A	90	42
$SiMe_3$	H	CHO	DMF	A	40[e]	43
$SiMe_3$	H	CHO	*N*-formylmorpholine	A	80[e]	43
$SiMe_3$	H	$CPh(OH)C_6H_3Cl_2$-2,4	2,4-$Cl_2C_6H_3COPh$	B	–	16

$SiMe_3$	H			C	68[f]	86
Ph	H	C(OH)Ph	PhCHO	A	76	106
OMe	H	CH(OH)Me	MeCHO	E	35	96
SMe	H	CH(OH)Me	MeCHO	E	63	96
SMe	H	Et	EtBr	D	~ 90	109
$N(SiMe_3)_2$	H	$C(OH)PhC_6H_3Cl_2$-2,4	2,4-$Cl_2C_6H_3COPh$	A	61[f]	16
NMe_2	H	CHO	DMF	C	95[g]	104
NEt_2	H	CHO	DMF	C	63[g]	104
piperidino	H	CHO	DMF	C	78[g]	104
morpholino	H	CHO	DMF	C	89[g]	104
NMe_2	H	COPh	$PhCONMe_2$	C	73[g]	104
NEt_2	H	COPh	$PhCONMe_2$	C	92[g]	104
pyrrolidino	H	COPh	$PhCONMe_2$	C	79[g]	104
morpholino	H	COPh	$PhCONMe_2$	C	86[g]	104
$SiMe_3$	$SiMe_3$	$SiMe_3$	$ClSiMe_3$	G	40	45
Br	Br	$SiMe_3$	$ClSiMe_3$	B	66	102
Br	Br	$SnMe_3$	$ClSnMe_3$	B	48	102

Br	Br	CHO	DMF	B	54	102
Br	Br	CO_2H	CO_2	B	68	102
Br	Br	$C(OH)Ph_2$	Ph_2CO	B	46	102
Br	Cl	$SiMe_3$	$ClSiMe_3$	C	61	102
Br	Cl	CO_2H	CO_2	C	47	102
Br	Cl	$C(OH)Ph_2$	Ph_2CO	C	59	102
Cl	Cl	$SiMe_3$	$ClSiMe_3$	B	71	102
Cl	Cl	$SnMe_3$	$ClSnMe_3$	B	69	102
Cl	Cl	CHO	DMF	C	88[a]	104
Cl	Cl	CO_2H	CO_2	B	40	102
Cl	Cl	CO_2Et	$ClCO_2Et$	B	66	102
Cl	Cl	CH(OH)Ph	PhCHO	B	74	102
Cl	Cl	$C(OH)Ph_2$	Ph_2CO	B	25	102
Cl	Ph	CHO	DMF	C	83[a]	104
Me	Me	Me	MeI	F	69	110
Me	Me	CO_2H	CO_2	F	73.5	110
Me	Me	CH_2OH	HCHO	F	64	110
Me	Me	CH_2CH_2OH	oxirane	F	39	110
Me	Me	CH(OH)Me	MeCHO	A,F	57, 41.5	65, 110
Me	Me	CH(OH)Pr	PrCHO	A	72	65

Me	Me	CH(OH)Ph	PhCHO	A	95[b]	79
Me	Me	$CH(OH)C_6H_4Cl$-2	2-ClC_6H_4CHO	A	–	18 (confusion over structure: see Table VI)
Me	Ph	Me	MeI	C	85	111
NMe_2	Cl	CHO	DMF	B, C	76, 84[g]	102, 104
piperidino	Cl	CHO	DMF	B	71	102
morpholino	Cl	CHO	DMF	C	90[g]	104
NMe_2	Me	CHO	DMF	C	89[g]	104
morpholino	Me	CHO	DMF	C	86[g]	104
NMe_2	Ph	CHO	DMF	C	94[g]	104
pyrrolidino	Ph	CHO	DMF	C	91[g]	104
piperidino	Ph	CHO	DMF	C	87[g], 72	104, 112
morpholino	Ph	CHO	DMF	C	93[g]	104
Ph	CF_3	[h]	dichlorodicyanopyrazine	not given	–	107
Ph	CF_3	[i]	octafluorocyclopentene	not given	–	107
Br	CF_3	CO_2H	CO_2	A	–[b,i]	97
$NHCOCF_3$	CF_3	D	D_2O	A	98	108
$NHCOCF_3$	CF_3	CF_2Br	CF_2Br_2	A	80[k]	108
$NHCOCF_3$	CF_3	CF_2H	CF_2Cl_2	A	29[l]	108

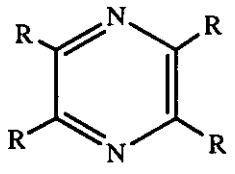
$NHCOCF_3$	CF_3	CHO	DMF	A	37[b,m]	108
$NHCOCF_3$	CF_3	COPh	PhCOCl	A	40	108
$NHCOCF_3$	CF_3	CH(OH)Ph	PhCHO	A	71	108
$NHCOCF_3$	CF_3	$C(OH)Ph_2$	Ph_2CO	A	58	108
$NHCOCF_3$	CF_3	$CO_2CH_2CCl_3$	$Cl_3CCH_2CO_2Cl$	A	47	108
$NHCOCF_3$	CF_3	SCF_3	$(F_3CS)_2$	A	76[m]	108
$NHCOCF_3$	CF_3	$SiMe_3$	$ClSiMe_3$	A	49	108
$NHCOCF_3$	CF_3	$PO(OEt)_2$	$ClPO(OEt)_2$	A	49	108

[a] Reaction conditions: A - BuLi/Et_2O/-45 → -80 °C; B - LDA/THF/low temp.; C - BuLi/THF/-70 °C to –80 °C; D - KNH_2/l. NH_3 (actually $NaNH_2$/l.NH_3 to deprotonate 2-methylthiothiazole prior to addition of EtBr); E - BuLi/Et_2O/0 °C; F - PhLi/Et_2O; G - *tert*-BuLi/THF/ -78 °C. [b] By the Br → Li exchange route. [c] After addition of **acid** prior to work-up. [d] 55% recovered Ph_2CO. [e] Yield of thiazole-5-carbaldehyde after desilylation of initial product during work-up. [f] Isolated yield of desilylated product; desilylation on work-up. [g] After addition of **water** prior to work-up. [h] Product is **27** (see text). [i] Product is **28** (see text). [j] 5-Bromo-4-trifluoromethylthiazole-2-carboxylic acid and 4-trifluoromethylthiazole-2,5-dicarboxylic acid are produced also in significant amounts. [k] Starting material (4%) and the 5-bromo compound (9%) isolated in addition. [l] Starting material (18% recovered). [m] Yield of amine after hydrolysis of trifluoroacetamide.

By monitoring the metallation of 2-chlorothiazole with LDA, using ^{1}H nmr spectroscopy, from -60 ° to -10 °C the 5-lithiated derivative has been shown to decompose at about - 20 °C;[101] LDA is preferred to butyllithium in THF for this metallation process.

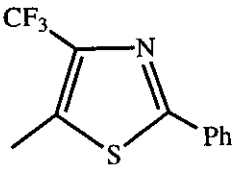
The product obtained by quenching the 5-lithiated derivatives of 2-chloro-, 2,4-dichloro-, 2-chloro-4-methyl- (see also ref. 101), and 2-chloro-4-phenylthiazoles with DMF depends on whether acid or water is added prior to the final work-up.[102,104] The corresponding 2-chlorothiazole-5-carbaldehyde is obtained following addition of acid (Table V) but addition of water yields the corresponding 2-(*N,N*-dimethylamino)thiazole-5-carbaldehyde. When *N*-formylpiperidine is used to introduce the formyl group and the reaction worked up by addition of water, the 2-piperidinothiazole-5-carbaldehyde is obtained instead.[102] 2,4-Dibromo(and dichloro)thiazol-5-yllithium react with dimethyl disulfide to give the corresponding 4-halogeno-2,5-*bis*(methylthio)thiazole (76% and 42% yield, respectively).[102] These reactions proceed *via* reaction of the initially generated 2,4-dihalogenothiazole-5-carbaldehyde or the corresponding 5-methylthio compound, respectively, with the liberated secondary amine or methylthiolate anion.

