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

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

CONTENTS

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

I 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 this review covers the literature through December 1993.

The imidazole (1,3-diazole) ring system has been studied more than any of the other azole systems covered in this series presumably because many of its derivatives possess biological activity.[3-9] The present review is comprehensive with respect to the discussion but omits in its Tables the examples presented in the Tables of our earlier review[8] on this topic. A comparison between these two reviews shows that there has been considerable recent interest in metallated imidazoles. We have made no attempt to cover the metallation reactions of imidazolines. However, noteworthy are the additions of methyl- and phenyllithium to the -C=N- and -C=$\overset{+}{N}$(O$^-$)- *bonds in 2H-imidazole 1-oxides, 4H-imidazole 1- and 3-oxides and 1,3-dioxides, and analogous imidazoline oxides.*[10]

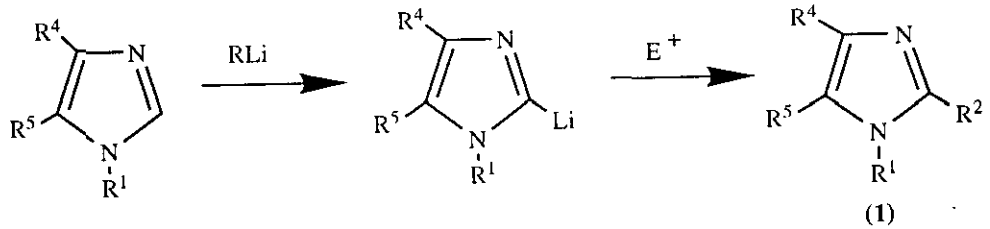
II MONOMETALLATION IN THE RING

Metallation of a ring C-atom, with the reactivity order C-2 > C-5 > C-4, is observed in imidazoles bearing suitable *N*-1 substituents, otherwise *N*-lithiated derivatives are formed.[11-16] Addition of an alkylating agent to the *N*-1 lithiated derivatives of 4(5)-substituted imidazoles leads to a mixture of *N*-alkylated products;[13,17] the presence of hexamethylphosphorictriamide (HMPA) helps with less reactive alkylating agents.[17]

A number of *N*-1 protecting groups have been studied; each has its own advantages and disadvantages[18-21] (see also ref. 22).

A Lithiation at position-2

Monolithiation of *N*-1 protected imidazoles occurs at position-2 even at low temperatures, most commonly -78 °C. The resulting 2-lithiated derivatives have been trapped with a variety of electrophilic quenching reagents, to give 1,2-di- or polysubstituted imidazoles (**1**) (Scheme 1) (Table I); e.g. with ketones, carbinols [**1**; R^2 = C(OH)R'R"] have been prepared in 50-96% yields (these are **not** listed in Table I).[23]

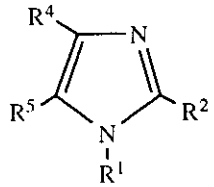


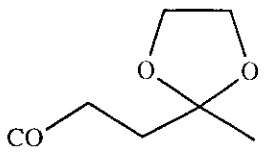
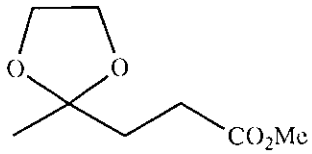
(**1**)

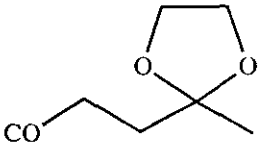
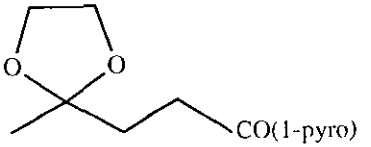
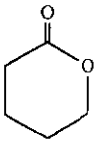
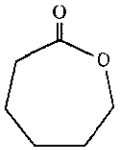
Scheme 1

Table I

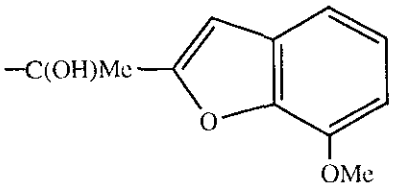
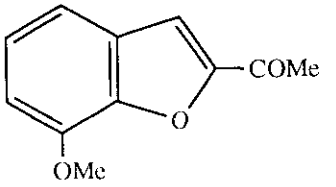
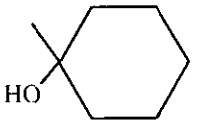
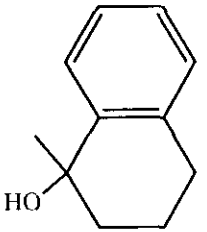
Imidazoles Synthesised from Imidazol-2-yllithium Compounds[a]

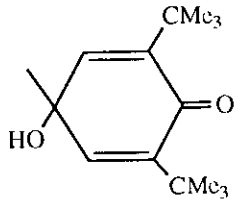
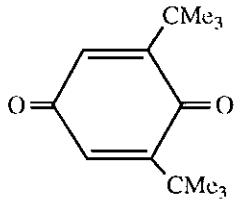
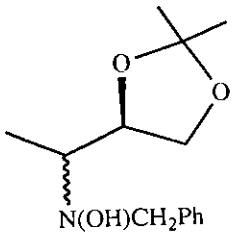
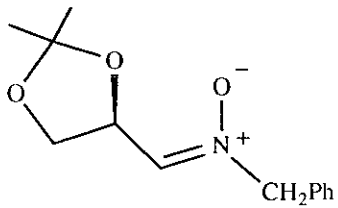
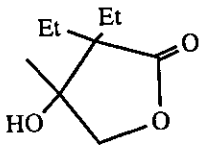
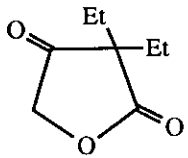


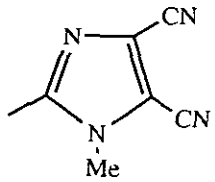
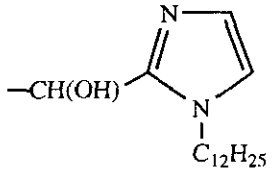
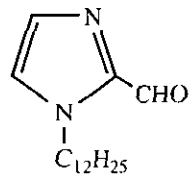
R^1	R^2	R^4	R^5	Reagent	Yield (%)	Ref.
Me	Br	H	H	Br_2	80	24, 25
Me	Br	H	H	NBS[b]	21	26
Me	I	H	H	I_2	–, 86,	27, 28
Me	2-Py	H	H	$ZnCl_2$/2-PyBr[b]/$Pd(PPh_3)_4$	93	29
Me	CHO	H	H	DMF	89[c]	30
Me	CHO	H	H	PhNMeCHO	–	31
Me	$CONMe_2$	H	H	$ClCONMe_2$	85	32
Me		H	H		35	33

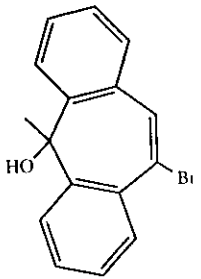
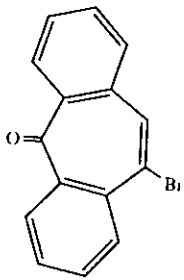
Me		H	H		79[b]	33-35
Me	$COCHMePr$	H	H	1-PyroCOCHMePr	89[b]	33, 34
Me	COC_6H_{13}	H	H	$C_6H_{13}COCl$	58	33
Me	COC_6H_{13}	H	H	$C_6H_{13}CO_2Me$	68	33
Me	COC_6H_{13}	H	H	1-PyroCOC_6H_{13}	100[b]	33, 34
Me	COC_6H_{11}-c	H	H	cyclohexylCO_2Me	45.5	33
Me	COC_6H_{11}-c	H	H	1-PyroCOcyclohexyl	100[b]	34
Me	$COCH=CHPh$	H	H	1-PyroCOCH=CHPh	62[b]	33, 34
Me	$COCH_2CHMe(CH_2)_2CH=CMe_2$	H	H	$Me_2C=CH(CH_2)_2CHMeCH_2CO_2Me$	27.5	33
Me	$CO(CH_2)_2CH(OH)Ph$	H	H	1-Pyro$CO(CH_2)_2CH(OH)Ph$	86[b]	33, 34
Me	$CO(CH_2)_3OH$	H	H		75	33
Me	$CO(CH_2)_5OH$	H	H		76	33
Me	$COPh$	H	H	PhCOCl	68	33

Me	COPh	H	H	$PhCO_2Me$	42	33
Me	COPh	H	H	PhCN	–	36
Me	COPh	H	H	1-PyroCOPh	100[b]	34
Me	$COC_6H_3(OCH_2O)$-3,4	H	H	3,4-$(OCH_2O)C_6H_3CO_2Me$	42	33
Me	$COC_6H_3(OCH_2O)$-3,4	H	H	1-Pyro$COC_6H_3(OCH_2O)$-3,4	100[b]	33, 34
Me	CO(2-Mim)[b]	H	H	$(MeO)_2CO$	93	32
Me	CO(2-Mim)[b]	H	H	$(EtO)_2CO$	76	37
Me	CO(4-Py)[b]	H	H	4-PyCN	5[d]	36
Me	CO(4-Py)[b]	H	H	1-PyroCO(4-Py)	84	33, 34
Me	$CH(OH)(CH_2)_5Me$	H	H	$Me(CH_2)_5CHO$	70	35
Me	$CH(OH)CH_2CHMe(CH_2)_2$Pr-*iso*	H	H	*iso*-$Pr(CH_2)_2CHMeCH_2CHO$	88	35
Me	$CH(OH)C_6H_{11}$-c	H	H	cyclohexylCHO	76	35
Me	CH(OH)Ph	H	H	PhCHO	74-77	38
Me	$CH(OH)C_6H_4NMe_2$-4	H	H	4-$Me_2NC_6H_4CHO$	74-77	38
Me	$CH(OH)C_6H_3(OMe)_2$-3,4	H	H	3,4-$(MeO)_2C_6H_3CHO$	74-77, 86	38, 35
Me	CH(OH)(3-In)[b]	H	H	indole-3-CHO	63	39
Me	$C(OH)Me_2$	H	H	Me_2CO	96	40
Me	C(OH)(Pr-*iso*)$_2$	H	H	(*iso*-Pr)$_2$CO	78	40
Me	$C(OH)MeC_6H_{13}$	H	H	$MeCOC_6H_{13}$	84.5	35

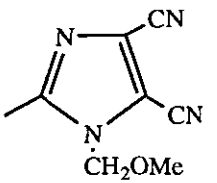
Me	C(OH)MePh	H	H	PhCOMe	92, 88	35, 40
Me	C(OH)Me(thien-2-yl)	H	H	thien-2-ylCOMe	83	40
Me	C(OH)Me(2-furyl)	H	H	2-furylCOMe	87	40
Me		H	H		79	35
Me	C(OH)BuPh	H	H	PhCOBu	82	35
Me	$C(OH)Ph_2$	H	H	Ph_2CO	90	35
Me	C(OH)(2-Mim)$_2$[b]	H	H	$ClCO_2Me$	–	41,42
Me		H	H	*cyclohexanone*	85	40
Me		H	H	1-tetralone	90	35

Me		H	H		–	43
Me	SMe	H	H	Me_2S_2	55	44
Me	SBu-*tert*	H	H	$(tert\text{-}Bu)_2S_2$	41	45
Me	SPh	H	H	Ph_2S_2	89	45
Me		H	H		81 (*syn:anti*-88:12) 76 (*syn:anti*-21:79)[g]	46
Me	$SnMe_3$	H	H	Me_3SnCl	–, 73	47, 48 (see also ref. 49)
Me	I	H	Cl	I_2	70	50
Me		H	Cl		–	51
Me	I	H	I	I_2	59	24

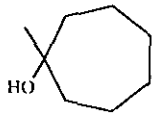
Me		CN	CN	$CuCl_2/O_2/H_3O^+$	54[e]	52
$C_{12}H_{25}$	CHO	H	H	DMF	80	53
$C_{12}H_{25}$		CH_2OTHP[h]	H		32[f]	53
CH_2Ph	D	H	H	D_2O	88	54
CH_2Ph	Me	H	H	MeI	13	54
CH_2Ph	I	H	H	2-$O_2NC_6H_4I$	35	54
CH_2Ph	$C_6H_4NO_2$-2	H	H	2-$O_2NC_6H_4I$	9	54
CH_2Ph	CHO	H	H	PhNMeCHO	–	31
CH_2Ph	COC_6H_4Cl-3	H	H	3-ClC_6H_4COCl	6	54
CH_2Ph	COC_6H_4Cl-4	H	H	4-ClC_6H_4COCl	14	54
CH_2Ph	COC_6H_4Cl-4	H	H	4-ClC_6H_4CHO	13[g]	54
CH_2Ph	$CH(OH)C_6H_4Cl$-4	H	H	4-ClC_6H_4CHO	9	54
CH_2Ph	$C(OH)Ph_2$	H	H	Ph_2CO	74, 2	55, 18
CH_2Ph	$C(OH)PhC_6H_4Cl$-2	H	H	2-ClC_6H_4COPh	8	18

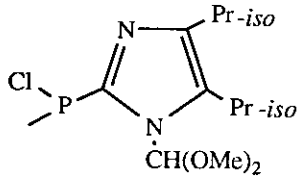
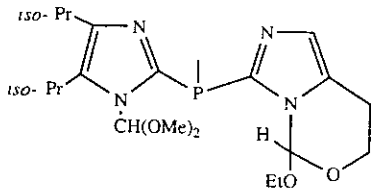
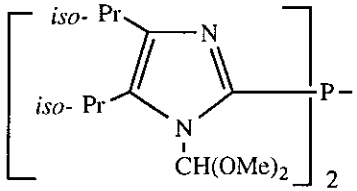
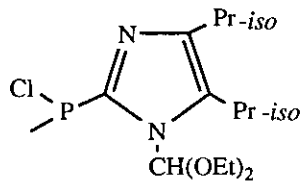
CH_2Ph	$C(OH)PhC_6H_4Cl$-4	H	H	4-ClC_6H_4COPh	12	18
CH_2Ph	$C(OH)PhC_6H_4OMe$-4	H	H	4-$MeOC_6H_4COPh$	37	18
CH_2Ph	$C(OH)PhC_6H_4CF_3$-4	H	H	4-$F_3CC_6H_4COPh$	21	18
CH_2Ph	$C(OH)(C_6H_4F\text{-}4)_2$	H	H	$(4\text{-}FC_6H_4)_2CO$	21	18
CH_2Ph	$C(OH)(C_6H_4Cl\text{-}4)_2$	H	H	$(4\text{-}ClC_6H_4)_2CO$	20	18
CH_2Ph		H	H		50	18
CH_2Ph	SMe	H	H	Me_2S_2	31	54
CH_2Ph	SPh	H	H	Ph_2S_2	38	54
CH_2Ph	CH(OH)Ph	Ph	Ph	PhCHO	73	55
CH_2Ph	C(OH)MePh	Ph	Ph	PhCOMe	80	55
CH_2Ph	$C(OH)Ph_2$	Ph	Ph	Ph_2CO	72	55
$CH_2C_6H_4Cl$-4	$C(OH)Ph_2$	H	H	Ph_2CO	7	18
$CH_2C_6H_4Cl$-4	$C(OH)(C_6H_4Cl\text{-}4)_2$	H	H	$(4\text{-}ClC_6H_4)_2CO$	5	18
CH_2(1-Bzt)[b]	COPh	H	H	$PhCO_2Et$	30	56
CH_2(1-Bzt)[b]	$CH(OH)C_6H_4Me$-4	H	H	4-MeC_6H_4CHO	74	56
$CH{=}CH_2$	$C(OH)PhC_6H_4Pr$-*iso*-4	H	H	4-*iso*-PrC_6H_4COPh	71	18
$CH{=}CH_2$	$C(OH)PhC_6H_4Bu$-*tert*-2	H	H	2-*tert*-BuC_6H_4COPh	61	18