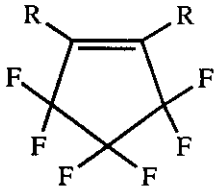
When 2-phenyl-4-trifluoromethylthiazol-5-yllithium reacts with 2,3-dichloro-5,6-dicyanopyrazine all four substituents in the pyrazine are displaced and 2,3,5,6-*tetrakis*(2-phenyl-4-trifluoromethylthiazol-5-yl)pyrazine (**27**) is produced in a moderate yield.[107] The two olefinic F-atoms in octafluorocyclopentene are displaced by the same thiazol-5-yllithium compound, to give a moderate yield of cyclopentene (**28**).[107]



(**27**)

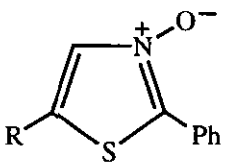
R =



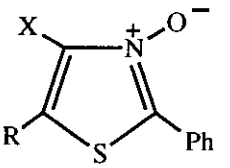


(**28**)

2-Phenylthiazole 3-oxide and its 4-bromo(and chloro) derivatives are deprotonated by sodium hydride in DMF at position-5 and the resulting anions can be trapped with various electrophiles, to yield compounds (**29**)-(**34**), respectively.[100] With hexachloroethane, tetrabromomethane, or dimethyl disulfide as the trapping reagent, the initially generated 5-substituted compound is deprotonated further at position-4 and the isolated products are 4,5-disubstituted, namely compounds (**35**), (**36**), and (**37**), respectively.[100]



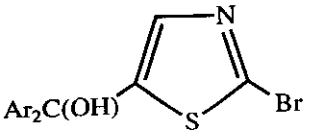
(29) R = CH_2OH (90%)
(30) R = CH(OH)Bu-*tert* (89%)
(31) R = COBu-*tert* (21%)
(32) R = SMe (83%)



(33) X = Cl, R = Br (52%)
(34) X = Br, R = Cl (99%)
(35) X = R = Cl (86%)
(36) X = R = Br (87%)
(37) X = R = SMe (87%)

C Halogen → lithium exchange reactions

We have mentioned already (Section III. B) the usefulness of 2-bromothiazoles in the synthesis of other 2-substituted thiazoles (Table IV) *via* bromine → lithium exchange. Katritzky's group[16] have debrominated a number of compounds with the general structure (**38**) through bromine → lithium exchange followed by hydrolysis of the resulting 2-lithiated derivative.



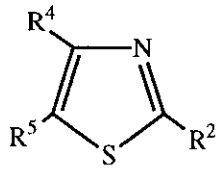
(38)

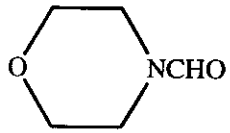
Whereas 4-bromothiazole metallates exclusively at position-2 with butyllithium[45] a number of other 4-bromothiazoles undergo bromine → lithium exchange with the same reagent (Et_2O at low temperatures) to give lithium derivatives which can be used to introduce other substituents at this position (Table VI). The difference in reactivities of bromine atoms in positions-4 and -5 of thiazole can be attributed to the effect of a nitrogen lone pair at N-3 (the "ALP effect")[113-115] which destabilises a developing negative charge at C-4.

The 2-chlorine atom in the ethylene acetal of 2,4-dichlorothiazole-5-carbaldehyde is reactive enough to be exchangeable with butyllithium (THF/-78 °C) and the resulting 2-lithiated derivative has been quenched with

Table VI

4-Substituted Thiazoles Prepared from Thiazol-4-yllithium Compounds

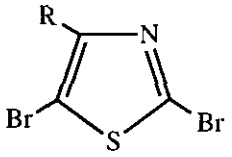


R^2	R^5	R^4	Reagent	Yield (%)	Ref.
$SiMe_3$	H	CHO	DMF	15	43
$SiMe_3$	H	CHO		75[a]	43
$SiMe_3$	H	CONHBu-*tert*	*tert*-BuNCO	73	95
$SiMe_3$	H	$SiMe_3$	$ClSiMe_3$	81	45
$SiMe_3$	H	$SnMe_3$	$ClSnMe_3$	75, –	42, 95
Me	Me	$CH(OH)C_6H_4Cl$-2	2-ClC_6H_4CHO	–	18[b]
Me	OEt	CH(OH)Ph	PhCHO	30	79

[a] Yield of thiazole-4-carbaldehyde following desilylation of initial product during work-up. [b] Confusion over structure; see Table V.

hydrochloric acid and dimethyl disulfide, which yields 4-chlorothiazole-5-carbaldehyde (78% yield) or 4-chloro-2-methylthiothiazole-5-carbaldehyde (59%), respectively;[116] see also ref. 16.

Whereas sequential reaction of 2,5-dibromo-4-methylthiazole with butyllithium (hexane/-60 °C) and carbon dioxide yields only 5-bromo-4-methylthiazole-2-carboxylic acid, 2,5-dibromo-4-trifluoromethylthiazole (**39**)



(39) R = CF_3
(40) R = Cl

undergoes bromine → lithium exchange at both positions-2 and -5 with butyllithium (hexane/-60 °C), as shown by trapping the lithium derivatives with carbon dioxide and conversion of the resulting carboxylic acids into their methyl esters with diazomethane:[97] 5-bromo-4-trifluoromethylthiazole-2-carboxylic acid, 2-bromo-4-trifluoromethylthiazole-5-carboxylic acid, and 4-trifluoromethylthiazole-2,5-dicarboxylic acid are produced, each in a significant amount. A similar lack of selectivity is observed when 2,5-dibromo-4-chlorothiazole (**40**) is treated with butyllithium in **ether** (-78 °C) but, **in THF** (-90 °C), we[102] have shown that reaction occurs exclusively at position-5; the resulting 5-lithiated species was trapped with carbon dioxide (47% yield of carboxylic acid), benzophenone (59%), and chlorotrimethylsilane (61%) (Table V).

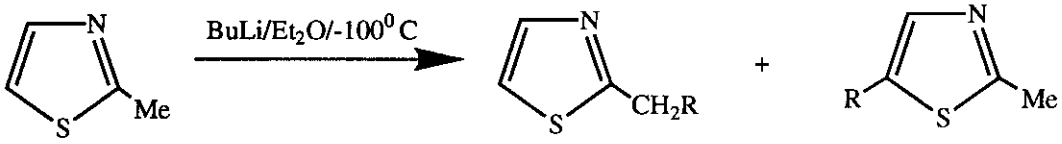
Unlike 4-bromothiazole, which is metallated in position-2 with butyllithium (Section III.B), 5-bromothiazole undergoes bromine → lithium exchange under the same conditions and the resulting 5-lithiated derivative can be trapped with chlorotrimethylsilane, to give a moderate (36%) yield of the 5-trimethylsilyl compound,[45] and with *bis*(4-chlorophenyl) ketone.[23] If thiazol-5-yllithium (Et_2O) is "frozen" in liquid nitrogen prior to its treatment with carbon dioxide, following hydrolysis of the resulting salt a poor yield (31%) of thiazole-5-carboxylic acid is obtained.[73] Thiazol-5-yllithium rearranges to the thermodynamically more stable thiazol-2-yllithium derivative.[73] 5-Bromo-2,4-dimethylthiazole (PhLi used in this case)[79,110] and 5-bromo-2-trifluoroacetamido-4-trifluoromethylthiazole[108] similarly give 5-lithiated derivatives which can be used to prepare a number of 5-substituted thiazoles (Table V).[108]

Both the 2- and 5-bromine atoms react when 2,4,5-tribromothiazole is treated with butyllithium in ether; the product composition is dependent on time and temperature.[102] With one mol. equiv. each of butyllithium (Et_2O/-78 °C) and dimethyl disulfide the product isolated is 4-bromo-2,5-*bis*(methylthio)thiazole (71% yield).

Greater selectivity is observed with methyllithium (Et_2O/-90 °C) but mixtures of products are obtained.[102] However, the reactions of the tribromo compound with organometallic reagents need examining in more detail. Unlike *N*-protected tribromoimidazoles,[1] which react with ethylmagnesium bromide selectively at position-2, 2,4,5-tribromothiazole appears unreactive towards this reagent in THF, either at ambient (5 hours) or reflux temperature (overnight).[102]

D Lateral metallation (see also Section III.E)

At -80 → -100 °C the kinetic acidities of the C-5 and 2-methyl protons in 2-methylthiazole are approximately the same and, if the mixture of lithium compounds (**41**) and (**47**) formed in ether is quenched at these low temperatures with various carbonyl compounds, varying ratios of mixtures of carbinols (**42**)-(**46**) and (**48**)-(**52**), respectively, are obtained (Scheme 5); for example, at -60 °C acetaldehyde yields a mixture of compounds (**43**) and (**49**) (ratio 42:58)[96] or (ratio 15:85),[105] whilst formaldehyde yields compounds (**42**) and (**48**) (ratio 16:84)[105] (Table VII). 2-Methylthiazol-4-yllithium is formed also but only in trace amounts under these conditions, as shown by the detection of the 4-deuteriated derivative in the product following deuteriolysis of the



(41) R = Li
(42) R = CH_2OH
(43) R = CH(OH)Me
(44) R = CH(OH)Et
(45) R = CH(OH)Pr
(46) R = CH(OH)Pr-*iso*

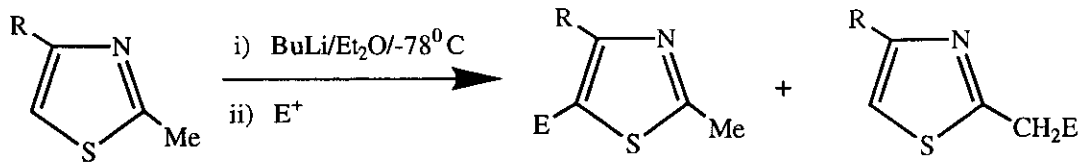
(47) R = Li
(48) R = CH_2OH
(49) R = CH(OH)Me
(50) R = CH(OH)Et
(51) R = CH(OH)Pr
(52) R = CH(OH)Pr-*iso*

Scheme 5

reaction mixture.[105] Crousier and Metzger[105] have provided evidence that the three lithiated derivatives are formed independently and not *via* transmetallation at these low temperatures [see also ref. 111]. As the temperature of metallation is increased, however, larger amounts of 5-substituted products arise due to thermodynamic control and instability of the 2-lithiomethyl derivative (**41**) as the temperature is increased.[105] Thus, when 2-methylthiazole is metallated with butyllithium in ether at these higher temperatures (e.g. 0 °C[96]) and the mixture is quenched with either acetaldehyde, carbon dioxide, or benzonitrile, only the 5-substituted product (**49**) (97%),[96] thiazole-5-carboxylic acid (42%),[105] or 5-benzoylthiazole (50%)[105] is isolated (Table V).

Table VII

Products Obtained from 2-Methylthiazoles Following Their Sequential Treatment with Butyllithium and an Electrophile



(53) (54)

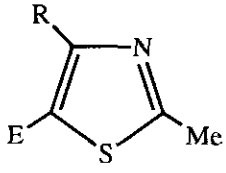
R	E	Reagent	% (53)	% (54)	Ref.
H	Me	MeI	e.g. 0.5	e.g. 27[a]	105
H	Me	4-$MeC_6H_4SO_3Me$	6	19[a]	105
H	CH_2OH	HCHO	84	16	105
H	CH(OH)Me	MeCHO	85	15	105
H	CH(OH)Me	MeCHO	58	42	96
H	CH(OH)Et	EtCHO	77	23	105
H	CH(OH)Pr	PrCHO	74	26	105
H	CH(OH)Pr-*iso*	*iso*-PrCHO	77	23	105
Me	D	D_2SO_4/D_2O[a,b]	9	58	105
Me	Me	MeI[c]	12	88	111

Me	CH_2Ph	$PhCH_2Cl$[d]	10	90	111
Me	CH_2OH	HCHO[e]	18	82	105
Me	CH(OH)Pr	PrCHO[f]	15	85	105
Et[g]	CH(OH)Me	MeCHO	0	60	65
Et[g]	CH(OH)Pr	PrCHO	0	60	65
Ph	Me	MeI	91	4	111, 117
Ph	Et	EtI	86	7	111
Ph	CH(OH)Ph	PhCHO	97	0	111
Ph	$SiMe_3$	$ClSiMe_3$	96	4	111
C_6H_4OMe-4	Me	MeI	86	6	111
C_6H_4Cl-4	Et	EtI	93	3	111

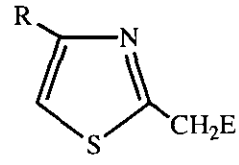
[a] Balance was starting material (mole ratios given). [b] Deuteriolysis at -30 °C. [c] Quenching the mixture of lithiated derivatives with methyl tosylate at -60 °C gives 2-ethyl-4-methylthiazole (40% yield) but quenching with this reagent at 15 °C gives only 2,4,5-trimethylthiazole.[105] [d] THF appears to promote regioselective metallation in the 2-methyl group.[118] [e] Reagent added at -50 °C: total yield of product 12% (ratio given in Table). [f] Total yield of product 70% (ratio given in Table). [g] These compounds also carry a 5-methyl substituent.

Increasing amounts of 2,5-dimethylthiazole are formed and equally decreasing amounts of 2-ethylthiazole when the temperature of addition of iodomethane is increased.[105] Deuteriolysis (D_2SO_4/D_2O or $DOAc/D_2O$) at the higher temperatures yield only 5-deuterio-2-methylthiazole.[105]

Metallation of 2,4-dimethylthiazole has been studied in even greater detail.[65,105,111,117-120] Metallation either with butyllithium in THF[111,117,119-121] or with lithium amide in ether[118] followed by quenching with various electrophiles yields only 2-substituted 4-methylthiazoles (Table VIII). When 2,4-dimethylthiazole is metallated in ether[105] or 2-methyl-4-arylthiazoles[111,117,119] are metallated in THF (at -78 °C) and the mixtures quenched with various reagents at these low temperatures, mixtures of products, (**53**) and (**54**), invariably arise (see Table VII). In 1962, Beraud and Metzger[65] reported the synthesis of carbinols [**53**; R = Me, E = CH(OH)Me] (57% yield)



(**53**)



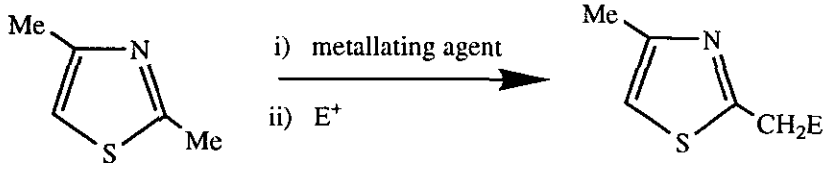
(**54**)

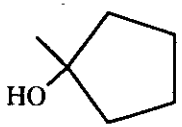
and [**53**; R = Me, E = CH(OH)Pr] (72%) *via* metallation of 2,4-dimethylthiazole with butyllithium in ether. From Table VII it can be seen clearly that a 4-alkyl substituent (exerting a +I effect on position-5) in 2-methylthiazole promotes lateral metallation whilst a 4-aryl substituent (-I effect) at position-4 promotes metallation in position-5.[111] The products given in Table VII (for the reactions in THF at -78 °C) are the products arising from *independent metallation at either* C-5 *or in the* 2-methyl group. Thus, when 2-methyl-4-phenylthiazole is added at -78 °C to a solution of 2-lithiomethyl-4-methylthiazole in THF at this temperature and the mixture is subsequently quenched with iodomethane at -78 °C, the 2-methyl-4-phenylthiazole is recovered almost quantitatively (94% recovery) whilst the only isolable product is 2-ethyl-4-methylthiazole (61% yield).[111] If, alternatively, 2,4-dimethylthiazole is added at -78 °C to a solution of 2-methyl-4-phenylthiazol-5-yllithium in ether at the same temperature and the mixture is quenched with iodomethane, the 2,5-dimethylthiazole is recovered and 2,5-dimethyl-4-phenylthiazole is formed in 85% yield.[111]

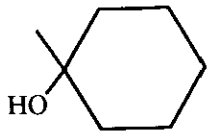
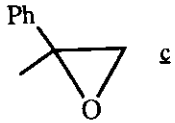
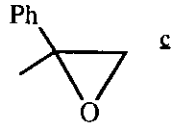
That the C-5 position in 2-methyl-4-phenylthiazole is more acidic (THF/–78 °C) than any of the protons in 2,4-dimethylthiazole is shown in a competition experiment between these two compounds and butyllithium; 2,5-dimethyl-4-phenylthiazole is the major product formed after addition of iodomethane.[111] 4-Aryl-2-methylthiazoles are metallated (THF/-78 °C) by butyllithium or LDA predominantly in position-5 but use of *tert*-

Table VIII

Regioselective Metallation of 2,4-Dimethylthiazole in its 2-Methyl Group



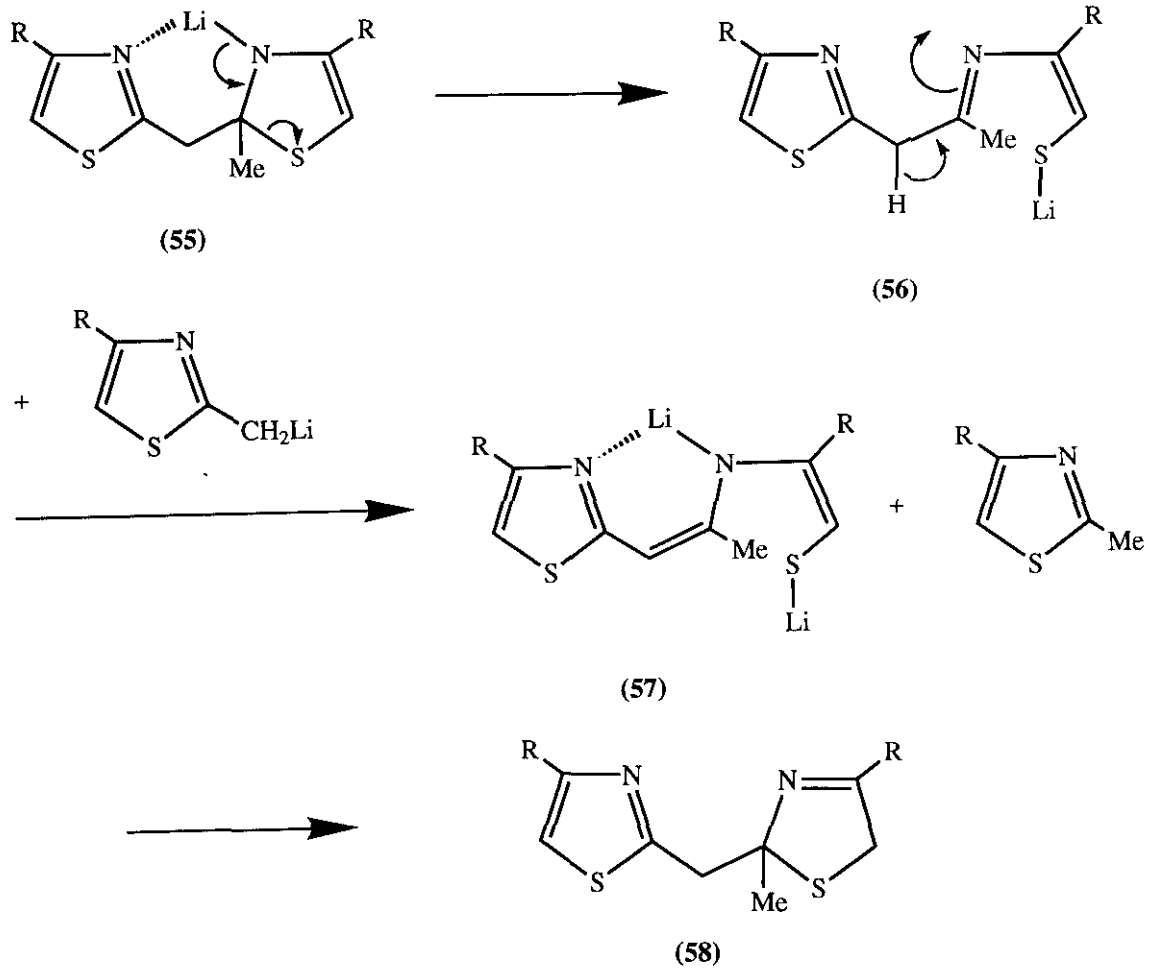
E	Reagent	Metallating system[a]	Yield (%)	Ref.
Me	MeI	B	61, 90	111, 117
Me	4-$MeC_6H_4SO_3Me$	B	40	105
CH_2Ph	$PhCH_2Cl$	B	94	121
CH(OH)Ph	PhCHO	A, B	35, –	118, 120
$CH(OH)C_6H_4Cl$-4	4-ClC_6H_4CHO	A	27	118
$C(OH)Pr_2$	Pr_2CO	A	79	118
CMe(OH)Ph	MeCOPh	A, B	51, –	118, 120
$CPh(OH)CH_2OMe$	$PhCOCH_2OMe$	B	–	120
$C(OH)Ph_2$	Ph_2CO	A	72	118
$CPh(OH)C_6H_4Cl$-4	$PhCOC_6H_4Cl$-4	A	55	118
$CPh(OH)CH_2Br$[b]	$PhCOCH_2Br$	B	–	120
	cyclopentanone	A	64	118