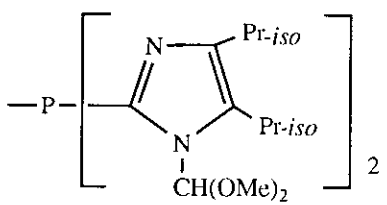
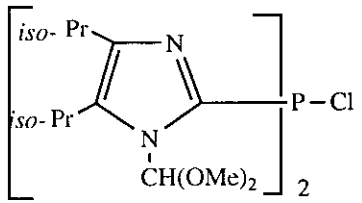
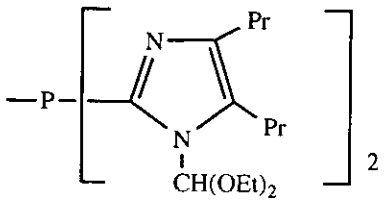
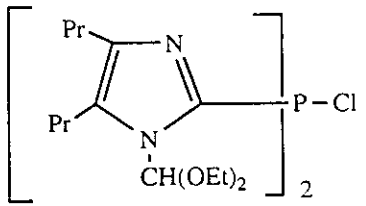
$CH=CH_2$	$C(OH)PhC_6H_4Bu$-*tert*-4	H	H	4-*tert*-BuC_6H_4COPh	81	18
$CH=CH_2$	$C(OH)PhC_6H_4CF_3$-4	H	H	4-$F_3CC_6H_4COPh$	52	18
$CH=CH_2$	$C(OH)(C_6H_4Bu$-*tert*-$4)_2$	H	H	(4-*tert*-$BuC_6H_4)_2CO$	80	18
$CH=CH_2$	$C(OH)(C_6H_4Cl$-$4)_2$	H	H	(4-$ClC_6H_4)_2CO$	60	18
$CH_2CH=CH_2$	$C(OH)PhC_6H_4Cl$-4	H	H	4-ClC_6H_4COPh	43	18
$CH_2CH=CH_2$	$C(OH)(C_6H_4Cl$-$4)_2$	C_6H_4Cl-4	H	(4-$ClC_6H_4)_2CO$	36	18
$CH_2CH=CH_2$	$C(OH)(C_6H_4Cl$-$4)_2$	Me	Me	(4-$ClC_6H_4)_2CO$	10	18
CH_2OMe	CHO	H	H	DMF	–	14
CH_2OMe	$C(OH)Ph_2$	H	H	Ph_2CO	78	18
CH_2OMe	$C(OH)PhC_6H_4Bu$-*tert*-2	H	H	2-*tert*-BuC_6H_4COPh	50	18
CH_2OMe	$C(OH)PhC_6H_4F$-4	H	H	4-FC_6H_4COPh	74	18
CH_2OMe	$C(OH)PhC_6H_4Cl$-4	H	H	4-ClC_6H_4COPh	47	18
CH_2OMe	$C(OH)PhC_6H_4CF_3$-3	H	H	3-$F_3CC_6H_4COPh$	64	18
CH_2OMe	$C(OH)PhC_6H_4CF_3$-4	H	H	4-$F_3CC_6H_4COPh$	81	18
CH_2OMe	$C(OH)PhC_6H_4OH$-4	H	H	4-$TMSOC_6H_4COPh$[b,f]	35	18
CH_2OMe	$C(OH)PhC_6H_4SMe$-4	H	H	4-$MeSC_6H_4COPh$	90	18
CH_2OMe	$C(OH)C_6H_3Cl_2$-2,4	H	H	2,4-$Cl_2C_6H_3COPh$	78	18
CH_2OMe	$C(OH)C_6H_3Cl_2$-2,6	H	H	2,6-$Cl_2C_6H_3COPh$	46	18
CH_2OMe	$C(OH)(C_6H_4F$-$4)_2$	H	H	(4-$FC_6H_4)_2CO$	53	18
CH_2OMe	$C(OH)(C_6H_4Cl$-$4)_2$	H	H	(4-$ClC_6H_4)_2CO$	50	18

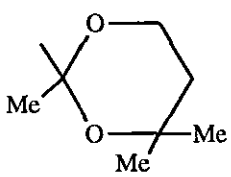
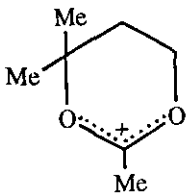
CH_2OMe	$C(OH)(C_6H_4CF_3\text{-}4)_2$	H	H	$(4\text{-}F_3CC_6H_4)_2CO$	15	18
CH_2OMe	$C(OH)(C_6H_4OH\text{-}4)_2$	H	H	$(4\text{-}TMSOC_6H_4)_2CO$[b,f]	26	18
CH_2OMe	$C(OH)(C_6H_4OMe\text{-}4)_2$	H	H	$(4\text{-}MeOC_6H_4)_2CO$	87	18
CH_2OMe	$C(OH)(C_6H_4OCH_2OMe\text{-}4)_2$	H	H	$(4\text{-}MeOCH_2OC_6H_4)_2CO$	25	18
CH_2OMe	$C(OH)(C_6H_3Cl_2\text{-}2,4)_2$	H	H	$(2,4\text{-}Cl_2C_6H_3)_2CO$	48	18
CH_2OMe	$C(OH)(C_6H_4Bu\text{-}tert\text{-}4)(C_6H_4Cl\text{-}4)$	H	H	4-*tert*-$BuC_6H_4COC_6H_4Cl$-4	51	18
CH_2OMe	$C(OH)(C_6H_4F\text{-}4)(C_6H_4Cl\text{-}4)$	H	H	$4\text{-}FC_6H_4COC_6H_4Cl\text{-}4$	51	18
CH_2OMe	$C(OH)(C_6H_4F\text{-}4)(C_6H_3Cl_2\text{-}2,4)$	H	H	$4\text{-}FC_6H_4COC_6H_3Cl_2\text{-}2,4$	60	18
CH_2OMe	$C(OH)(C_6H_4Cl\text{-}4)(4\text{-}Py)$[b]	H	H	$4\text{-}PyCOC_6H_4Cl\text{-}4$[b]	60	18
CH_2OMe	SPh	H	H	Ph_2S_2	76	22
CH_2OMe	$SiMe_2Bu\text{-}tert$	H	H	*tert*-$BuMe_2SiCl$	94	32
CH_2OMe	$C(OH)(C_6H_4Cl\text{-}4)_2$	Me	Me	$(4\text{-}ClC_6H_4)_2CO$	53	18
CH_2OMe	$SiMe_3$	Cl	Cl	Me_3SiCl	–	57
CH_2OMe	$C(OH)PhC_6H_4SMe\text{-}4$	$C_6H_4Cl\text{-}4$	H	$4\text{-}MeSC_6H_4COPh$	25	18
CH_2OMe	$C(OH)(C_6H_4Cl\text{-}4)_2$	$C_6H_4Cl\text{-}4$	H	$(4\text{-}ClC_6H_4)_2CO$	35	18
CH_2OMe		CN	CN	$CuCl_2/O_2/H_3O^+$	27[c]	50
CH_2OEt	I	H	H	I_2	90	58
CH_2OEt	2-Py-[b]	H	H	$ZnCl_2$/2-PyBr/$Pd(PPh_3)_4$	93	29

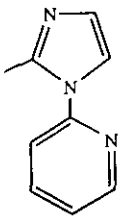
CH_2OEt	I	*iso*-Pr	*iso*-Pr	I_2	87	58
CH_2OBu-*tert*	D	H	H	D_2O	100	59
CH_2OBu-*tert*	Me	H	H	MeI	94	59
CH_2OBu-*tert*	CHO	H	H	HCO_2Me	78	59
CH_2OBu-*tert*	CH(OH)Ph	H	H	PhCHO	88	59
CH_2OBu-*tert*	$C(OH)Ph_2$	H	H	Ph_2CO	96	59
CH_2OCH_2Ph	D	H	H	D_2O	100	59
CH_2OCH_2Ph	CHO	H	H	HCO_2Me	81	59
CH_2OCH_2Ph	$C(OH)Ph_2$	H	H	Ph_2CO	82	59
CH_2OCH_2Ph	$C(OH)PhC_6H_4Cl$-4	H	H	4-ClC_6H_4COPh	30	18
CH_2OCH_2Ph	CHO	I	I	DMF	5-10	60
$CH_2O(CH_2)_2OMe$	D	H	H	D_2O	100	59
$CH_2O(CH_2)_2OMe$	Me	H	H	MeI	97	59
$CH_2O(CH_2)_2OMe$	CHO	H	H	HCO_2Me	70	59
$CH_2O(CH_2)_2OMe$	CO_2Et	H	H	$ClCO_2Et$	63	59
$CH_2O(CH_2)_2OMe$	$C(OH)Ph_2$	H	H	Ph_2CO	83	59
$CH_2O(CH_2)_2SiMe_3$	I	H	H	I_2	90	58
$CH_2O(CH_2)_2SiMe_3$	Me	H	H	MeI	94	61
$CH_2O(CH_2)_2SiMe_3$	CHO	H	H	DMF	96	62
$CH_2O(CH_2)_2SiMe_3$	CH(OH)(2-furyl)	H	H	2-furylCHO	82	61

$CH_2O(CH_2)_2SiMe_3$		H	H	cycloheptanone	72	61
$CH_2O(CH_2)_2SiMe_3$	OH	H	H	$(Me_3SiO)_2$	98	63
$CH_2O(CH_2)_2SiMe_3$	OH	H	H	$(PhCO_2)_2O$	91	63
$CH_2O(CH_2)_2SiMe_3$	CPh(NHCOMe)CONHOMe	H	H	MeCON=CPhCONHOMe	46[h]	61
$CH_2O(CH_2)_2SiMe_3$	CHO	H	Me	DMF	89	62
$CH_2O(CH_2)_2SiMe_3$	Me	CH_2Pr-*iso*	H	MeI	64	61
$CH_2O(CH_2)_2SiMe_3$	CHO	CH_2Pr-*iso*	H	DMF	85	61
$CH_2O(CH_2)_2SiMe_3$	COC_6H_{11}-c	CH_2Pr-*iso*	H	cyclohexylCOCl	42	61
$CH_2O(CH_2)_2SiMe_3$	COMe	CH_2Pr-*iso*	H	MeCOCl	20	61
$CH_2O(CH_2)_2SiMe_3$	COMe	CH_2Pr-*iso*	H	Ac_2O	40	61
$CH_2O(CH_2)_2SiMe_3$	CH(OH)Ph	CH_2Pr-*iso*	H	PhCHO	99	61
$CH_2O(CH_2)_2SiMe_3$	$CH(C_6H_{11}$-c)$NHCH_2Ph$	CH_2Pr-*iso*	H	c-$C_6H_{11}CH$=NCH_2Ph/ $BF_3.OEt_2$	87	61
$CH_2O(CH_2)_2SiMe_3$	D	Ph	H	D_2O	100	61
$CH_2O(CH_2)_2SiMe_3$	$CH(OH)C_6H_{11}$-c	Ph	H	cyclohexylCHO	86	61
$CH_2O(CH_2)_2SiMe_3$	CH(OH)CH=CHPh	Ph	H	PhCH=CHCHO	100	61
$CH_2O(CH_2)_2SiMe_3$	SPh	Ph	H	Ph_2S_2	95	61
CHMeOEt	Me	H	H	MeI	91	20
CHMeOEt	CHO	H	H	DMF	90	20

CHMeOEt	$C(OH)Ph_2$	H	H	Ph_2CO	88	20
CHMeOEt[k]	NO_2	$C_6H_3Cl_2$-3,4	Ph	N_2O_4	–	64
CHMeOEt	NO_2	C_6H_4OEt-4	C_6H_4F-4	N_2O_4	–	64
CHMeOEt	NO_2	C_6H_4F-4	3-Py[h]	N_2O_4	–	64
$CH(OMe)_2$		Pr-*iso*	Pr-*iso*	$^1/_2\ PCl_3$	–	65
$CH(OMe)_2$[l]		Pr-*iso*	Pr-*iso*		21[i]	65
$CH(OEt)_2$	$C(OH)Me_2$	H	H	Me_2CO	65[i]	40
$CH(OEt)_2$	C(OH)MePh	H	H	MeCOPh	76[i]	40
$CH(OEt)_2$	SPh	H	H	Ph_2S_2	8	22
$CH(OEt)_2$		Pr	Pr	$^1/_2\ PCl_3$	–	65

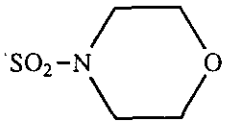
$CH(OEt)_2$		H	H		24[h]	65
$CH(OEt)_2$		Pr	Pr		25[h]	65
$CMe(OEt)_2$	$C(OH)(C_6H_4Cl\text{-}4)_2$	H	H	$(4\text{-}ClC_6H_4)_2CO$	60[h]	66
THP[b]	SCF_3	Ph	Ph	F_3CSCl	31[h]	67
THP[b]	SCF_3	Ph	Ph	$(F_3CS)_2$	–	68
THP[b]	SCF_3	Ph	$C_6H_3Cl_2\text{-}3,4$	$(F_3CS)_2$	–	68
THP[b]	SCF_3	$C_6H_4F\text{-}4$	$C_6H_4F\text{-}4$	F_3CSCl	–	67
THP[b]	SCF_3	$C_6H_4F\text{-}4$	$C_6H_4F\text{-}4$	$(F_3CS)_2$	–	68
THP[b]	SCF_3	$C_6H_4F\text{-}4$	$C_6H_4OMe\text{-}4$	$(F_3CS)_2$	–	68
THP[b]	SCF_3	$C_6H_4OMe\text{-}4$	$C_6H_4OMe\text{-}4$	$(F_3CS)_2$	–	68
THP[b]	SCF_2CF_3	$C_6H_4F\text{-}4$	$C_6H_4F\text{-}4$	$(F_3CCF_2S)_2$	–	68
THP[b]	NO_2	$C_6H_4F\text{-}4$	$C_6H_4F\text{-}4$	N_2O_4	–	64