	cyclohexanone	A	60	118
 [c]	$PhCOCH_2Br$	B	–	120
 [c]	$PhCOCH_2OTs$	B	–	120
$CMe(OH)CH_2Br$	$MeCOCH_2Br$	B	–	120
$CMe(OH)CH_2Cl$	$MeCOCH_2Cl$	B	–	120

[a] A - $LiNH_2/Et_2O$; B - BuLi/THF/-70 °C; [b] Isolated when mixture is worked up at < 55 °C. [c] Isolated when mixture is worked-up at ambient temperature.

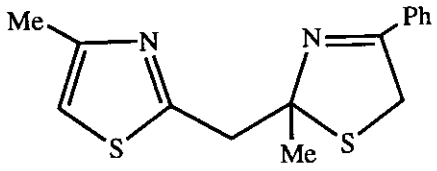
butyllithium (the strongest base) leads to metallation predominantly in the 2-methyl group, presumably due to steric factors.[111] Nevertheless, there are only small acidity differences between C-5 and the 2-methyl groups in these compounds as shown by an isotope study.[111]

When either 4-aryl-2-methylthiazoles or 2,4-dimethylthiazole are metallated by butyllithium (THF/-78 °C), then the mixture is allowed to warm up to ambient temperature, thermodynamic conditions are brought into play and the most stable anion is produced, i.e. by formation of the 2-lithiomethyl derivatives.[111,117,119,122] Thus, if this is carried out *in the absence of an added electrophile*, a dimer (**58**; R = Me, 82% yield; R = Ph, 90%; R = 4-$MeOC_6H_4$, 90%) is produced by the mechanism shown in Scheme 6.[111,117,119] The lithiomethyl derivative, generated under thermodynamic control of the mixture, adds to the azomethine bond of a **trace** of unreacted 4-substituted 2-methylthiazole to generate adduct (**55**), which undergoes a ring-opening reaction to give the open-chain imine (**56**). Subsequent reaction of this with the 2-lithiomethyl compound converts it into the dilithiated



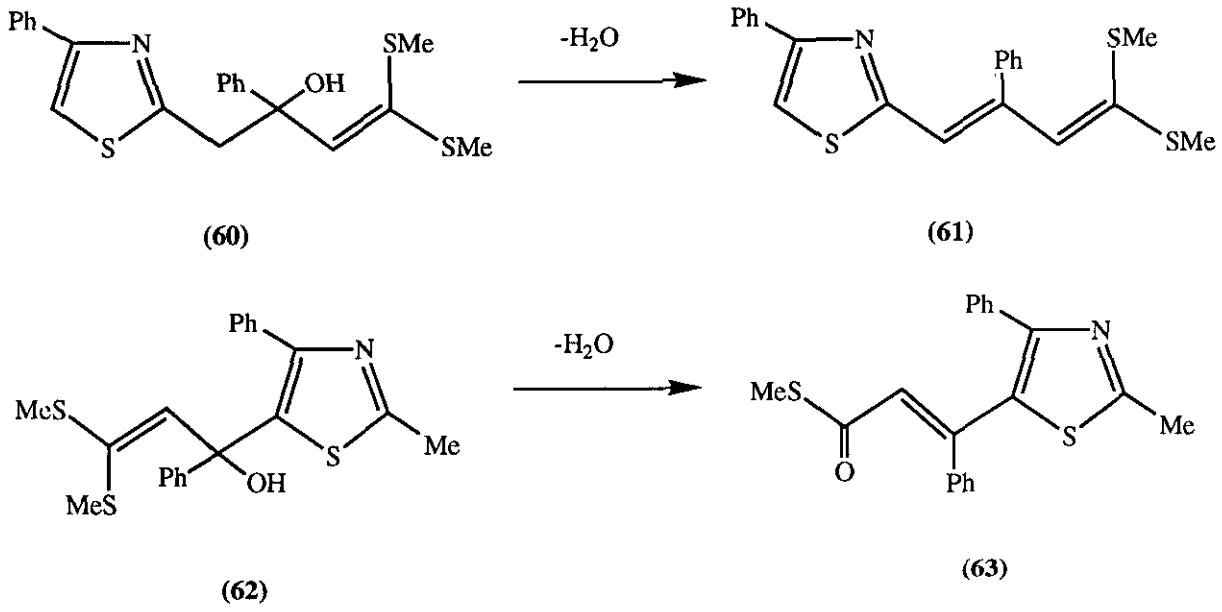
Scheme 6

species (**57**) and starting material, which is recycled, and hydrolysis during work-up yields the dimer (**58**). Support for this mechanism is provided by metallating 2,4-dimethylthiazole with 2.5 mol. equiv. of butyllithium (THF/-78 °C) and allowing the mixture to warm up to ambient temperature. Following deuteriolysis (with D_2O) only 5-deuterio-2-deuteriomethyl-4-methylthiazole (84% yield) is isolated and no dimer.[119] Under these conditions *all* the starting material is removed and the mechanism shown in Scheme 6 cannot operate.[119] When a mixture of 2,4-dimethylthiazole and 2-methyl-4-phenylthiazol-5-yllithium (THF/-78 °C) is allowed to warm up to ambient temperature the "symmetrical" dimer (**58**; R = Me) is formed (43-48% yield) and 2-methyl-4-phenylthiazole is recovered (75-80%).[111] As the mixture warms up the initially formed 2-methyl-4-phenyl-thiazol-5-yllithium (kinetically controlled product) transmetallates the 2-methyl group of 2,4-dimethylthiazole to give its 2-lithiomethyl derivative (thermodynamically controlled product), which proceeds to dimerise at ambient temperature. A cross-over experiment involving generation of 2-lithiomethyl-4-methylthiazol-5-yllithium (THF/-78 °C) and addition to it at this temperature of 2-methyl-4-phenylthiazole gave, after warming the mixture up to ambient temperature and work-up by hydrolysis, the "symmetrical" dimer (**58**; R = Me) (36% yield) together with 2-methyl-4-phenylthiazole (79% recovery) and the "unsymmetrical" dimer (**59**) (19%).[119]



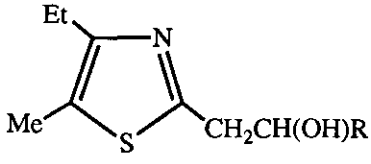
(59)

When 2-methyl-4-phenylthiazole is treated successively with butyllithium (THF-Et_2O) and the α-oxoketene dithioacetal, $PhCOCH{=}C(SMe)_2$, 1,2-addition to the carbonyl group of both its 2-lithiomethyl derivative and the thiazol-5-yllithium derivative occurs, to yield a mixture of carbinols (**60**) and (**62**) (Scheme 7);[122] after dehydration ($BF_3.Et_2O/C_6H_6$/heat) the isolated products are compounds (**61**) and (**63**), respectively. At -78 °C the yields of **61** and **63** are 38% and 22%, respectively, whilst at 25 °C the yields are 45% and 10%, demonstrating the competitive kinetic and thermodynamic control of this reaction. Use of LDA or *tert*-butyllithium under varying reaction conditions affords mixtures of the same products in varying yields or intractable tars.



Scheme 7

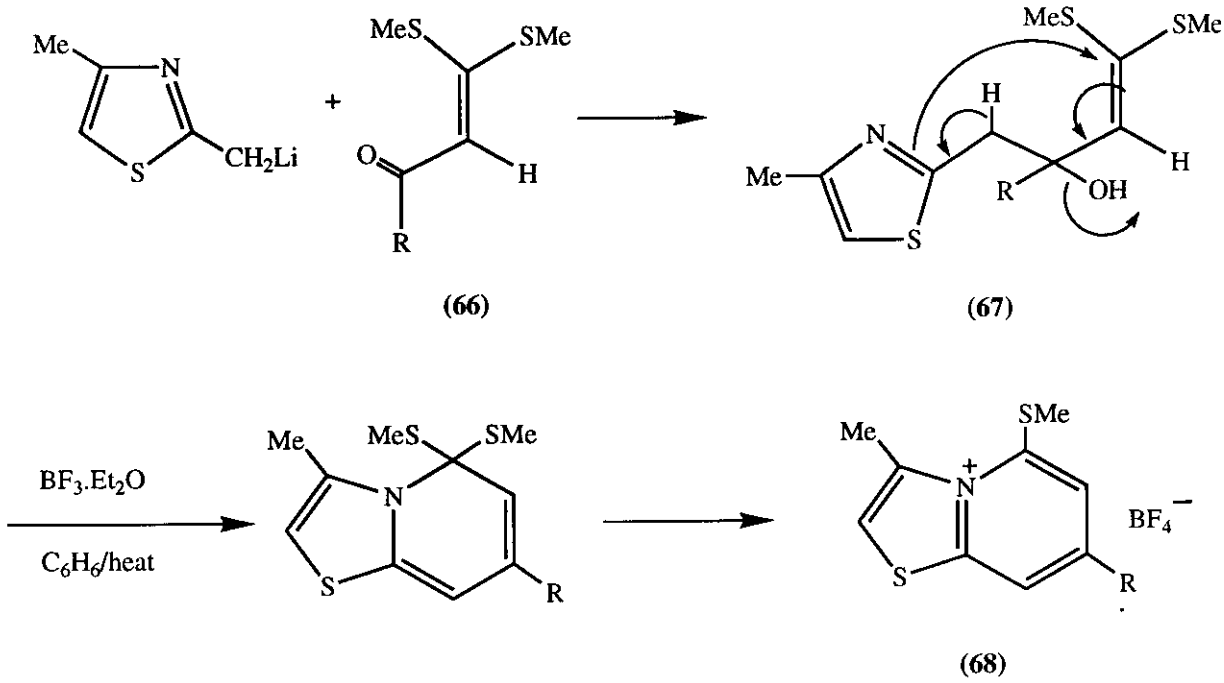
2-Benzylthiazole undergoes metallation by butyllithium both in its methylene group and in the position-5, as shown by deuteriolysis of the reaction mixture, which yields a mixture of the two monodeuteriated derivatives.[105] 2,5-Dimethyl-4-ethylthiazole has been metallated by butyllithium exclusively in its 2-methyl group and the product has been trapped with acetaldehyde and propionaldehyde to give compounds (**64**) (60% yield) and (**65**) (60%), respectively.[65]



(64) R = Me

(65) R = Pr

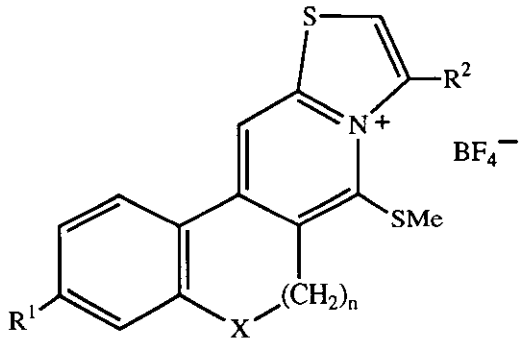
The α-oxoketene dithioacetals (**66**) undergo regioselective 1,2-addition with 2-lithiomethyl-4-methylthiazole (generated with BuLi/THF-Et_2O/-78 °C) to afford intermediate carbinols (**67**) in almost quantitative yield which, on treatment with boron trifluoride diethyl etherate, undergo cyclization as shown in Scheme 8, to give 7-substituted 3-methyl-5-methylthiothiazolo[3,2-*a*]pyridinium tetrafluoroborates (**68**) (R = Me, 51% yield; R = Ph, 55%; R = 4-$MeOC_6H_4$, 68%; R = naphth-2-yl, 66%; R = 2-furyl, 53%; R = 2-thienyl, 62%; R = 3-$MeOC_6H_4CH$=CH-, 42%).[122] Compounds (**69**) (R^1 = H, Me, MeO; R^2 = Me, Ph; X = CH_2, S; n = 1,2) may be prepared similarly in good yields using 2-lithiomethyl-4-methyl(or phenyl)thiazole.



(66) (67)

(68)

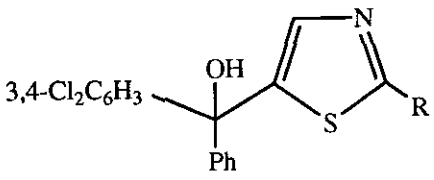
Scheme 8



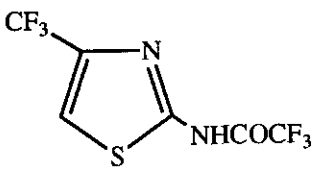
(69)

E Polylithiated derivatives

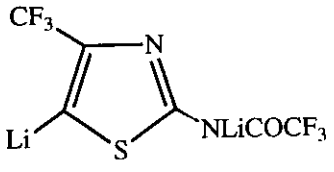
Carbinol (**70**) is metallated by LDA (2 mol. equiv.) in position-2 and the resulting dianion yields the corresponding 2-methyl compound (**71**) with iodomethane,[16] whilst amide (**72**) gives dianion (**73**) with butyllithium (THF/-78 °C), which can be trapped with a range of electrophiles thus allowing substituents to be introduced at position-5[108] (Table V).



(70) R = H
(71) R = Me

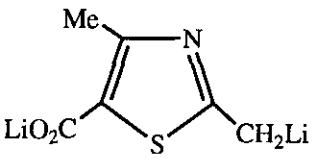


(72)

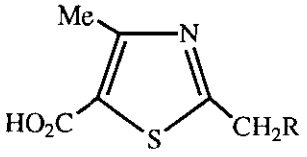


(73)

Metallation of 2,4-dimethylthiazole-5-carboxylic acid (two mol. equiv. LDA or BuLi/THF/-78 °C) yields the stable dianion (**74**) which can be trapped with various electrophiles, e.g. to give good yields of compounds (**75**)-(**80**).[123,124] 2-Ethyl-4-methyl- and 4-ethyl-2-methylthiazole-5-carboxylic acids are metallated similarly in both their carboxyl and 2-alkyl groups; the resulting dianions can be trapped with iodomethane.[124] 4-Methyl-2-phenylthiazole-5-carboxylic acid reacts too slowly with butyllithium in THF at temperatures below -50 °C and, at

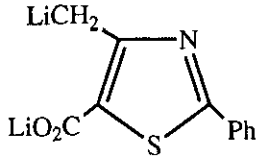


(74)

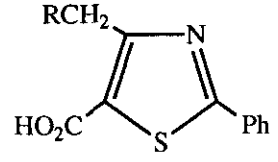


(75) R = Me (82%)
(76) R = Et (77%)
(77) R = $CH_2CH{=}CH_2$ (71%)
(78) R = CH(OH)Ph (83%)
(79) R = $CH(OH)C_6H_{13}$ (80%)
(80) R = $C(OH)Ph_2$ (70%)

higher temperatures, the thiazole ring is destroyed.[123,124] For generation of dianion (**81**) LDA (two mol. equiv./THF) is preferred and a higher temperature (-18 °C) is essential for good conversion; addition of suitable electrophiles yields compounds (**82**)-(**85**).[123,124] Dianions (**86**) and (**87**) are available similarly, and have been

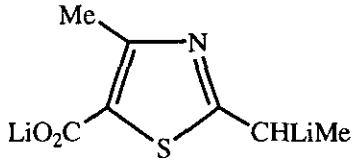


(81)

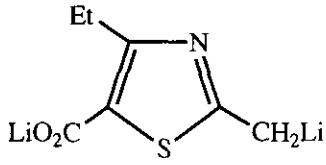


(82) R = Me (89%)
(83) R = $CH_2CH{=}CH_2$ (84%)
(84) R = C(OH)MePh (50%)
(85) R = $CH_2CH(OH)Et$ (66%)

trapped with iodomethane to give the corresponding 2-isopropyl (61% yield) and 2-ethyl compounds (95%), respectively.[124]

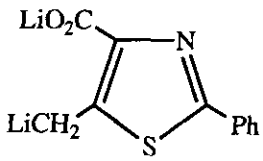


(86)

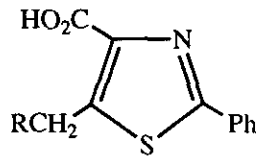


(87)

2,5-Dimethylthiazole-4-carboxylic acid is metallated with LDA (THF/-78 °C) in both methyl groups, as shown by isolation of 2-ethyl-5-methyl- and 5-ethyl-2-methylthiazole-4-carboxylic acids (ratio 59:41) following addition of iodomethane.[123,124] Complexation of butyllithium with the carboxyl group (THF/-78 °C) is indicated by a reversed ratio (46:54) of these two products. With LDA (THF/-78 °C) 5-ethyl-2-methylthiazole-4-carboxylic acid similarly metallates in both alkyl groups and, following addition of iodomethane, 2,5-diethyl- and 2-methyl-5-



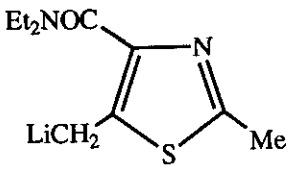
(88)