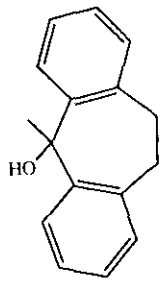
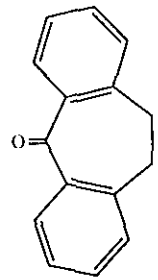
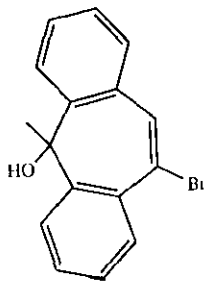
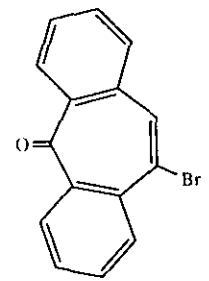
THP[b]	NO_2	C_6H_4OMe-4	C_6H_4OMe-4	N_2O_4	–	64
THP[b]	NO_2	C_6H_4F-4	thien-2-yl	N_2O_4	–	64
CH_2NMe_2	Bu	H	H	BuI	76[h]	21
CH_2NMe_2	CHPrBu	H	H	BuBr	27[h]	21
CH_2NMe_2	COC_6H_4Me-4	H	H	4-$MeC_6H_4CO_2Et$	65[h]	21
CH_2NMe_2	CONHBu-*tert*	H	H	*tert*-BuNCO	62[h]	21
CH_2NMe_2	$CH(OH)C_6H_4Me$-4	H	H	4-MeC_6H_4CHO	60[h]	21
CH_2NMe_2	$C(OH)Ph_2$	H	H	Ph_2CO	72[h]	21
$(CH_2)_3N{=}CPh_2$	COPh	H	H	PhCOCl		69
$(CH_2)_3N{=}CPh_2$	COC_6H_4F-4	H	H	4-FC_6H_4COCl	71-90	69
$(CH_2)_3N{=}CPh_2$	COC_6H_4OMe-4	H	H	4-$MeOC_6H_4COCl$		69
CPh_3	$C(OH)Ph_2$	H	H	Ph_2CO	37	18
CPh_3	SPh	H	H	Ph_2S_2	99[g]	22
CPh_3	Me	Br	H	MeI	63	22
CPh_3	NO_2	Me	H	$PrONO_2$	50[i]	70 [see also ref. 71
Ph	CO(4-Py)[b]	H	H	4-PyCN	40	36
Ph		H	H	 ClO_4^-	85	72, 73

2-Py[d]	$C(OH)Ph_2$	H	H	Ph_2CO	46	74
2-Py[d]		H	H	$CuCl_2$	18	74
SO_2NMe_2	2-Py[b]	H	H	$ZnCl_2$/2-PyBr/$Pd(PPh_3)_4$	60	29
SO_2NMe_2	CHO	Ph	H	DMF	–	75
SO_2NMe_2	CHO	$C_6H_3Cl_2$-2,4	H	DMF	–	75
SO_2NMe_2	CHO	$CH(OTMS)C_6H_2Cl_3$-2,4,6	H	DMF	–	75
SO_2NMe_2	CO_2Et	Ph	H	$ClCO_2Et$	–	57
SO_2NMe_2	CO_2Et	Cl	Ph	$ClCO_2Et$	–	57
SO_2NMe_2	CO_2Et	Cl	$(CH_2)_3Cl$	$ClCO_2Et$	–	57
SO_2NMe_2	CN	H	H	PhOCN	69	76
SO_2NMe_2	CN	Me	H	TosCN	–	75
SO_2NMe_2	CN	Bu-*tert*	H	TosCN	50	76
SO_2NMe_2	CN	CH_2OH	H	TosCN	–	77
SO_2NMe_2	CN	CH_2OR (various)	H	TosCN	–	77
SO_2NMe_2	CN	CHR^1OR (various)	H	TosCN	–	77
SO_2NMe_2	CN	CHMe(OTMS)-$C_6H_2Cl_3$-2,4,6	H	PhOCN	83	76

SO_2NMe_2	CN	CR^1R^2OR (various)	H	TosCN	–	77
SO_2NMe_2	CN	CH_2SPh	H	TosCN	–	77
SO_2NMe_2	CN	$CH_2NMeCOC_6H_4Cl$-4	H	TosCN	–	77
SO_2NMe_2	CN	$CH_2NMeSO_2C_6H_4Cl$-4	H	TosCN	–	77
SO_2NMe_2	CN	CF_3	H	TosCN	–	75
SO_2NMe_2	CN	$CH{=}CHC_6H_4Cl$-4	H	TosCN	–	75
SO_2NMe_2	CN	Ph	H	TosCN	–	75
SO_2NMe_2	CN	C_6H_4F-2	H	TosCN	–	75
SO_2NMe_2	CN	C_6H_4F-3	H	TosCN	–	75
SO_2NMe_2	CN	C_6H_4F-4	H	TosCN	–	75
SO_2NMe_2	CN	C_6H_4Cl-2	H	TosCN	–	75
SO_2NMe_2	CN	C_6H_4Cl-3	H	TosCN	–	75
SO_2NMe_2	CN	C_6H_4Cl-4	H	TosCN	–	75
SO_2NMe_2	CN	C_6H_4Br-4	H	TosCN	–	75
SO_2NMe_2	CN	C_6H_4Br-4	H	PhOCN	72	76
SO_2NMe_2	CN	$C_6H_4CF_3$-2	H	TosCN	–	75
SO_2NMe_2	CN	$C_6H_4CF_3$-3	H	TosCN	–	75
SO_2NMe_2	CN	$C_6H_4CF_3$-4	H	TosCN	–	75
SO_2NMe_2	CN	C_6H_4OMe-4	H	TosCN	–	75
SO_2NMe_2	CN	C_6H_4CN-4	H	TosCN	–	75

SO_2NMe_2	CN	$C_6H_3Me_2$-2,4	H	TosCN	–	75
SO_2NMe_2	CN	$C_6H_3F_2$-2,4	H	TosCN	–	75
SO_2NMe_2	CN	$C_6H_3Cl_2$-2,4	H	TosCN	–, 75	75, 76
SO_2NMe_2	CN	$C_6H_3Cl_2$-3,4	H	TosCN	–	75
SO_2NMe_2	CN	$C_6H_2Cl_3$-2,3,4	H	TosCN	–	75
SO_2NMe_2	CN	$C_6H_2Cl_3$-2,4,5	H	TosCN	–	75
SO_2NMe_2	CN	$C_6H_2Cl_2CN$-2,4,3	H	TosCN	–	75
SO_2NMe_2	CN	thien-2-yl	H	TosCN	50	76
SO_2NMe_2	CN	5-chlorothien-2-yl	H	TosCN	–	75
SO_2NMe_2	CN	2,5-dichlorothien-3-yl	H	TosCN	–	75
SO_2NMe_2	CN	$CH(OMe)_2$	H	TosCN	–	78
SO_2NMe_2	CN	$CH(OMe)_2$	H	PhOCN	70	76
SO_2NMe_2	CN	$COC_6H_3Cl_2$-2,6	H	TosCN	–	75
SO_2NMe_2	CN	$COC_6H_4Me_3$-2,4,6	H	TosCN	–	75
SO_2NMe_2	CN	$COC_6H_2Cl_3$-2,4,6	H	$(CN)_2$	–	75
SO_2NMe_2	CN	CN	H	TosCN	–	75
SO_2NMe_2	CN	SPh	H	TosCN	–	75
SO_2NMe_2	CN	SCH_2Ph	H	TosCN	–, 58	75, 76
SO_2NMe_2	CN	SO_2NR_2 (various)	H	TosCN	–	75, 79
SO_2NMe_2	CN	H	Me	TosCN	–	75
SO_2NMe_2	CN	$C(OEt)Ph_2$	Me	TosCN	–	75

SO_2NMe_2	CN	CH_2O(pyran-2-yl)	Me	TosCN	–	77
SO_2NMe_2	CN	CPh_2OEt	Me	TosCN	75	77
SO_2NMe_2	CN	H	Ph	TosCN	–	75
SO_2NMe_2	SPh	H	H	Ph_2S_2	56	22
SO_2NMe_2	$SiMe_3$	H	H	Me_3SiCl	–	80
SO_2NMe_2	$SiEt_3$	H	H	Et_3SiCl	–[i]	81
SO_2NMe_2	$SiMe_2Bu$-*tert*	H	H	*tert*-$BuMe_2SiCl$	90, 91, –[i]	32, 82, 83
	CN	$C_6H_3Cl_2$-2,4	H	TosCN	–	75
$SO_2C_6H_4Me$-4	$C(OH)(C_6H_4Cl$-4$)C_6H_{11}$-c	H	H	4-ClC_6H_4COcyclohexyl	25	18
$SO_2C_6H_4Me$-4	$C(OH)PhC_6H_4Cl$-2	H	H	2-ClC_6H_4COPh	40	18
$SO_2C_6H_4Me$-4	$C(OH)PhC_6H_4Cl$-4	H	H	4-ClC_6H_4COPh	29	18
$SO_2C_6H_4Me$-4	$C(OH)PhC_6H_4Br$-4	H	H	4-BrC_6H_4COPh	50	18
$SO_2C_6H_4Me$-4	$C(OH)PhC_6H_4Me$-4	H	H	4-MeC_6H_4COPh	55	18
$SO_2C_6H_4Me$-4	$C(OH)(C_6H_4F$-4$)_2$	H	H	$(4\text{-}FC_6H_4)_2CO$	29	18
$SO_2C_6H_4Me$-4	$C(OH)(C_6H_4Cl$-4$)_2$	H	H	$(4\text{-}ClC_6H_4)_2CO$	26	18
$SO_2C_6H_4Me$-4	$C(OH)(C_6H_4Br$-4$)_2$	H	H	$(4\text{-}BrC_6H_4)_2CO$	43	18

$SO_2C_6H_4Me$-4		H	H		10	18
$SO_2C_6H_4Me$-4		H	H		12	18
$SiMe_3$	$SiMe_3$	H	H	Me_3SiCl	62	84

[a] With BuLi unless stated otherwise. [b] The following abbreviations have been used: 1-Pyro = pyrrolidin-1-yl; 2-Mim = 1-methylimidazol-2-yl; 2-Mom = 1-methoxymethylimidazol-2-yl; 2-Eom = 1-ethoxymethylimidazol-2-yl; 2-, 3-, and 4-Py = pyrid-2(3 and 4)-yl; 3-In = indol-3-yl; 1-Bzt = *benzotriazol-1-yl*; TMS = trimethylsilyl; THP = tetrahydropyran-2-yl; NBS, NCS, NIS = *N*-halogenosuccinimide (X = Br, Cl, I). [c] With LDA. [d] Minor product of the reaction. [e] In the presence of Et_2AlCl. [f] *Yield after removal* of THP or TMS protecting group. [g] Other products (see **Scheme 7**). [h] After removal of 1-protecting group. [i] In this case the 2-lithiated imidazole employed was that derived from the cyclic amide of 4(5)-hydroxyethylimidazole. [j] Generated *in situ* and used in further synthesis.

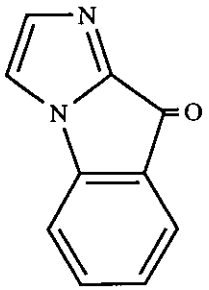
Butyllithium is most commonly used as the metallating reagent whilst lithium diisopropylamide (LDA) is the reagent of choice when the imidazole carries substituents prone to nucleophilic attack. Ethereal solvents [diethyl ether (Et_2O), tetrahydrofuran (THF), or dimethoxyethane (DME)] are normally used. Lithium naphthalenide has been used to "metallate" 1-methylimidazole[85] but it does not find general use; e.g. it does not metallate 1-phenylimidazole. In view of the ease of *C*-2 metallation of imidazoles the addition of chelating reagents, such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA), to enhance basicity of the organolithium reagent is not usually necessary. The ease of *C*-2 deprotonation is exemplified with substrates capable also of halogen → metal exchange.

4-(And 5)-chloro (the Cl-atom is exchangeable if position-2 is blocked) and 4-bromo derivatives (Br-atom exchangeable with positions-2 and -5 blocked) are metallated in position-2 (Table I). Thus, e.g., 4-chloro-*N,N*-dimethyl-5-phenylimidazole-1-sulfonamide is lithiated at position-2 (BuLi/THF/-70 °C), quenching with ethyl chloroformate gives the ethyl 2-carboxylate (Table I).[57]

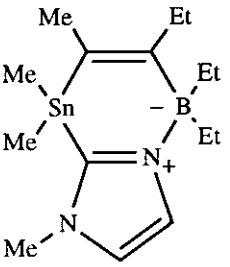
By judicial choice of reaction conditions it is possible to metallate imidazoles at position-2 which carry functional groups also capable of reacting with the reagent. Thus, e.g. with one mol. equiv. of butyllithium (THF/-100 °C) it is possible to selectively *C*-2 metallate 4,5-dicyano-1-methylimidazole;[15] see also refs. 52 and 75 (addition of TMEDA is reported to help). At -80 °C complications arise as a result of attack of the butyllithium on one of the cyano groups. Quenching the *C*-2 anion is only possible with electrophilic reagents which react at -100 °C. It is preferable to prepare this anion *via* bromine → lithium exchange (Section IV.A). Deprotonation of 4,5-dicyano-1-methylimidazole with LDA (THF/-80 °C) gives the *C*-2 anion which proceeds to yield oligomers by its attack on the cyano groups of other molecules.[15] With two mol. equiv. of butyllithium followed by quenching with water 4,5-dicyano-1-methylimidazole yields a butyl ketone.