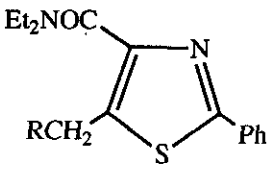
(89) R = Me (86%)
(90) R = $CH_2CH{=}CH_2$ (75%)
(91) R = C(OH)MePh (51%)
(92) R = $CH_2CH(OH)Et$ (66%)

isopropylthiazole-4-carboxylic acids (ratio 60:40) are obtained.[124] With butyllithium (THF/-78 °C) 5-methyl-2-phenylthiazole-4-carboxylic acid yields only dianion (**88**), which can be used to synthesise compounds (**89**)-(**92**).[123,124]

An amide group is a much more powerful *ortho*-directing group, as shown by exclusive generation of anion (**93**) when *N,N*-diethyl-2,5-dimethylthiazole-4-carboxamide is metallated with butyllithium (THF/-78 °C); products (**94**)-(**98**) are produced following addition of the appropriate reagent.[123,124]



(93)



(94) R = Me (97%)
(95) R = Et (98%)
(96) R = $CH_2CH{=}CH_2$ (96%)
(97) R = CH(OH)Ph (89%)
(98) R = C(OH)MePh (92%)

F Other organometallic reagents

We have referred to some Grignard chemistry and deprotonation of thiazoles with sodium hydride in Section III.B.

Early attempts to obtain thiazole Grignard derivatives by reacting magnesium with 5-bromo-2,4-dimethyl-,[125] 2-iodo-, 2-amino(or acetamido)-5-iodo-, or 2-acetamido-5-iodo-4-methyl(or phenyl)thiazoles[126] failed. 2-Bromo- and 5-bromo(and iodo)-2,4-dimethylthiazoles fail to form a Grignard reagent under classical conditions.[79] However, each of these compounds[79,127] together with 2-chloro-,[127] 2-bromo-5-methyl-, 2-chloro-4-methyl-, 2-bromo-4,5-dimethyl-, 5-bromo-4-methyl-, and 4-bromo-5-ethoxy-2-methylthiazoles[79] form Grignard compounds under entrainment conditions and these react with oxygen, formaldehyde, benzaldehyde, acetophenone or benzophenone (Table IX). When thiazole is treated with ethylmagnesium bromide at 0 °C, and the initially formed adduct is heated at 27 °C, thiazol-2-ylmagnesium bromide is produced which reacts with acetic anhydride, to give 2-acetylthiazole.[128] The 2-acetyl derivatives of 4-methyl-, 5-methyl(or ethyl)-, and 4,5-dimethyl(or diethyl)thiazole[128] and 2-butanoyl-4-methylthiazoles[91] may be prepared similarly. 2-Propionyl-4-methylthiazole has been prepared[91] by treating 4-methylthiazol-2-ylmagnesium bromide with propionyl chloride (Table IX).

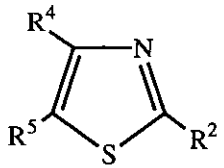
Thiazolyl-2-magnesium bromide may be prepared by addition of magnesium bromide to thiazol-2-yllithium (see Section III.B).[58]

Attempts to react 2,4,5-tribromothiazole with ethylmagnesium bromide have failed[102] (see Section III.C).

When thiazole is treated with mercuric acetate in aqueous acetic acid, it gives a *tris*mercurated derivative which can be used to synthesise 2,4,5-triiodothiazole.[129] Monomercuration in position-2 has been achieved[129] by

Table IX

Thiazoles Prepared from Thiazolylmagnesium Halides



R^2	R^4	R^5	Reagent	Yield (%)	Ref.
OH	H	H	O_2	15	127
COMe	H	H	Ac_2O	14	128
CH_2OH	H	H	HCHO	35	79
CH(OH)Ph	H	H	PhCHO	50-71	79
C(OH)MePh	H	H	PhCOMe	42	79
$C(OH)Ph_2$	H	H	Ph_2CO	93	79
COMe	Me	H	Ac_2O	17	128
COEt	Me	H	EtCOCl	–	91
COPr	Me	H	$(PrCO)_2O$	–	91
CH(OH)Ph	Me	H	PhCHO	20	79
COMe	H	Me	Ac_2O	19	128
CH(OH)Ph	H	Me	PhCHO	90	79

C(OH)MePh	H	Me	PhCOMe	48	79
$C(OH)Ph_2$	H	Me	Ph_2CO	10	79
COMe	H	Et	Ac_2O	11	128
COMe	Me	Me	Ac_2O	8	128
CH_2OH	Me	Me	HCHO	35	79
CH(OH)Ph	Me	Me	PhCHO	85	79
C(OH)MePh	Me	Me	PhCOMe	70	79
$C(OH)Ph_2$	Me	Me	Ph_2CO	32	79
COMe	Et	Et	Ac_2O	7	128
H	Me	CH(OH)Ph	PhCHO	65	79
Me	Me	CH(OH)Ph	PhCHO	65-73	79
Me	Me	C(OH)MePh	PhCOMe	39	79
Me	CH(OH)Ph	OEt	PhCHO	31	79

diazotising 2-aminothiazole in the presence of mercuric chloride followed by treating the resulting thiazole-diazonium chloride - mercuric chloride complex with copper in acetone. Thiazol-2-ylmercury(II) chloride yields 2-bromothiazole on treatment with bromine in trichloromethane and 2-iodothiazole with an aqueous solution of iodine and potassium iodide.[129] 4,5-Dimethylthiazole is mercurated similarly in position-2 with mercuric acetate.[130]

Surprisingly, it is claimed[130] that both 4- and 5-methylthiazoles are mercurated with mercuric acetate in the position (-5 or -4, respectively) adjacent to the methyl group and not in the free position-2. The order of reactivity for mercuration of thiazoles appears to be C-5 > C-4 > C-2.[130]

2,5-Dimethylthiazole is mercurated in position-4 with mercuric acetate.[130]

2-Amino- [$Hg(OAc)_2$,[126] 2-acetamido- [$Hg(OAc)_2$[126] or $HgCl_2$[131]], 2-acetamido-4-methyl(or phenyl)- [$Hg(OAc)_2$[126]], several other 2-acetamido-4-aryl- [$HgCl_2$[132]], 2-methyl-,[130] 2,4-dimethyl- [$Hg(OAc)_2$],[130,133] 2,4-diphenyl-,[134] and 4-methyl-2-phenylthiazoles [$Hg(OAc)_2$[133]] are all mercurated in position-5 and the resulting 5-mercurated derivatives have been used to introduce halogen and thiocyanato groups into this position (Table X).

4,5-Dimethyl-[134] and 2,4,5-trimethylthiazoles[130,134] are unreactive towards mercuric salts. 4,5-Dimethyl-2-phenylthiazole reacts with mercuric acetate in the *para*-position of the phenyl ring (9% conversion only), as shown by conversion into the corresponding bromo derivative.[133] Likewise *bis*mercuration of 2,4-diphenylthiazole occurs with mercuric acetate in acetic anhydride at 60-70 °C; treatment of the *bis*mercurated derivative with bromine yields 5-bromo-2-(4-bromophenyl)-4-phenylthiazole.[134] The order of reactivity of the following thiazoles towards mercuric acetate in acetic acid has been established: 2-Ph > 2-Ph-4-Me > 2-Me > 2-Ph-4,5-Me_2(thiazole).[134] A phenyl group is activating towards mercuration.

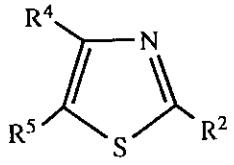
2-Acetamidothiazole and various of its 4-aryl derivatives are monomercurated with mercuric chloride in position-5 and the resulting 5-mercurated derivatives have been used to introduce bromine, iodine or a thiocyanato group into this position (Table X).[132]

When 2-acetamidothiazole is treated with mercuric acetate in aqueous acetic acid at 100 °C, it is *bis*mercurated in positions-4 and -5 (74% yield), as shown by conversion of the 4,5-*bis*mercurated derivative into 2-acetamido-4,5-diiodothiazole.[131] 2-Methylthiazole similarly yields a 4,5-*bis*mercurated derivative.[130]

Thiazolylmercuric acetates are convertible into the corresponding mercuriochlorides with aqueous sodium chloride.[126,130,132,133]

Table X

5-Substituted Thiazoles Prepared from Thiazol-5-ylmercuric Salts



R^2	R^4	R^5	Yield (%)	Ref.
NH_2	H	I	~ 10	126
NHAc	H	I	100, 56	126, 131
NHAc	H	Br	42	131
NHAc	H	SCN	50	131
NHAc	I	I	–	131
NHAc	Me	I	–	126
NHAc	Ph	I	–	126
NHAc	C_6H_4Cl-4	I	55	132
NHAc	C_6H_4Cl-4	Br	45	132
NHAc	C_6H_4Cl-4	SCN	60	132
NHAc	C_6H_4OMe-4	I	–	132

NHAc	C_6H_4OMe-4	Br	–	132
NHAc	C_6H_4OEt-4	SCN	–	132
NHAc	C_6H_4OEt-4	I	–	132
NHAc	C_6H_4OEt-4	Br	–	132
NHAc	C_6H_4OEt-4	SCN	–	132
NHAc	naphth-2-yl	I	–	132
NHAc	naphth-2-yl	SCN	–	132
NHAc	thien-2-yl	I	–	132
NHAc	thien-2-yl	SCN	–	132
NHAc	1-hydroxynaphth-2-yl	I	–	132
NHAc	1-hydroxynaphth-2-yl	SCN	–	132
Me	Me	Br	–	133
Ph	Me	Br	–	133
Ph	Ph	Br	–	134

Addition of diethylaluminium chloride to thiazol-2-yllithium yields diethylthiazol-2-ylaluminium (see also Section III.B).[58]

Reaction of various chlorogold(I) complexes with 4-methylthiazol-2-yllithium followed by protonation or alkylation produces novel gold(I) mono- and *bis*(carbene) complexes of thiazole.[135]

We have made no attempt here to cover metallation of Δ^2-thiazolines (see refs. 34, 122 and 136-138).

ACKNOWLEDGEMENT

We thank Sandra Fahy for help in preparing the manuscript.

REFERENCES

1. Part IV: B. Iddon and R.I. Ngochindo, *Heterocycles,* 1994, **38**, 2487.
2. Part I: B. Iddon, *Heterocycles*, 1994, **37**, 1263.
3. R. Slack and K.R.H. Wooldridge, *Adv. Heterocycl. Chem.*, 1965, **4**, 107.
4. K.R.H. Wooldridge, *Adv. Heterocycl. Chem.*, 1972, **14**, 1.
5. S.D. Sokolov, *Russ. Chem. Rev. (Engl. Transl.)*, 1979, **48**, 289.
6. R.G. Micetich, *Can. J. Chem.*, 1970, **48**, 2006.
7. M.P.L. Caton and R. Slack, *J. Chem. Soc. (C)*, 1968, 1402.
8. R.G. Micetich and C.G. Chin, *Can. J. Chem.*, 1970, **48**, 1371.
9. M.P.L. Caton, D.H. Jones, R. Slack, and K.R.H. Wooldridge, *J. Chem. Soc.*, 1964, 446.
10. T. Naito, S. Nakagawa, and T. Takahashi, *Chem. Pharm. Bull.*, 1968, **16**, 148.
11. T. Naito and S. Nakagawa, U.S. Pat. 3,341,518/1967 [*Chem. Abstr.*, 1968, **68**, 95810].
12. A. Koerts, G.F. de Wit, R. Leopold, and G.E. Bakker, Neth. Pat. Appl. 6,607,796/1966 [*Chem. Abstr.*, 1967, **67**, 100136].
13. R.U. Lemieux and R.G. Micetich, U.S. Pat. 3,311,611/1967 [*Chem. Abstr.*, 1968, **68**, 59570].
14. R.G. Micetich and R. Raap, *J. Med. Chem.*, 1968, **11**, 159.
15. S. Rajappa, A.S. Akerkar, and V.S. Iyer, *Indian J. Chem.*, 1969, **7**, 103.
16. A.R. Katritzky, K.S. Laurenzo, and D.I. Relyea, *Can. J. Chem.*, 1988, **66**, 1617.
17. R. Raap, R.U. Lemieux, and R.G. Micetich, U.S. Pat. 3,271,407/1966 [*Chem. Abstr.*, 1967, **66**, 28767].
18. M.J. Ashton, A. Ashford, A.H. Loveless, D. Riddell, J. Salmon, and G.V.W. Stevenson, *J. Med. Chem.*, 1984, **27**, 1245.

19. A.J. Layton and E. Lunt, *J. Chem. Soc. (C)*, 1968, 611.

20. R. Kalish, E. Broger, G.F. Field, T. Anton, T.V. Steppe, and L.H. Sternbach, *J. Heterocycl. Chem.*, 1975, **12**, 49.

21. D.S. Noyce and B.B. Sandel, *J. Org. Chem.*, 1975, **40**, 3381.

22. K.S. Hirsch, C.D. Jones, H.M. Taylor, and M.A. Winter, Europ. Pat. Appl. 0,165,784,A2/1985 [*Chem. Abstr.*, 1986, **104**, 186400].

23. C.D. Jones, M.A. Winter, K.S. Hirsch, N. Stamm, H.M. Taylor, H.E. Holden, J.D. Davenport, E.V.Krumkalns, and R.G. Suhr, *J. Med. Chem.*, 1990, **33**, 416.

24. M. Hatanaka and T. Ishimaru, *J. Med. Chem.*, 1973, **16**, 978.

25. R.G. Micetich and R. Raap, *Org. Prep. Proceed. Int.*, 1971, **3**, 167.

26. D.E. Horning and J.M. Muchowski, *Can. J. Chem.*, 1974, **52**, 2950.

27. M. Béringer, B.Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, 1966, **49**, 2466.

28. G.P. Volpp, quoted by J.Z. Gougoutas, Ph.D. Thesis, Harvard University (1964) (see ref. 105 in our ref. 4).

29. R.B. Woodward, *Harvey Lect. Ser.*, 1965, **59**, 31 (see ref. 67 in our ref. 4).

30. D. Buttimore, D.H. Jones, R. Slack, and K.R.H. Wooldridge, *J. Chem. Soc.*, 1963, 2032.

31. A. Alberola, C. Andrés, J.L. Casado, A. González, and R. Pedrosa, *Synth. Commun.*, 1990, **20**, 617.

32. A. Alberola, F. Alonso, P. Cuadrado, and M.C. Sanudo, *Gazz. Chim. Ital.*, 1987, **117**, 461.

33. D. Buttimore and R. Slack, personal communication quoted as ref. 106 in our ref. 4 (see p. 20).

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

35. "Thiazole and Its Derivatives", ed. J.V. Metzger, *Chem. Heterocycl. Compd.*, **34**, in three parts, Wiley Interscience, New York, 1979.

36. A. Dondoni, G. Fantin, M. Fogagnolo, A. Mastellari, A. Medici, E. Negrini, and P. Pedrini, *Gazz. Chim. Ital.*, 1988, **118**, 211.

37. A. Medici, P. Pedrini, and A. Dondoni, *J. Chem. Soc., Chem. Commun.*, 1981, 655.

38. A. Dondoni, T. Dall'Occo, G. Galliani, A. Mastellari, and A. Medici, *Tetrahedron Lett.*, 1984, **25**, 3637.

39. A. Dondoni, M. Fogagnolo, A. Medici, and P. Pedrini, *Tetrahedron Lett.*, 1985, **26**, 5477.

40. A. Dondoni, *Lectures Heterocycl. Chem.*, 1985, **8**, 13.

41. A. Dondoni, *Phosphorus and Sulfur*, 1985, **24**, 1.

42. A. Dondoni, A.R. Mastellari, A. Medici, E. Negrini, and P. Pedrini, *Synthesis*, 1986, 757.

43. A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, *Synthesis*, 1987, 998.

44. A. Dondoni, *Il Farmaco,* 1988, **43**, 1119.

45. A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, *J. Org. Chem.*, 1988, **53**, 1748.

46. A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, *J. Org. Chem.*, 1989, **54**, 693 (see also ref. 39).

47. A. Dondoni, G. Fantin, M. Fogagnolo, and P. Pedrini, *Tetrahedron*, 1989, **45**, 5141.

48. A. Dondoni, *Phosphor., Sulfur, Silica*, 1989, **43**, 25.

49. A. Dondoni, *Pure Appl. Chem.*, 1990, **62**, 643.

50. A. Dondoni, F. Junquera, F.L. Merchán, P. Merino, and T. Tejero, *Tetrahedron Lett.*, 1992, **33**, 4221.

51. A. Dondoni and D. Perrone, *Tetrahedron Lett.*, 1992, **33**, 7259.

52. A. Dondoni, in "New Aspects of Organic Chemistry II; Proceedings of the Fifth International Kyoto Conference on New Aspects of Organic Chemistry", ed. Z. Yoshida and Y. Oshiro, VCH, Weinheim, 1992, ch. 7, p. 105.

53. A. Dondoni, in "Modern Synthetic Methods 1992", R. Scheffold, ed., VHCA and VCH, Basel and Weinheim, 1992, p. 377.

54. A. Dondoni, *Bull. Soc. Chim. Belg.,* 1992, **101**, 433.

55. A. Dondoni, P. Merino, and D. Perrone, *Tetrahedron*, 1993, **49**, 2939.

56. A. Dondoni, S. Franco, F. Merchan, P. Merino, and T. Tejero, *Synlett*, 1993, 78.

57. A. Dondoni and P. Merino, *Org. Synth.*, 1993, **72**, 21.

58. A. Dondoni, S. Franco, F.L. Merchán, P. Merino, and T. Tejero, *Tetrahedron Lett.*, 1993, **34**, 5475.

59. A. Dondoni and M.-C. Scherrmann, *Tetrahedron Lett.*, 1993, **34**, 7319.

60. A. Dondoni and D. Perrone, *Synthesis*, 1993, 1162.

61. A. Dondoni, F.L. Merchan, P. Merino, T. Tejero, and V. Bertolasi, *J. Chem. Soc., Chem. Commun.*, 1994, 1731.

62. A. Dondoni, A. Marra, and P. Merino, *J. Am. Chem. Soc.*, 1994, **116**, 3324.

63. A. Dondoni, A. Marra, and D. Perrone, *J. Org. Chem.*, 1993, **58**, 275.

64. J. Metzger and B. Koether, *Bull. Soc. Chim. Fr.,* 1953, 708.

65. J. Beraud and J. Metzger, *Bull. Soc. Chim. Fr.*, 1962, 2072.

66. B.D. Compton, *Diss. Abstr. Int.*, 1972/73, **33B**, 2994.

67 H. Kojima, K. Yamamoto, Y. Kinoshita, and H. Inoue, *J. Heterocycl. Chem.*, 1992, **29**, 1473.

68. P. Roussel and J. Metzger, *Bull. Soc. Chim. Fr.*, 1962, 2075.

69. P.E. Iversen, *Acta Chem. Scand.*, 1968, **22**, 1690.

70. P.E. Iversen and H. Lund, *Acta Chem. Scand.*, 1966, **20**, 2649.

71. J. Tirouflet, E. Laviron, J. Metzger, and J. Boichard, *Coll. Czech. Chem. Commun.*, 1960, **25**, 3277.

72. P.E. Iversen, *Acta Chem. Scand.*, 1968, **22**, 694.

73. H.C. Beyerman, P.H. Berben, and J.S. Bontekoe, *Recl. Trav. Chim. Pays-Bas*, 1954, **73**, 325.

74. P.E. Iverson and H. Lund, *Acta Chem. Scand.*, 1967, **21**, 389; these authors obtained 75-90% yields of thiazole-2-carboxylic acid using the method of Beyerman *et al.*[73]