Whilst 1-phenylimidazole-2-carboxylic acid is obtained when 1-phenylimidazole is treated successively with one mol. equiv. of butyllithium and carbon dioxide, when this reaction is repeated using three mol. equiv. of butyllithium, compound (**2**) is produced through carbonation of a dilithiated species.[86] The 2-lithiated derivative of 1-(quinol-3-yl)imidazole (LDA/THF) reacts with starting material as it forms, to give the product (**3**) (Scheme 2) of azomethine bond addition which can be transformed to the macrocyclic dimer (**4**) by further 2-lithiation, intramolecular bond addition, hydrolysis, and oxidation.[87,88]

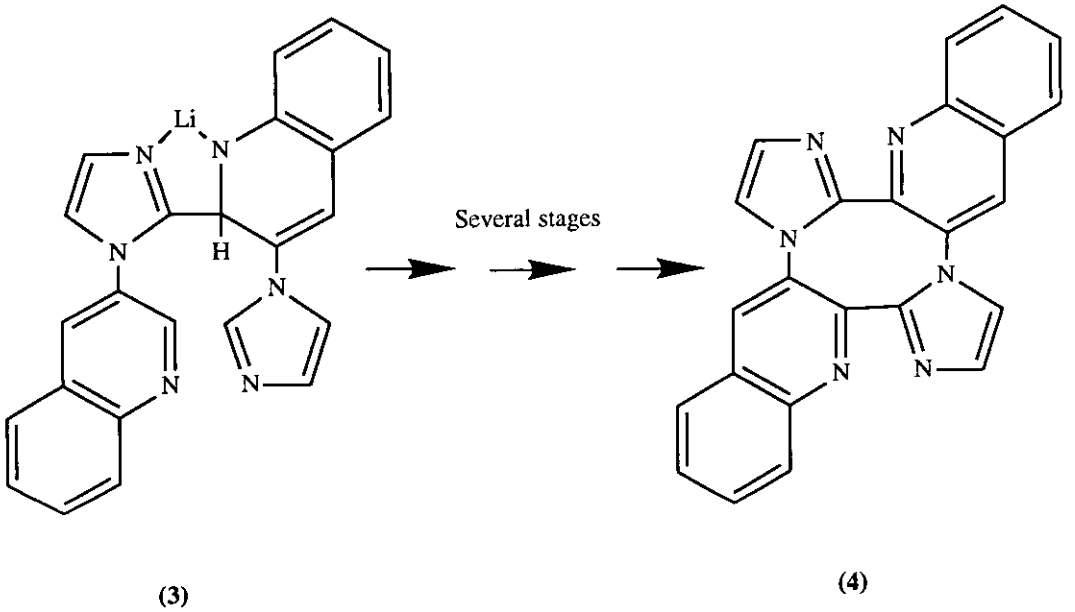
Condensation of 1-methylimidazol-2-yllithium with (*E*)-2-dimethyl(chloro)stannyl-3-diethylborylpent-2-ene [$Me_2Sn(Cl)MeC{=}CEtBEt_2$] gives rise to the bicyclic compound (**5**) (83% yield).[89]



(2)



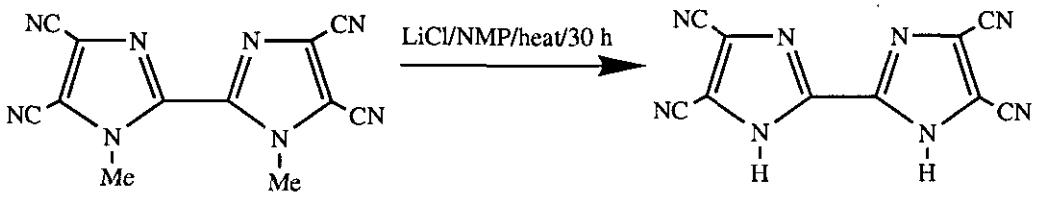
(5)



(3) (4)

Scheme 2

Lithiation of 1-methylimidazole and subsequent reactions of the imidazol-2-yllithium derivative with electrophiles has been most studied (Table I) presumably because it is commercially available and able to withstand extreme metallation conditions.[90] Use of the *N*-methyl substituent as a protecting group has been reported,[52] e.g. in the synthesis of compound (**6**) (Scheme 3). In this case the ease of demethylation, (**6**) → (**7**) (Scheme 3), is attributable to the presence of the cyano groups which stabilise the leaving imidazolium anions involved.

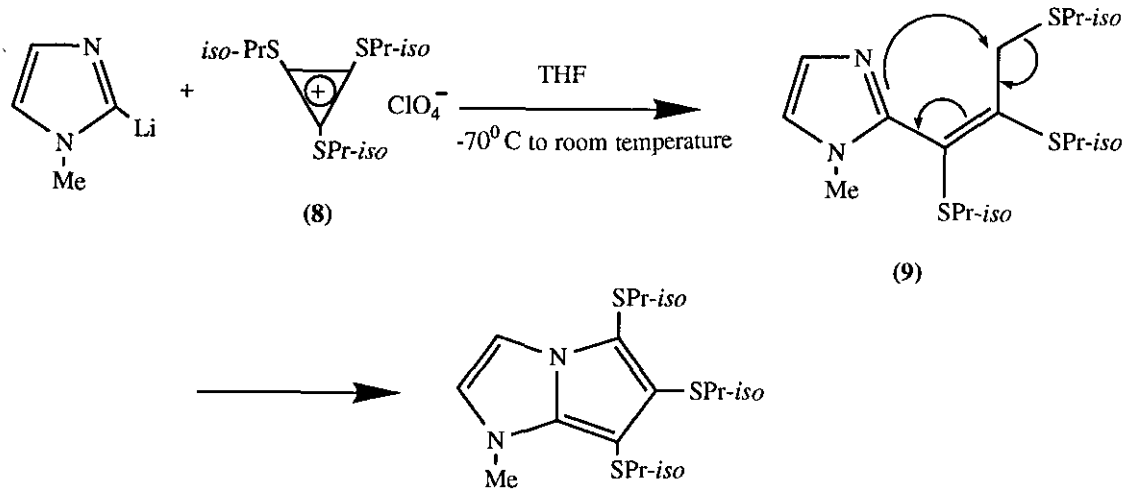


(6) **(7)** (59%)

Scheme 3

Demethylation, however, is usually very difficult. An attempt, e.g., to demethylate 4-bromo-1-methyl-2-nitroimidazole was unsuccessful.[71]

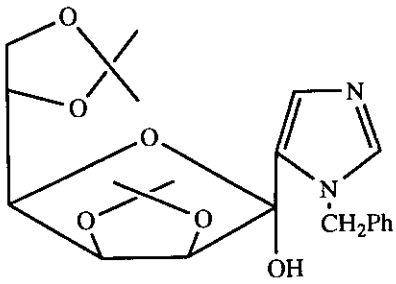
1-Methylimidazol-2-yllithium reacts with 1,2,3-*tris*(isopropylthio)cyclopropylium perchlorate (**8**) to give the pyrrolo[2,1-*b*]imidazole (**10**) in 98% yield.[91] The reaction proceeds *via* formation of the intermediate vinyl carbene (**9**) (Scheme 4).



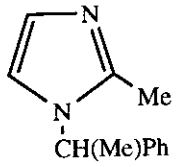
(8) **(9)** **(10)**

Scheme 4

N-Benzyl protecting groups may be removed by reductive cleavage techniques.[18,31,55,86,92] The major disadvantage associated with the use of this protecting group is competitive α-(or lateral)metallation[19,52,54,93,94] (see also ref. 18) (Section V). The 1-benzylimidazol-2-yl anion appears to be thermodynamically preferred to the N-C_α anion but it is not clear which of the two possible anions is kinetically preferred.[54] With the exception of benzyl halides and iodomethane most electrophiles appear to react at position-2; a steric argument has been advanced to account for this preference.[54] 1-Benzylimidazoles have been dialkylated in their benzyl groups[94] (see also Section V). The reported[95] synthesis of compound (**11**) through metallation of 1-benzylimidazole at position-5 has been shown to be faulty.[19] Quenching the anion formed under the literature conditions with iodomethane gave compound (**12**) (however, see also ref. 54). Removal of the benzyl group from 1-benzyl-α-(4-chlorophenyl)-α-phenylimidazole-2-methanol with sodium in liquid ammonia results in loss of the chlorine atom.[18]



(11)



(12)

With butyllithium (THF/0 °C/1 hour) *bis*(imidazol-1-yl)methane yields both the 2-mono- and 2,2'-dimetallated derivative depending on the conditions of the reaction and the quenching reagent (Table II).[96] There is no evidence for lateral metallation in the methylene group. Use of LDA or an increase in the temperature produces results similar to those with butyllithium, which suggests that ring metallation is both kinetically and thermodynamically favoured.

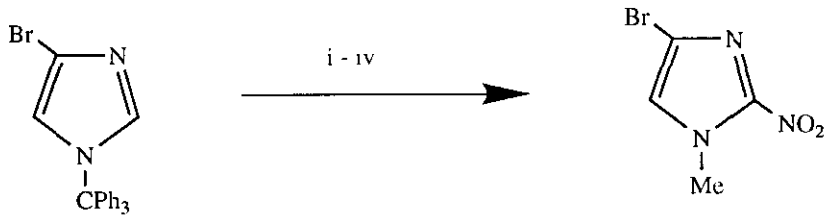
The triphenylmethyl(trityl) group[97] has problems associated with solubility;[19] (see also ref. 18). Reaction temperatures and solvents are thus restrictive. Deprotection, however, occurs readily by mild acid hydrolysis. A typical one-pot procedure is summarised in Scheme 5 for conversion of compound (**13**) into compound (**14**) (37% yield).[71] Some of the moderate yields reported in Table I may be accounted for by steric hindrance towards metallation arising from the presence of a bulky *N*-1 protecting group (see Section II.B).

Table II

Ring Substitution of *Bis*(imidazol-1-yl)methane

Reagent	Substrate:BuLi:E+	Monosubstitution (%)[a]	Disubstitution (%)[a]
MeI	1 : 1 : 1	53	31
MeI	1 : 2.1 : 2.1	0	100
Me_2S_2	1 : 1 : 1	57	14
Me_2S_2	1 : 1 : 1[b]	58	12
Me_2S_2	1 : 1 : 1[c]	50	16
Me_2S_2	1 : 2.4 : 2.4	12	75
Me_3SiCl	1 : 1 : 1	57	43
Me_3SiCl	1 : 2.1 : 2.1	38	62
$(HCHO)_n$	1 : 1 : 1	55	12
$(HCHO)_n$	1 : 2.1 : 2.1	36	64

[a] By ^1H nmr spectroscopy. [b] With LDA. [c] At 60 °C.



(13) (14)

Reagents: i) BuLi/THF/0°C; ii) $PrNO_2$; iii) H_3O^+; iv) $Me_2SO_4/K_2CO_3/Me_2CO$.

Scheme 5

Alkoxymethyl and aryloxymethyl protecting groups are reported to be the most stable so far employed in imidazole metallation processes.[59] Deprotection, however, requires more severe conditions. Thus, 1-methoxymethylimidazoles have been reported[98] to be stable to prolonged boiling in 6M-hydrochloric acid. A mixture of hydrochloric and acetic acids has been found, however, to be effective in deprotection studies.[18] Deprotection of 1,1'-*bis*(methoxymethyl)-4,4',5,5'-tetracyano-2,2'-bi-imidazole has been achieved by heating in a 1.2M-hydrochloric acid-THF mixture at 60 °C for 3 hours.[52] A 2-(trimethylsilyl)ethoxymethyl (SEM) protecting group is cleaved similarly with 0.5M-ethanolic hydrochloric acid at 50 °C but 1.0M-

tetrabutylammonium fluoride in THF heated under reflux is equally effective.[61,62] The latter system has been used for the simultaneous removal of a 5-trimethylsilyl group and an *N*-SEM group.[16] Removal of an *N*-ethoxyethyl protecting group is possible with 0.1M-methanolic hydrogen chloride (at 55 °C/4 hours).[20] A tetrahydropyran-2-yl (THP) protecting group can be removed similarly with 0.1M-ethanolic hydrogen chloride.[64,68] In addition to restrictive deprotection conditions, yields of isolated products are often moderate or low when these protecting groups are employed (Table I).

By contrast with alkoxymethyl protecting groups, dialkoxymethyl and trialkylsilyl protecting groups are very labile. Imidazoles carrying these protecting groups are deprotected by work-up procedures. Problems can arise too following chromatography on silica when the protecting group can be lost and the C-S bond of 2-phenylthio derivatives can be cleaved simultaneously.[22]

An *N*-dialkylaminomethyl protecting group can be introduced under Mannich reaction conditions and removed by acidic work-up of reaction mixtures[21] (but see ref. 99). The 2-lithiated derivatives of such protected imidazoles give poor yields on reaction with hindered electrophiles and with acidic substrates. In one reaction, when iodobutane was replaced with bromobutane as the electrophilic quenching reagent, further α-(or lateral)-deprotonation (Section V) of the initially introduced 2-butyl group occurred and the resulting anion captured another butyl group.[21] Presumably reaction with iodobutane is faster and this side-reaction is avoided. With 2-arylethyl halides elimination occurs to produce the corresponding styrenes.[99]

1-Aminopropylimidazole, protected as its diphenylmethylidene derivatives [i.e. *N*-$(CH_2)_3N{=}CPh_2$], can be metallated at position-2 and the resulting 2-lithiated derivative can be quenched with aroyl chlorides (71-90% yield).[69]

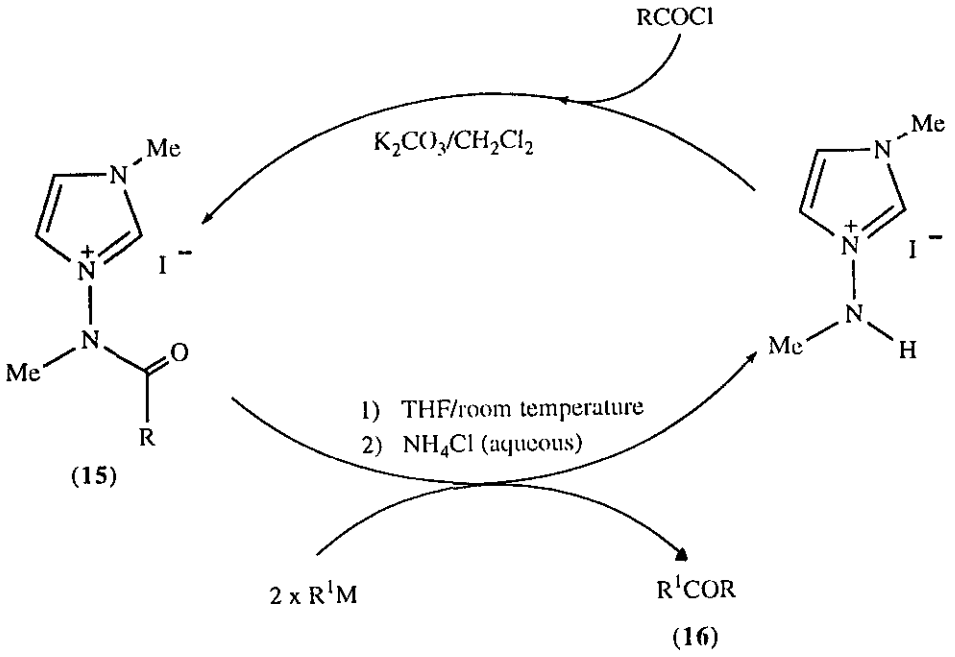
Although there is evidence that 1-phenylsulphonylimidazole is metallated quantitatively in position-2 with *n*- or *tert*-butyllithium (THF/0° or -20 °C),[100] quenching the resulting anion with carbonyl compounds gives low yields (< 20%) of products.[8] Similarly, whilst 1-tosylimidazole is metallated in position-2 with butyllithium reaction of the resulting anion with electrophiles results in product yields not exceeding 50%.[8,18] Both these *N*-protecting groups appear to decrease the nucleophilicity of the 2-anions. The tosyl group is reported to be cleaved by phenylmagnesium bromide.[18] High yields (up to 90%) of 2-substituted derivatives are obtained *via* metallation of *N,N*-dimethylimidazole-1-sulfonamide (Table I) but, again, there is evidence for decreased nucleophilicity of the 2-anion, e.g. quenching with *N,N*-dimethylformamide (DMF) fails to give the corresponding aldehyde.[20]

Sulfonyl groups are cleaved by hydrolysis with either acid or base (which can be advantageous).

N-Protection with alkenyl (e.g. vinyl) groups is possible.[18] These groups have been little exploited; they have the advantage that they can be cleaved by oxidation with potassium permanganate (alkaline conditions). With an *N*-vinyl group the vinyl protons are not removed. Whilst an *N*-allyl group is isomerised during the metallation step this is advantageous, for oxidative deprotection becomes feasible.

1-Methylimidazole can be quaternized at *N*-3 with 4-methoxybenzyl chloride, the resulting imidazolium salt is readily deprotonated at *C*-2 with sodium hydride (DMF), and addition of hexachloroethane allows chlorine to be introduced at this position.[101] Other 2-substituents may be introduced similarly.[102] 1,3-Dimethylimidazolium salts are deprotonated similarly at position-2 by butyllithium and the resulting anions have been quenched with deuterium oxide, bromomethane, chlorodiphenylphosphine, sulfur dioxide, sulfines, *N*-sulfinylamines, and thiirane (see also ref. 102).[103]

The *N*-(*N*-acyl-*N*-methylamino)imidazolium salts (**15**; R = Me, -CH=CHPh, Ph, thien-2-yl) react with two mol.



Scheme 6

equiv. of an organometallic reagent R^1M (R^1 = Me, Et, Ph; M = MgBr or R^1 = Ph, PhC≡C-; M = Li) first by metallation in position-2, then by cleavage to give good yields (75-90%) of ketones (**16**), as shown in Scheme 6.[104] The cleaved imidazolium salt can be recycled. Organolithium reagents react faster than Grignard reagents.

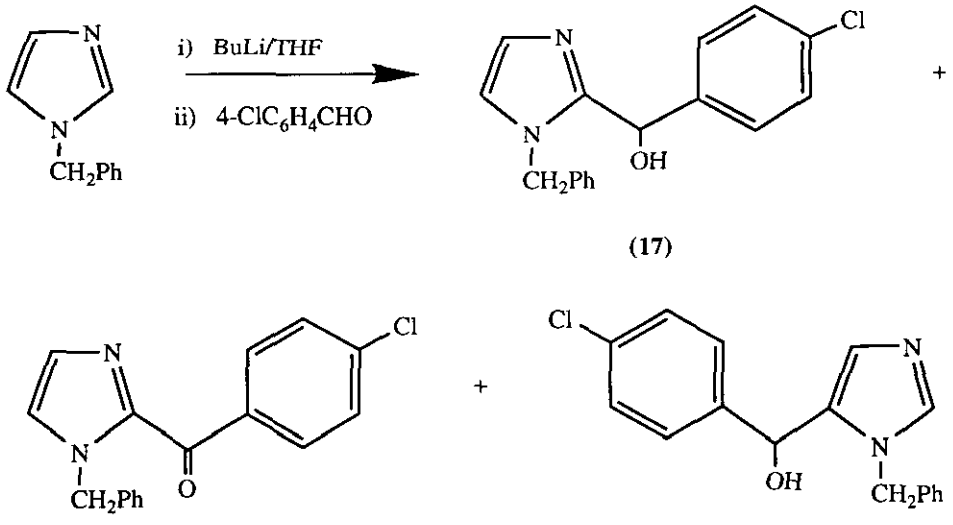
B Lithiation at position-4 (see also next Section)

Direct metallation at this position is only possible in the presence of a sterically demanding *N*-1 substituent or with activated imidazolium salts in which the adjacent position is blocked. Thus, with *tert*-butyllithium (also sterically demanding) in THF, even at -75 °C, 2-fluoro-1-tritylimidazole is metallated at position-4.[105] In the case of 2-phenylthio-1-tritylimidazole, however, position-5 is hindered and position-4 is insufficiently reactive towards LDA in THF. Metallation of this substrate with *tert*-butyllithium in THF leads to a mixture of 4- and 5-substituted products in low yields.[22]

The imidazolium salt formed by reacting 5-chloro-1-methyl-2-phenylimidazole with 4-methoxybenzyl chloride is readily deprotonated at position-4 (NaH/CH_2Cl_2, KNH_2/liquid NH_3, or BuLi) and the resulting anion can be quenched with various electrophilic reagents [MeI → Me (82%), Cl_3CCCl_3 → Cl (51%), CBr_4 → Br (63%), PhCHO → CH(OH)Ph (100%), MeCOCl → COMe (50%), MeNCS → NHCSMe (8%)].[101] When halogen is introduced the 4-methoxybenzyl group is removed at the same time. Both this group and the chlorine atom are removed by nickel boride, thus providing an overall route to 4-substituted 1-methyl-2-phenylimidazoles.

C Lithiation at position-5

Lithiation at this position is only possible when position-2 is blocked (Table III). The reported formation of compound (**11**) has been discussed earlier (Section II.A). Formation of compound (**19**) (Scheme 7) (13%



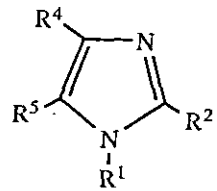
(**17**)

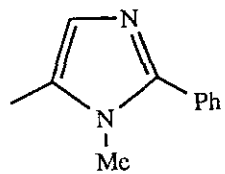
(**18**) (**19**)

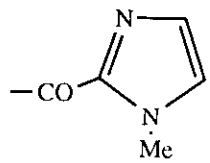
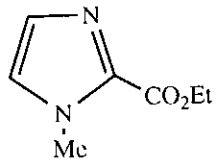
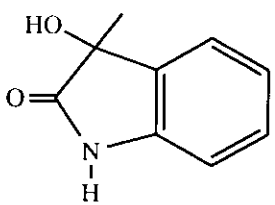
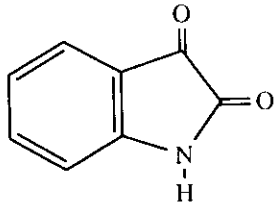
Scheme 7

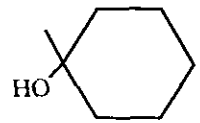
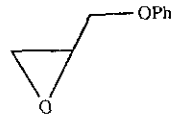
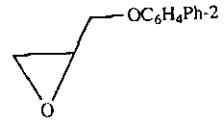
Table III

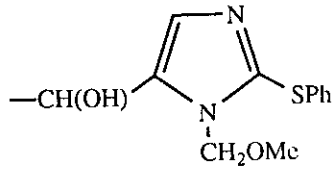
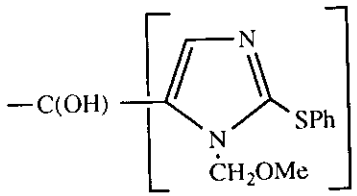
Imidazoles Synthesised from Imidazol-5-yllithium Compounds

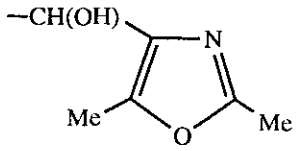
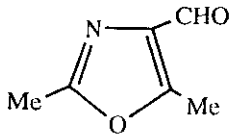
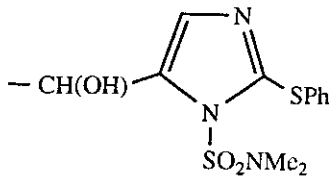


R^1	R^2	R^4	R^5	Reagent	Yield (%)	Ref.
Me	Ph	H	CHO	DMF	23	106
Me	Ph	H	CO_2H	CO_2	53	106
Me	Ph	H	COPh	PhCN	27	106
Me	Ph	H	CH(OH)Ph	PhCHO	36	106
Me	Ph	H		$CuCl_2$	20	106
Me	$CONMe_2$	H	Cl	$ClSO_2NMe_2$	95	32
Me	$CONMe_2$	H	Me	MeI	96	32
Me	$CONMe_2$	H	$C(OH)Ph_2$	Ph_2CO	91	32

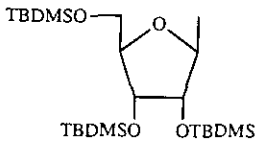
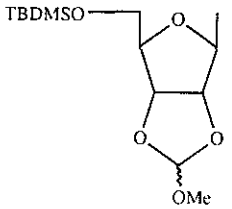
Me	$CON(Pr\text{-}iso)_2$	H			19	32
Me	NMe_2	H			45	107
Me	SH	H	$CH(OH)Bu\text{-}tert$	*tert*-BuCHO	80	108
Me	SH	H	$CH(OH)C_6H_{11}$-c	cyclohexylCHO	42	108
Me	SH	H	CH(OH)Ph	PhCHO	63	108
Me	SH	H	$CH(OH)C_6H_4Me$-2	$2\text{-}MeC_6H_4CHO$	76	108
Me	SH	H	$CH(OH)C_6H_4Me$-3	$3\text{-}MeC_6H_4CHO$	79	108
Me	SH	H	$CH(OH)C_6H_4Me$-4	$4\text{-}MeC_6H_4CHO$	67	108
Me	SH	H	$CH(OH)C_6H_4Ph$-4	$4\text{-}PhC_6H_4CHO$	59	108
Me	SH	H	$CH(OH)C_6H_4OPh$-2	$2\text{-}PhOC_6H_4CHO$	65	108
Me	SH	H	$CH(OH)C_6H_4OPh$-4	$4\text{-}PhOC_6H_4CHO$	76	108
Me	SH	H	$C(OH)Ph_2$	Ph_2CO	88	108

Me	SH	H		cyclohexanone	45	108
Me	SH	H	$CH_2CH(OH)CH_2OPh$		17	108
Me	SH	H	$CH_2CH(OH)CH_2OC_6H_4Ph$-2		26	108
Me	SH	H	SPh	Ph_2S_2	66	108
Me	SBu-*tert*	H	D	D_2O	64[a]	45
Me	SPh	H	CH(OH)Pr	PrCHO	50[a]	45
Me	SPh	H	CH(OH)Pr-*iso*	*iso*-PrCHO	56[a]	45
Me	SPh	H	CH(OH)Bu-*tert*	*tert*-BuCHO	63[a]	45
Me	SPh	H	CH(OH)Ph	PhCHO	74[a]	45
Me	SPh	H	$CH(OH)C_6H_4OMe$-4	4-$MeOC_6H_4CHO$	57[a]	45
Me	SPh	H	$CH(OH)C_6H_3Cl_2$-2,4	2,4-$Cl_2C_6H_3CHO$	57[a]	45
Me	SPh	H	$C(OH)Me_2$	Me_2CO	39[a]	45
Me	SPh	H	$C(OH)Et_2$	Et_2CO	54[a]	45

Me	SPh	H	C(OH)(Pr-*iso*)$_2$	(*iso*-Pr)$_2$CO	69[a]	45
Me	SPh	H	C(OH)MePh	PhCOMe	70[a]	45
Me	SPh	H	C(OH)Ph$_2$	Ph$_2$CO	91[a]	45
Me	NO_2	Br	Bu	BuLi	18	71
CH_2OMe	SPh	H		$(EtO)_2CO$	97	22
CH_2OMe	SPh	H		HCO_2Et	90	22
CH_2OMe	Ph	H	CHO	DMF	–	14
CH_2OMe	$SiMe_2Bu$-*tert*	H	D	D_2O	100	32
CH_2OMe	$SiMe_2Bu$-*tert*	H	C(OH)Ph$_2$	Ph$_2$CO	90	32
CH_2OEt	SPh	H	pyrid-2-yl	$ZnCl_2$/pyrid-2-ylBr/-$Pd(PPh_3)_4$	58	29

CH_2OEt	SPh	H			> 98	109
CH_2OEt	Ph	H	$SiMe_3$	Me_3SiCl	52	16
$CH_2O(CH_2)_2SiMe_3$	SPh	H	CHO	DMF	90[b]	63
$CH_2O(CH_2)_2SiMe_3$	SPh	H	$OSiMe_3$	$(Me_3SiO)_2$	79[b]	63
$CH_2O(CH_2)_2SiMe_3$[c]	Ph	H	I	I_2	78	58
$CH_2O(CH_2)_2SiMe_3$	Ph	H	$SiMe_3$	Me_3SiCl	54	16
$CH_2O(CH_2)_2SiMe_3$	$SiMe_3$	H	CHO	DMF	83[b,d]	63
$CH_2O(CH_2)_2SiMe_3$	$SiMe_3$	H	SPh	Ph_2S_2	83[b,d]	63
CHMeOEt	$CH(OMe)_2$	H	CHO	DMF	78 (crude)	20
CHMeOEt	Ph	H	Me	MeI	62	20
CHMeOEt	Ph	H	CHO	DMF	61	20
CHMeOEt	Ph	H	$C(OH)Ph_2$	Ph_2CO	55	20
SO_2NMe_2	SPh	H		HCO_2Et	84	22
SO_2NMe_2	$SiMe_3$	H	CH(OH)pyrid-4-yl	pyrid-4-ylCHO	–	80