75. N. Irako, Y. Hamada, and T. Shioiri, *Tetrahedron*, 1992, **48**, 7251.

76. T. Shioiri, K. Hayashi, and Y. Hamada, *Tetrahedron*, 1993, **49**, 1913.

77. D.S. Noyce and S.A. Fike, *J. Org. Chem.*, 1973, **38**, 3316.

78. M.T. Reetz, W. Reif, and X. Holdgrün, *Heterocycles*, 1989, **28**, 707.

79. R.P. Kurkjy and E.V. Brown, *J. Am. Chem. Soc.*, 1952, **74**, 6260.

80. K. Kohata, Y. Kawamonzen, T. Odashima, and H. Ishii, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 3398.

81. C.T. Eyles, P. Sykes, and J.E. Downes, *J. Chem. Soc.*, 1965, 4265.

82. L. Arabshahi and F.J. Schmitz, *Tetrahedron Lett.*, 1988, **29**, 1099.

83. J.E. Downes and P. Sykes, *Chem. Ind. (London)*, 1959, 1156.

84. G.I.I. Moore, U.S. Pat. 4,535,165/1985.

85. T. Yagodzinski, T. Dzembovska, E. Yagodzinskaya, and Z. Yablonski, *Chem. Heterocycl. Compds. (Engl. Transl.)*, 1986, **22**, 1139.

86. D.L. Selwood and K.S. Jandu, *Heterocycles*, 1988, **27**, 1191.

87. P. Jutzi and U. Gilge, *J. Organomet. Chem.*, 1983, **246**, 163.

88. S.S. Moore and G.M. Whitesides, *J. Org. Chem.*, 1982, **47**, 1489 (see also ref. 89).

89. Y. Uchida, Y. Takaya, and S. Oae, *Heterocycles*, 1990, **30**, 347.

90. R. Breslow and E. McNelis, *J. Am. Chem. Soc.*, 1959, **81**, 3080.

91. M. Winter, F. Gautschi, I. Flament, and M. Stoll, U.S. Pat., 3,931,246/1976 [*Chem. Abstr.*, 1976, **84**, 180019].

92. R. Baker, R.J. Snow, J. Saunders, and G.A. Showell, Europ. Pat. Appl. 0,307,141,A2/1988.

93. D. Sorg, Ger. Pat. Offen. DE 3,620,643/1987 [*Chem. Abstr.*, 1987, **106**, 156454].

94. M. Robba and R.C. Moreau, *Ann. Pharm. Franc.*, 1964, **22**, 201 [*Chem. Abstr.*, 1964, **61**, 3086].

95. T.R. Kelly, C.T. Jagoe, and Z. Gu, *Tetrahedron Lett.*, 1991, **32**, 4263.

96. D.S. Noyce and S.A. Fike, *J. Org. Chem.*, 1973, **38**, 3318.

97. P.T. Kaye, G.D. Meakins, C. Willbe, and P.R. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2335.

98. M. Erne and H. Erlenmeyer, *Helv. Chim. Acta*, 1948, **31**, 652.

99. M. Begtrup and L.B.L. Hansen, Abstracts of The Thirteenth International Congress of Heterocyclic Chemistry, Oregon State University, 1991, abstract no. P02-73.

100. M. Begtrup and L.B.L. Hansen, *Acta Chem. Scand.*, 1992, **46**, 372.

101. S.C. Dillender, T.D. Greenwood, M.S. Hendi, and J.F. Wolfe, *J. Org. Chem.*, 1986, **51**, 1184.

102. S. Athmani, A. Bruce, and B. Iddon, *J. Chem. Soc., Perkin Trans. 1*, 1992, 215.

103. L.S. Fuller, G. Jones, H. Ollivierre, and J.H. Young, Abstracts of the XIVth European Colloquium on Heterocyclic Chemistry, Toledo (Spain), October 1-3rd, 1990, p. 24.

104. I. Sawhney, and J.R.H. Wilson, *J. Chem. Soc., Perkin Trans. 1*, 1990, 329.

105. J. Crousier and J. Metzger, *Bull. Soc. Chim. Fr.*, 1967, 4134.

106. D.S. Noyce and S.A. Fike, *J. Org. Chem.*, 1973, **38**, 2433.

107. S. Iwata, Y. Ishihara, and K. Tanaka, *J. Fluorine Chem.*, 1991, **54**, 121.

108. M.S. South and K.A. Van Sant, *J. Heterocycl. Chem.*, 1991, **28**, 1017.

109. L. Brandsma, R.L.P. De Jong, and H.D. Verkruijsse, *Synthesis*, 1985, 948.

110. B.M. Mikhailov and V.P. Bronovitskaya, *Zh. Obschei. Khim.*, 1956, **26**, 66 [*Chem. Abstr.*, 1956, **50**, 13874].

111. G. Knaus and A.I. Meyers, *J. Org. Chem.*, 1974, **39**, 1192.

112. K. Hirai and H. Sugimoto, *Chem. Pharm. Bull.*, 1977, **25**, 2292.

113. K.L. Kirk, *J Heterocycl. Chem.*, 1985, **22**, 57.

114. Y. Takeuchi, H.J.C. Yeh, K.L. Kirk, and L.A. Cohen, *J. Org. Chem.*, 1978, **43**, 3565.

115. Y. Takeuchi, K.L. Kirk, and L.A. Cohen, *J. Org. Chem.*, 1978, **43**, 3570.

116. S. Athmani, M.F. Farhat, and B. Iddon, *J. Chem. Soc., Perkin Trans. 1*, 1992, 973.

117. A.I. Meyers and G.N. Knaus, *J. Am. Chem. Soc.*, 1973, **95**, 3408.

118. C. Ivanov, V. Dryanska, and I. Arnaudova, *Dokl. Bolg. Akad. Nauk*, 1969, **22**, 891 [*Chem. Abstr.*, 1970, **72**, 31674].

119. G. Knaus and A.I. Meyers, *J. Org. Chem.*, 1974, **39**, 1189.

120. J.C. Brindley, D.G. Gillon, and G.D. Meakins, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1255.

121. L.J. Altman and S.L. Richeimer, *Tetrahedron Lett.*, 1971, 4709.

122. A. Thomas, H. Ila, and H. Junjappa, *Tetrahedron*, 1990, **46**, 4295.

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

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

125. K. Ganapathi and A. Venkataraman, *Proc. Ind. Acad. Sci., Sect. A*, 1945, **22**, 343.

126. G. Travalgi, *Gazz. Chim. Ital.*, 1948, **78**, 592.

127. G. Klein and B. Prijs, *Helv. Chim. Acta*, 1954, **37**, 2057.

128. J. Metzger and B. Koether, *Bull. Soc. Chim. Fr.*, 1953, 702.

129. G. Travagli, *Gazz. Chim. Ital.*, 1955, **85**, 926.

130. G. Travagli and G. Mazzoli, *Studi Urbinati, Fac. Farm.*, 1956, **30**, 101 [*Chem. Abstr.*, 1960, **54**, 24661].

131. C.D. Hurd and H.L. Wehrmeister, *J. Am. Chem. Soc.*, 1949, **71**, 4007.

132. B. Das, *J. Sci. Ind. Res. India*, 1956, **15B**, 613.

133. S.L. Gusinskaya, V. Yu Telly, and T.P. Makagonova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1970, **6**, 322.

134. S.L. Gusinskaya, V. Yu. Telly, and N.L. Ovchinnikova, *Uzb. Khim. Zh.*, 1971, **15**, 47 [*Chem. Abstr.*, 1972, **76**, 72617].

135. H.G. Raubenheimer, F. Scott, M. Roos, and R. Otte, *J. Chem. Soc., Chem. Commun.*, 1990, 1722.

136. G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, *Heterocycles*, 1993, **36**, 473.

137. O. Bortolini, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, *Heterocycles*, 1990, **31**, 1213.

138. A.I. Meyers, R. Munavu, and J. Durandetta, *Tetrahedron Lett.*, 1972, 3929

Received, 11th October, 1994