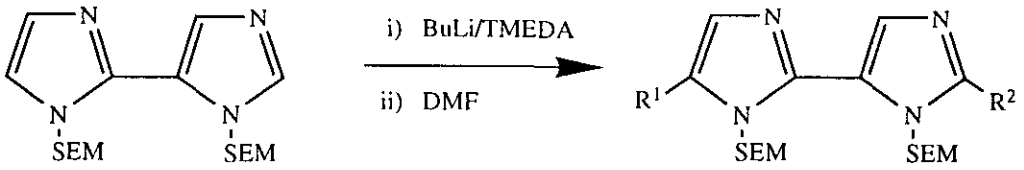
SO_2NMe_2	$SiEt_3$	H	D	MeOD	89[d]	110
SO_2NMe_2	$SiEt_3$	H	Cl	$ClSO_2NMe_2$	72[e]	110
SO_2NMe_2	$SiEt_3$	H	Me	MeI	96[d]	110
SO_2NMe_2	$SiEt_3$	H	CH_2Ph	$PhCH_2Br$	64[e]	110
SO_2NMe_2	$SiEt_3$	H	$CH_2CH=CH_2$	$CH_2=CHCH_2I$	85[d]	110
SO_2NMe_2	$SiEt_3$	H	CHO	DMF	–	81
SO_2NMe_2	$SiEt_3$	H	CO_2H	CO_2	74[e,f]	110
SO_2NMe_2	$SiEt_3$	H	$C(OH)Ph_2$	Ph_2CO	78[b]	110
SO_2NMe_2	$SiEt_3$	H	SMe	Me_2S_2	92[d]	110
SO_2NMe_2	$SiEt_3$	H	$SiMe_3$	Me_3SiCl	88[d]	110
SO_2NMe_2	$SiMe_2Bu$-*tert*	H	D	D_2O	100	32
SO_2NMe_2	$SiMe_2Bu$-*tert*	H	Cl	$ClSO_2NMe_2$	86	32
SO_2NMe_2	$SiMe_2Bu$-*tert*	H	Me	MeI	–	32
SO_2NMe_2	$SiMe_2Bu$-*tert*	H	$(CH_2)_3Cl$	$Cl(CH_2)_3I$	26[g]	83
SO_2NMe_2	$SiMe_2Bu$-*tert*	H	$(CH_2)_4Cl$	$Cl(CH_2)_4I$	35[g]	83
SO_2NMe_2	$SiMe_2Bu$-*tert*	H	$(CH_5)_5Cl$	$Cl(CH_2)_5I$	51[g]	83
SO_2NMe_2	$SiMe_2Bu$-*tert*	H	CH(OH)Ph	PhCHO	66[d]	32
SO_2NMe_2	$SiMe_2Bu$-*tert*	H	$C(OH)Ph_2$	Ph_2CO	86	32
SO_2NMe_2	$SiMe_2Bu$-*tert*	H	$COC_6H_3Me_2$-2,3	2,3-$Me_2C_6H_3COCl$	91	82

	Cl	$CONH_2$	CHO	HCO_2Me	13[h,i]	111
	Cl	CO_2Me	D	CD_3OD	93	112
"	Cl	CO_2Me	I	I_2	24	112
"	Cl	CO_2Me	Me	MeI	83	112-114
"	Cl	CO_2Me	CHO	HCO_2Et	–	112, 113
"	Cl	CO_2Me	CO_2Me	$ClCO_2Me$	84, 86	113, 114
"	Cl	CO_2Me	COPh	PhCOCl	86	112-114
"	Cl	CO_2Me	SPh	Ph_2S_2	84	112-114
"	Cl	CO_2Me	$SiMe_3$	Me_3SiCl	87	112-114
"	Cl	$CONH_2$	Me	MeI	32	111
"	Cl	$CONH_2$	CHO	HCO_2Me	–	111
"	Cl	$CONEt_2$	CHO	HCO_2Me	63	111

[a] With LiTMP/DME/THF at –78 °C. [b] The starting material was 1-SEM protected imidazole ("one-pot" reaction sequences). [c] 2,2'-*Bis*{5-iodo-1-{2-(trimethylsilyl)ethoxymethyl]imidazol-2-yl}biphenyl (72% yield) was prepared similarly from 2,2'-*bis*{1-[2-(trimethylsilyl)ethoxymethyl]imidazol-2-yl}biphenyl. [d] After 2-deprotection. [e] After 1- and 2-deprotection. [f] Isolated as the ethyl ester. [g] Overall yield starting from *N,N*-dimethylimidazole-1-sulfonamide. [h] With LDA (83% starting material recovered); use of LiTMP increased yield to 38%. [i] TBDMS = $SiMe_2Bu$-*tert.*

yield) has been reported following successive treatment of 1-benzylimidazole with 1 mol. equiv. each of butyllithium and 4-chlorobenzaldehyde in THF.[54] The other products isolated, **17** (9%) and **18** (13%), are derived from the 2-lithiated species.

Choice of the metallating system seems to be determined by the structure of the imidazole to be metallated. The biimidazole (**20**) gave a mixture of compounds **21** (7% yield) and **22** (23%) (Scheme 8) following its



(**20**)

SEM = $CH_2O(CH_2)_2SiMe_3$

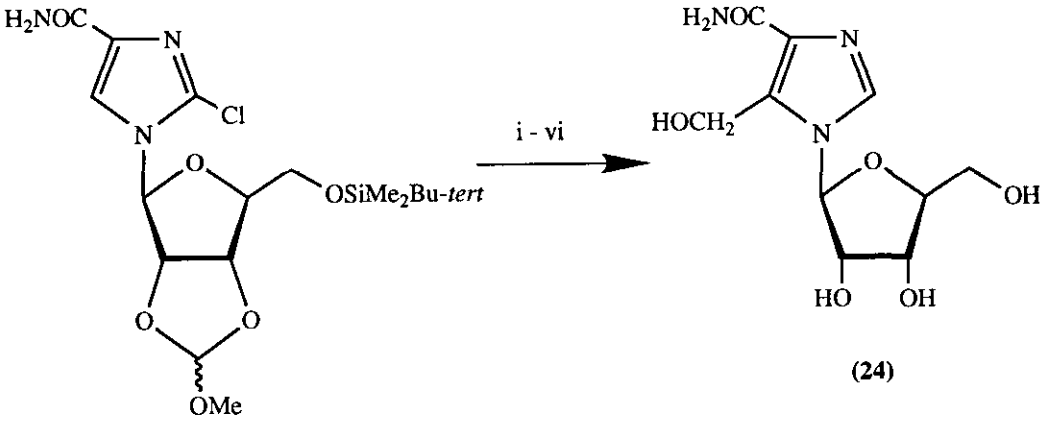
(**21**) (R^1 = R^2 = CHO)

(**22**)(R^1 =H; R^2 = CHO)

Scheme 8

successive treatment with butyllithium (in the presence of TMEDA) and DMF.[62] 2-(2-Furyl)-1-methylimidazole is metallated (BuLi/Et_2O-hexane/-70 °C) exclusively in the furan ring.[106]

Imidazole nucleosides carrying a Cl-atom at *C*-2 and an ester or amide functionality at *C*-4 have been deprotonated by LDA[111-114] as a means to the introduction of a substituent at *C*-5, e.g. the conversion **23** → **24** (Scheme 9) has been achieved in 19% overall yield[111] (see also ref. 112).



(**23**)

(**24**)

Reagents: i) LDA; ii) HCO_2Me; iii) $NaBH_4$; iv) H_2/10% Pd-C/MeOH; v) 20% AcOH; vi) NH_3/MeOH.

Scheme 9

Attempts to deprotonate imidazoles protected at *C*-2 with trimethyl- or triethylsilyl groups have been less successful. With these substrates *sec*-butyllithium is the reagent of choice. These silyl groups are labile and are introduced immediately prior to metallation in the same pot; work-up invariably is accompanied by deprotection.[19,63,81,110,115] Only with a *tert*-butyldimethylsilyl protecting group are the 2-protected compounds generally stable and isolable prior to metallation with butyllithium at position-5.[32,83] The 2-substituent in 1-protected 2-triorganostannylimidazoles is similarly labile.[49]

Recently, however, Winter and Rétey[81] have claimed that 1-(*N,N*-dimethylsulfamoyl)-2-triethylsilylimidazole-*4*-carbaldehyde is produced in 87% yield when *N,N*-dimethylimidazole-1-sulfonamide is treated successively with butyllithium, chlorotriethylsilane (1 mol. equiv.), *sec*-butyllithium, and DMF, which suggests that *N,N*-dimethyl-2-triethylsilylimidazole-1-sulfonamide undergoes direct metallation at *C*-4 (see also Section III.A). This result, if correct, is out-of-line with the other results discussed in this Section.

N-Protected 2-phenylthioimidazoles are metallated also at position-5 (Table III).[12,22,29,45,63,93,116,117] The preferred use of LDA was based on an observation[93] that *n*- and *tert*-butyllithium caused C-S bond cleavage. In later studies, however, use of butyllithium was reported to be successful.[12,117] For the metallation of 1-methyl-2-phenylthioimidazole lithium 2,2,6,6-tetramethylpiperidide (LiTMP) has been used in a DME-THF mixture;[45] use of *n*- or *sec*-butyllithium gave complex mixtures whilst metallation with LDA was incomplete. When 1-methyl-2-phenylthioimidazol-5-yllithium is allowed to stand for 90 minutes in THF at 0 °C, the phenylthio group migrates to position-5 and 1-methyl-5-phenylthioimidazole and starting material (1:1) are the major products isolated[25] (see also Section IV.A). 1-Methylimidazole-2-thiol is metallated by two mol. equiv. of *tert*-butyllithium (THF/-78 °C) at position-5 and in the thiol group and the resulting dianion can be quenched with a wide range of electrophiles, to give the corresponding 5-substituted derivative.[108] Benzyl chloride, however, gave the *S*-benzylated product.

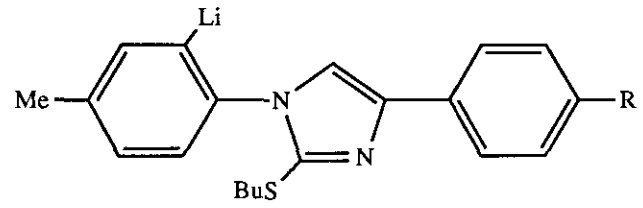
Though of limited application a carboxamide group is a useful 2-protecting group.[32] Metallation is achieved with lithium amides.

A number of other *N*-protected 2-substituted imidazoles have been metallated at position-5 (Table III), recently 2-dimethylamino-1-methylimidazole with *sec*-butyllithium in THF.[107] 4-(4-Bromophenyl)- and 4-(2,4-dichlorophenyl)-1-(*N,N*-dimethylsulfamoyl)imidazole-2-carbonitrile apparently can be metallated at C-5 (BuLi/THF/-78 °C) without affecting the other functional groups and the resulting anions have been quenched with ethyl chloroacetate or iodomethane or tosyl cyanide, respectively.[75] 1,2-Dimethylimidazole is lithiated in

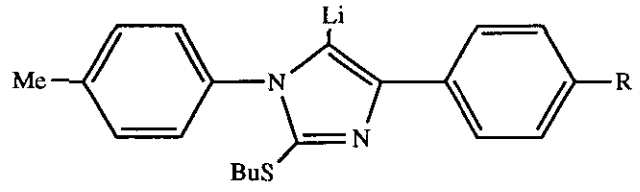
position-5 with butyllithium and LDA but, in addition, α-(or lateral)metallation is observed in the 2-methyl group (Section V)[32,118] (see also ref. 119).

Various bases, including *tert*-butyllithium and potassium diisopropylamide (KDA), have failed to deprotonate *N*-protected 2-nitroimidazoles (*N*-protecting group = CPh_3, SO_2NMe_2, or SEM).[71] With butyllithium alone, however, 4-bromo-1-methyl-2-nitroimidazole gives a low yield (18%) of its 5-butyl derivative.[71] In this reaction the reagent is behaving as a nucleophile.

The transmetallation reactions **25** → **26** (R = H, Me) (Scheme 10) have been proposed to account for the formation of imidazole-5-carboxylic acids following successive treatment of 2-arylimidazo[2,1-*b*]benzothiazoles (C-S bond cleavage) with butyllithium (THF/-70 °C) and carbon dioxide.[120]



(25)



(26)

Scheme 10

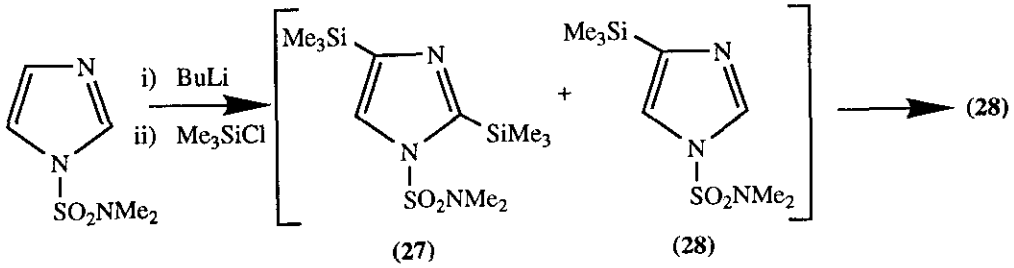
4-Chloro-1,3-dimethyl-2-phenylthioimidazolium salts are deprotonated with sodium hydride in DMF at position-5.[102] Attempts to methylthiolate (with $MeSSO_3Na$/DMF) the resulting anion results in the formation of a 4-

chloro-1,3-dimethyl-2-methylthio-5-phenylthioimidazolium salt *via* transfer of the phenylthio group from position-2 to position-5.

III POLYLITHIATED DERIVATIVES

A 2,4-Dilithiation

Recently Effenberger *et al.*[121] have claimed that treatment of *N,N*-dimethylimidazole-1-sulfonamide with two mol. equiv. of butyllithium in DME followed by quenching with chlorotrimethylsilane (TMS) and a work-up which results in loss of the 2-trimethylsilyl group from the initial product (**27**) yields *N,N*-dimethyl-4-trimethylsilylimidazole-1-sulfonamide (**28**) (Scheme 11), whilst similar treatment of the same substrate with LDA in THF gives *N,N*-dimethyl-5-trimethylsilylimidazole-1-sulfonamide. It is well-known that imidazol-4-yl sp^2



Scheme 11

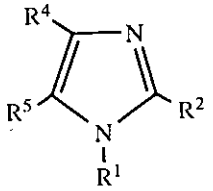
anions are less stable than their 5-counterparts. This has been attributed to the "adjacent lone pair effect".[122-124] Therefore, Effenberger's results[121] seen surprising and merit further investigation (see also Sections II.B and II.C).

B 2,5-Dilithiation

N-Protected imidazoles are *di*lithiated in positions-2 and -5 for the reasons given in Section III.A.[19,49,90,115] The resulting 2,5-dilithiated species have been quenched with a variety of electrophilic reagents to give 1,2,5-trisubstituted imidazoles; in some cases mixtures of 1,2-di- and 1,2,5-trisubstituted products are isolated (Table IV). Yields of trisubstituted products are related to the ability of the initially generated 2-anion to undergo further

Table IV

Synthesis of 1,2,5-Trisubstituted Imidazoles by 2,5-Dilithiation of 1-Substituted Imidazoles

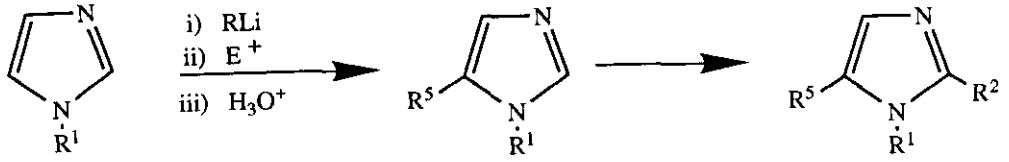


R^1	R^2	R^5	Reagent	Yield (%)	Ref.
Me	CO_2H	CO_2H	CO_2	–	22
Me	SMe	SMe	Me_2S_2	34	44
Me	$SiMe_3$	$SiMe_3$	Me_3SiCl	58[a], 68	22, 115
Me	$SnBu_3$	$SnBu_3$	Bu_3SnCl	91[b]	49
CH_2OBu-*tert*	D	D	D_2O	50	59
$CH_2O(CH_2)_2OMe$	D	D	D_2O	40	59
SO_2NMe_2	$SiMe_3$	$SiMe_3$	Me_3SiCl	85[c]	121

[a] After 2-desilylation. [b] After 2-destannylation [c] After 1-deprotection.

deprotonation, to yield the 2,5-dianion.[90] Whereas a large excess of reagent is required to quantitatively dilithiate 1-methyl- and 1-methoxymethylimidazoles, *N,N-dimethylimidazole-1-sulfonamide* is 2,5-dilithiated in quantitative yield under milder conditions.[19]

Some of the 1,2,5-trisubstituted imidazoles initially generated by quenching are prone to lose their labile 2-substituents. This is observed, e.g., with compounds carrying trimethylsilyl, tributylstannyl, or carboxyl groups at position-2.[22,49,90,121] [Scheme 12 for generation of compounds (**29**)].

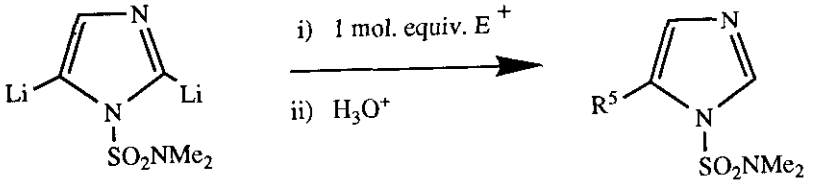


(29)

(R^1 = Me, SO_2NMe_2; R^2 = R^5 = $SiMe_3$, CO_2H)

Scheme 12

Another advantage of the sulfonamide group as an *N*-protecting group in dilithiation studies is that the negligible excess of lithiating reagent over substrate required permits reaction of the 2,5-dilithiated intermediate with one mol. equiv. of an electrophile, which yields a 1,5-disubstituted product (**30**) (Scheme 13).[19] Dimethyl sulfate is



(30)

R^5 = CH_2CH_2OH,Me

Scheme 13

preferred to iodomethane for introduction of a 5-methyl group. Position-5 in the 2,5-dilithiated intermediate is more reactive than position-2. Hydrolysis on work-up removes lithium at position-2 but presumably a different substituent could be introduced at this position if a further mol. equiv. of the same or a different electrophile was added.

C Others

When treated with two mol. equiv. of butyllithium (THF/-78 °C) 4-(2,4-dichlorophenyl)-*N,N*-dimethylimidazole-1-sulfonamide is metallated both at C-2 and between the Cl-atoms in the 4-aryl ring; the corresponding dialdehyde is isolated following quenching with DMF.[75]

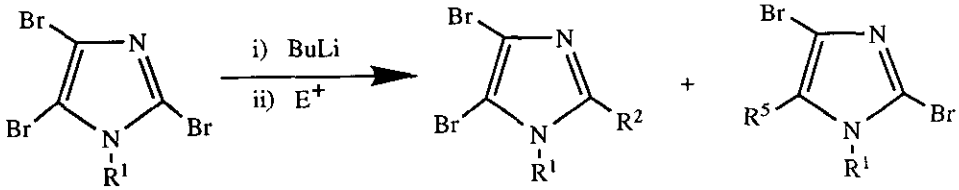
Several polylithiated imidazoles have been synthesised *via* Br → Li exchange reactions (see Section IV).

IV HALOGEN → LITHIUM EXCHANGE REACTIONS

Halogenated imidazoles undergo halogen → metal exchange reactions with organolithium reagents and the derived imidazolyllithium derivatives have been used for the introduction of a variety of substituents. These reactions have the advantage that they can be carried out at low temperatures, even as low as -100 °C, often in the presence of other substituents normally reactive towards the reagent at higher temperatures. The order of reactivity is 2-X > 5-X > 4-X ("ALP effect" applicable; see Section III.B) (X = halogen, usually Br but occasionally I and, rarely, Cl).

A *N*-Protected imidazoles

It is possible to exchange bromine (and iodine) atoms for lithium at any position in an *N*-protected bromo(or iodo)imidazole. With *N*-protected 2,4,5-tribromoimidazoles the bromine atoms can be replaced selectively in the order 2 → 5 → 4 in good to excellent yields,[8,125-128] thus providing a useful route to polysubstituted imidazoles (Table V). For selective exchange at position-2 in the presence of halogens at other positions yields are dependent on the metallating reagent and its rate of addition to the substrate. Careful temperature control is important also. In THF or ether at -78 °C *N*-protected 2,4,5-tribromoimidazoles (**31**) seem to react with butyllithium to give mixtures of the 2- (**32**; R^2 = Li) and 5-lithiated derivatives (**33**; R^5 = Li) (Scheme 14),[125-126] although a recent



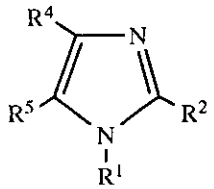
(31) (32) (33)

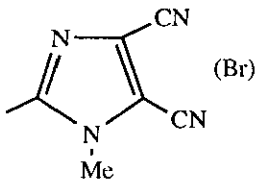
R^1 = CH_2Ph, CH_2OMe, CH_2OEt; R^2, R^5 = H,SMe.

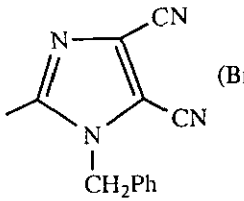
Scheme 14

Table V

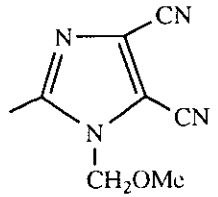
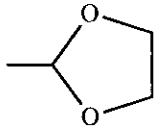
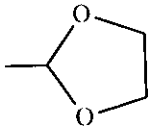
1-Protected Imidazoles Synthesised *via* Halogen → Lithium Exchange Reactions[a]



R^1	R^2	R^4	R^5	Reagent	Yield (%)	Ref.
Me	SPh (Br)	H	Br	$PhSO_2Ph$	80	25
Me	$SiMe_3$ (Br)	H	Br	Me_3SiCl	–	25
Me	$SiMe_2Bu$-*tert* (Br)	H	Br	*tert*-$BuMe_2SiCl$	–	25
Me	SMe (Br)	Br	Br	Me_2S_2	93	128
Me	H (Br)	CN	CN	H_2O	48	52, 15
Me	Me (Br)	CN	CN	MeI	–	15
Me	CO_2H (Br)	CN	CN	CO_2	42	15
Me		CN	CN	$CuCl_2/O_2/H_3O^+$	58	52
Me	H	CHO (I)	$CH(OEt)_2$	DMF	47[b]	129

Me	H	Br	H (Br)	H_2O	80	24
Me	H	Br	CO_2Me (Br)	$(MeO)_2CO$	50	130
Me	SPh	H	Bu (Br)	BuBr[c]	65	25
Me	H	I	H (I)	H_2O	85	24
Me	H (Br)	Br	H (Br)	H_2O	–	24
Me	CHO (Br)	H	CHO (Br)	DMF	48[d]	25
Me	SMe (Br)	Br	CHO (Br)	Me_2S_2, DMF	85[e]	128
Me	$SiMe_3$ (Br)	H	$SiMe_3$ (Br)	Me_3SiCl	88[d]	25
Me	SMe (Br)	CHO (Br)	CHO (Br)	Me_2S_2/DMF/DMF	51[e]	128
Me	SMe (Br)	$SnBu_3$ (Br)	H (Br)	Me_2S_2/*iso*-PrOH/Bu_3SnCl	40[e]	128
CH_2Ph	SMe (Br)	Br	Br	Me_2S_2	72	125, 126
CH_2Ph	SPh (Br)	Br	Br	Ph_2S_2	97	128
CH_2Ph	 (Br)	CN	CN	$CuCl_2/O_2/H_3O^+$	60	52
CH_2Ph	SMe (Br)	Br	CHO (Br)	Me_2S_2/DMF	60[e]	126
CH_2Ph	H	Br	CHO (Br)	DMF	53	125
CH_2Ph	H	Br	CO_2H (Br)	CO_2	67	125

CH_2Ph	H	Br	CO_2Me (Br)	$ClCO_2Me$	61	125
CH_2Ph	H	Br	SH (Br)	S_8	68	125
CH_2Ph	SCH_2Ph	Br	CHO (Br)	DMF	54	125
CH_2Ph	SPh	Br	CHO (Br)	DMF	52	125
CH_2Ph	Ph	Br	CHO (Br)	DMF	82	131
CH_2Ph	H (Br)	Br	H (Br)	H_2O	71[c]	126
CH_2Ph	SMe (Br)	Br	SMe (Br)	Me_2S_2	72[c]	126
CH_2Ph	SMe (Br)	SMe (Br)	SMe (Br)	Me_2S_2	67[c]	126
CH_2Ph	SMe (Br)	CH(OH)Ph (Br)	H (Br)	Me_2S_2/*iso*-PrOH/PhCHO	55[c]	128
CH_2Ph	SMe (Br)	$CH(OH)C_6H_{13}$ (Br)	H (Br)	Me_2S_2/*iso*-PrOH/$C_6H_{13}CHO$	66[c]	128
CH_2Ph	SMe (Br)	$C(OH)Me_2$ (Br)	H (Br)	Me_2S_2/*iso*-PrOH/Me_2CO	71[c]	128
CH_2Ph	SMe (Br)	CHO (Br)	$SiMe_3$ (Br)	Me_2S_2/Me_3SiCl/DMF	59[c]	128
CH_2Ph	SMe (Br)	$CH(OH)C_5H_{11}$ (Br)	$SiMe_3$ (Br)	Me_2S_2/Me_3SiCl/$C_5H_{11}CHO$	61[c]	128
CH_2Ph	SPh (Br)	Cl (Br)	H (Br)	Ph_2S_2/*iso*-PrOH/Cl_3CCCl_3	44[c]	128
CH_2Ph	SPh (Br)	CHO (Br)	H (Br)	Ph_2S_2/*iso*-PrOH/DMF	64[c]	128
CHBuPh	SMe (Br)	SMe (Br)	SMe (Br)	Me_2S_2/BuBr[c]	33[c]	126
CHBuPh	SMe (Br)	CHO (Br)	SMe (Br)	Me_2S_2/DMF/BuBr[c]	46[c]	126
$CH_2C_6H_4OMe$-4	H	Br	CHO (Br)	DMF	50	125
$CH_2C_6H_3(OMe)_2$-3,4	H	Br	CHO (Br)	DMF	55	125

	(Br)	CN	CN	$CuCl_2/O_2/H_3O^+$	27	52
CH_2OMe	SCH_2Ph	Br	H (Br)	H_2O	66	125
CH_2OMe	SCH_2Ph	Br	CHO (Br)	DMF	54	125
CH_2OMe	SPh	Br	CHO (Br)	DMF	51	125
CH_2OMe	SPh	Br	$C(OH)Ph_2$ (Br)	Ph_2CO	41	125
CH_2OMe	$SiMe_3$	Cl	$(CH_2)_2Cl$ (Cl)	$Cl(CH_2)_2I$	–	57
CH_2OCH_2Ph	H (I)	I	I	aq. NH_4Cl	99	60
CH_2OCH_2Ph	SPh (I)	I	I	Ph_2S_2	94	127
CH_2OCH_2Ph	H	H (I)		aq. NH_4Cl	76	60
CH_2OCH_2Ph	SPh	CO_2Me (I)		$ClCO_2Me$	80	127
CH_2OCH_2Ph	H	I	H (I)	aq. NH_4Cl	85	60
CH_2OCH_2Ph	H	I	CHO (I)	DMF	75	60
CH_2OCH_2Ph	Bu	I	CHO (I)	2-PyMeNCHO[f]	66	132

CH_2OCH_2Ph	SPh	I	CHO (I)	DMF	99	127
CPh_3	H	CHO (I)	H	DMF	83	124

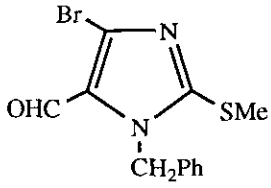
[a] Position of halogen → lithium exchange in parentheses; butyllithium used in all cases except for ref. 126 in which methyllithium was used to introduce substituents into position-2 (first) of 1-benzyl-2,4,5-tribromoimidazole. [b] After deprotection with H_3O^+ at position-5. [c] Generated by the initial Br → Li exchange reaction. [d] 2-Substituent lost on work-up. [e] "One pot" reactions starting with 1-substituted 2,4,5-tribromoimidazole. [f] 2-Py = pyrid-2-yl.

report[128] claims exclusive bromine → lithium exchange at position-2 with butyllithium (THF/-78 °C). The electrophilic quenching reagents were added just 5 minutes following addition of the butyllithium, which might be significant.

Selective exchange of the 2-bromine atom in compound (**31**; $R^1 = CH_2Ph$) is possible, however, with methyl-, phenyl-, or *sec*-butyllithium, to give the 2-lithiated derivative (**32**; $R^1 = CH_2Ph$, $R^2 = Li$).[125,126] With methyl-lithium compound (**31**; $R^1 = CH_2OMe$) yields lithium derivative (**32**; $R^1 = CH_2OMe$, $R^2 = Li$) which has been converted to the 2-methylimidazole (**32**; $R^1 = CH_2OMe$, $R^2 = Me$) with bromomethane.[125] To avoid coupling of imidazolyllithium derivatives with the bromo(or iodo)alkanes released by the initial halogen → metal exchange reaction it is preferable to quench them without too much delay.

When 5-bromo-2-*tert*-butyldimethylsilyl-1-methylimidazole is treated with butyllithium (THF/-70 °C) and the reaction mixture quenched (with aqueous NH_4Cl) the product is 5-*tert*-butyldimethylsilyl-1-methylimidazole (55% yield); the 2-silyl group migrates to position-5.[25] When 1-methyl-2-trimethylsilylimidazol-5-yllithium is prepared similarly and quenched with DMF prior to work-up, the product is a mixture (50% yield) of 1-methylimidazole-5-carbaldehyde and 5-trimethylsilyl-1-methylimidazole-2-carbaldehyde (40:60).[25] 5-Butyl-1-methyl-2-phenylthioimidazole is formed in 65% yield when 5-bromo-1-methyl-2-phenylthioimidazole is treated with butyllithium in THF at -70 °C, and the resulting lithiated imidazole is allowed to warm up to 0 °C.[25]

The result of bromine → lithium exchange at position-5 is dependent on the nature of the substituent at position-2 (Table V). In a one-pot procedure exchange at position-2 in 1-benzyl-2,4,5-tribromoimidazole (**31**; $R^1 = CH_2Ph$) with one mol. equiv. methyllithium, quenching with one mol. equiv. of dimethyl disulfide, exchange at position-5 with one mol. equiv. of butyllithium, and quenching with DMF gave compound (**34**) (60% overall yield).[126] Compound (**35**; R = I) (62% yield) was obtained similarly from 1-benzyloxymethyl-2,4,5-



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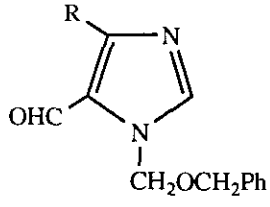
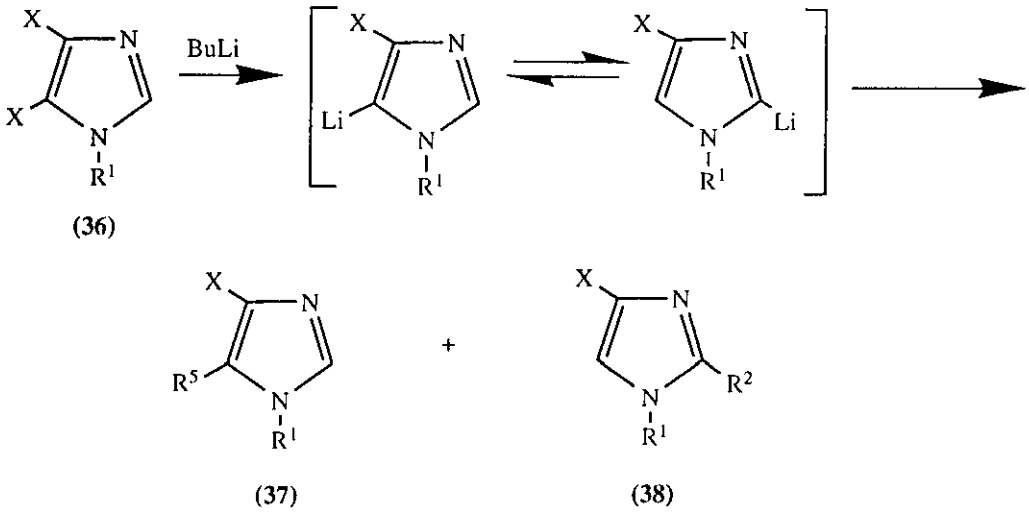


(35)

triiodoimidazole when the 2-protecting group and metallating agent were the labile trimethylsilyl group and butyllithium, respectively.[127] A one-pot exchange procedure gave **35** (R = Me) (29%) and **35** (R = CO_2Me)

(25%) after sequential work-up of the lithiated intermediate (generated with BuLi) with chlorotrimethylsilane, 1-formyl-1,2,2-trimethylhydrazine, and iodomethane (R = Me) or chlorotrimethylsilane, 1-formyl-1,2,2-trimethylhydrazine, and dimethylpyrocarbonate (R = CO_2Me), respectively.[127] The different atoms or functional groups can be introduced into *N*-protected 2,4,5-trihalogenoimidazoles *via* these halogen → lithium exchange techniques in the order position-2 → -5 → -4.[8,125-128,132] Thus, e.g. starting with 1-benzyloxymethyl-2,4,5-tri-iodoimidazole the following groups can be introduced in the following order: 2-SPh with diphenyl disulfide (94% yield), 5-CHO with DMF (99%), 4-CO_2Me with methyl chloroformate [80% after protection of the formyl group (58% yield) as its ethylene acetal].[127] Recently Lipshutz and Hagen[128] have used this methodology to good effect to synthesise 1-methyl-2-methylthioimidazole-4,5-dicarbaldehyde, a starting material for a preparation of the antitumour agent carmethizole, in 51% yield in a "one-pot" reaction sequence. Starting with 1-benzyl(or methyl)-2,4,5-tribromoimidazole a number of *N*-protected 2,4-di- or 2,4,5-trisubstituted imidazoles were prepared similarly (40-71% yields) in "one-pot" reaction sequences, e.g. (1-benzyl-2-methylthioimidazol-4-yl)dimethylmethanol (71%) (H was introduced at position-5 using 2-propan-ol). 1-Benzyloxymethyl-2-butyl-4,5-diiodoimidazole may be converted similarly into 1-benzyloxymethyl-2-butyl-4-iodoimidazole-2-carbaldehyde (66% yield; 19% of product arising from hydrolysis of imidazol-5-yllithium compound isolated also), a starting material for the synthesis of Angiotensin II inhibitors related to Losartan (DuP 753).[132]

Complications arise when *N*-protected 4,5-dihalogenoimidazoles (**36**; X = Br or I) are allowed to react with organolithium reagents. Exchange initially occurs at position-5 but transmetallation with position-2 can occur, even at -78 °C, resulting in the formation of mixtures of products, (**37**) and (**38**) (Scheme 15) (Table VI) [*cf.*

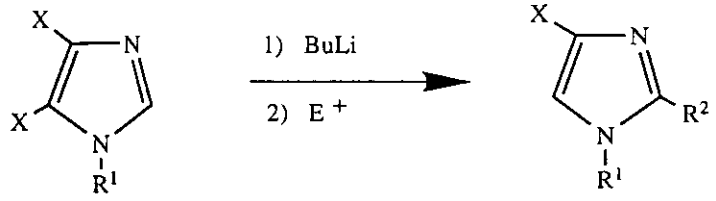


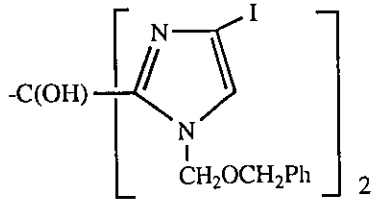
(**36**) (**37**) (**38**)

Scheme 15

Table VI

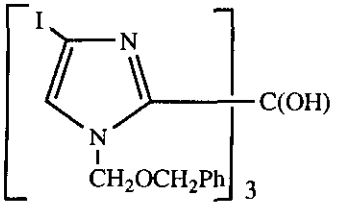
Imidazoles Synthesised *via* Halogen → Metal Exchange Followed by Transmetallation of a 5-Lithiated to a 2-Lithiated Intermediate



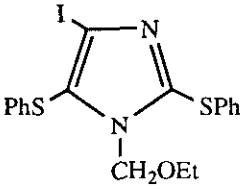
R^1	X	R^2	Reagent	Yield (%)	Ref.
Me	Br	Br	Br_2	87	24
Me	I	I	I_2	53	24
Me	Br	CHO	DMF	52	134
CH_2OCH_2Ph	I	CHO	DMF	68	60
CH_2OCH_2Ph	I		$^1/_3(EtO)_2CO$	59	60

the behaviour of similar Grignard compounds (Section VI)].

Compound (**39**) was isolated in 59% yield when the lithium derivative (**36**; X = I, $R^1 = CH_2OCH_2Ph$) was allowed to react with 0.33 mol. equiv. of diethyl carbonate.[60] 5-Bromo-1-methylimidazole is reported to give its 5-lithiated derivative with butyllithium;[133] quenching with acetaldehyde yields the corresponding carbinol (no rearrangement). In the reaction of 1-ethoxymethyl-4,5-diiodoimidazole (**36**; X = I, $R^1 = CH_2OEt$) with one mol. equiv. of butyllithium followed by quenching with diphenyl disulfide compound (**38**; X = I, $R^1 = CH_2OEt$, R^2 = SPh) was obtained together with imidazole (**40**) (ratio 4.6:1).[13] The formation of compound (**40**) is indicative



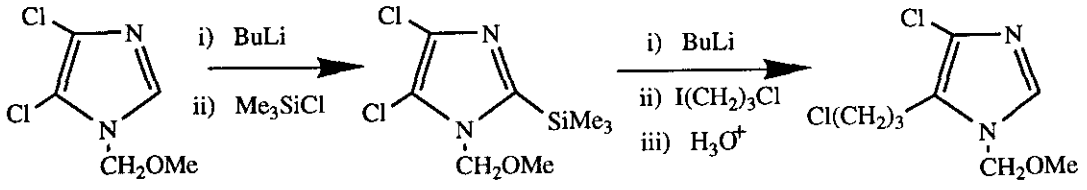
(**39**)



(**40**)

of competing metallation at position-2 and iodine → lithium exchange at position-5. Transmetallation from position-5 to position-2 is common when quenching is carried out with weak electrophiles.

4,5-Dichloro-1-methoxymethylimidazole undergoes metallation at position-2 with butyllithium (THF/-70 °C).[57] However, initial protection of position-2 by a silyl group (**41**) followed by addition of butyllithium apparently results in exchange of chlorine at position-5; quenching the 5-lithiated intermediate with 1-chloro-3-iodopropane gives imidazole (**42**) (Scheme 16). Other examples of 2-lithiation of 5-chloroimidazoles are given in Table I.

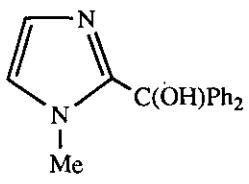


(**41**) (**42**)

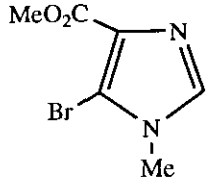
Scheme 16

With lithium naphthalenide, however, 5-chloro-1-methylimidazole gives compound (**43**) (83% yield) on quenching the lithiated derivative with benzophenone, presumably due to transmetallation of the initially generated 5-lithiated compound (*cf.* Scheme 15).[85]

Rapoport's group isolated products different from those expected from Scheme 15 when they allowed 4,5-dibromo-1-methylimidazole to react with butyllithium (Et_2O/-78 °C) and quenched the reaction mixture with dimethyl carbonate, which gave the expected 5-carboxylate (**37**; X = Br, R^1 = Me, R^5 = CO_2Me) (50% yield) together with compound (**44**) (10%).[130] This result suggests that both the bromine atoms undergo exchange in ether, with the lower yield of compound (**44**) reflecting the expected lower reactivity at position-4.

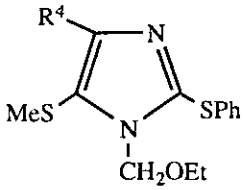


(43)



(44)

Exchange of bromine at position-4 is feasible when both positions-2 and -5 are blocked.[126] Starting with 1-benzyl-2,4,5-tribromoimidazole exchange of the bromine atoms at positions-2 and -5 with butyllithium followed by addition of dimethyl disulfide yields 1-benzyl-4-bromo-2,5-*bis*(methylthio)imidazole (72% yield). The remaining bromine atom can be exchanged by addition of another mol. equiv. of butyllithium and the resulting 4-lithiated species can be quenched with various electrophiles. Similarly 1-benzyl-2,4,5-tribromoimidazole can be converted in a "one-pot" sequence into 1-benzyl-2,4,5-*tris*(methylthio)imidazole (67%).[126] Compound (**45**; R^4 = Br) yields a 4-lithiated derivative with butyllithium (Et_2O/-70 °C) which can be quenched with carbon dioxide, dimethyl disulfide, and DMF to give the expected products (**45**; R^4 = CO_2H, SMe, or CHO, respectively) in high yields.[12,117]



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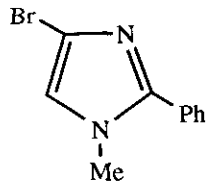


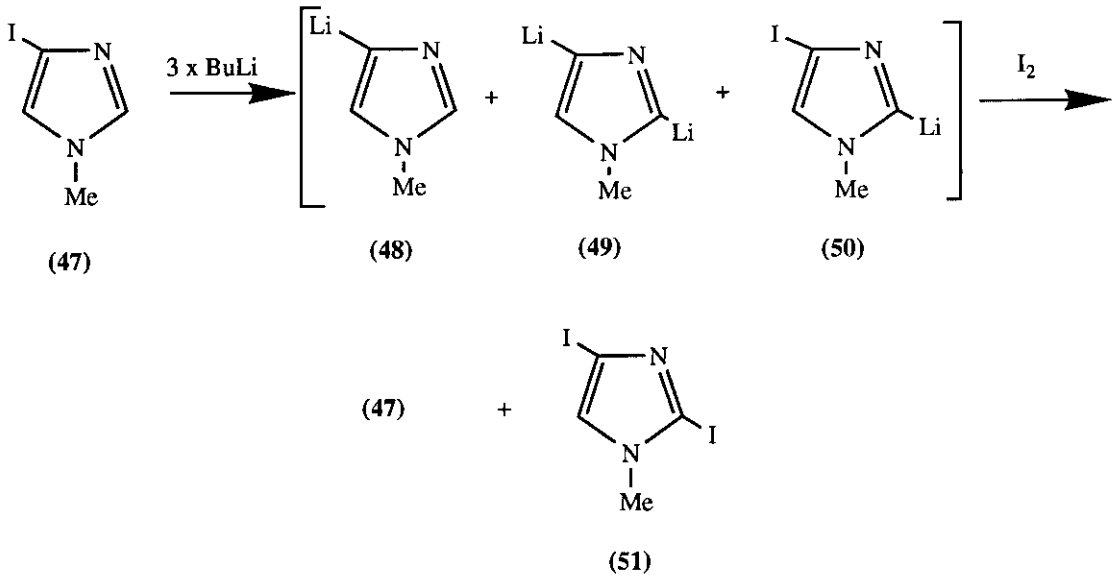
(46)

Exchange of bromine at position-4 with position-5 unprotected (BuLi/THF/-78 °C) has been claimed[116] for compound (**46**). With diethyl carbonate the resulting 4-lithiated derivative gave ethyl 1-methyl-2-phenyl-imidazole-4-carboxylate. Attempts to exchange the bromine atoms in 4- and 5-bromo-1-methylimidazole for

lithium with butyllithium have been reported as unsuccessful.[13,22,93] 4-Bromo-1-methylimidazole is metallated instead at position-2 (Table I).[133]

Exchange of iodine at position-4 with butyllithium is known to occur in imidazoles unprotected at positions-2 and -5. 4-Iodo-1-triphenylmethylimidazole, e.g., readily gives its 4-lithiated derivative which can be quenched after 2 seconds with DMF, to give the corresponding 4-carbaldehyde (83% yield).[124] A two-three mol. equiv. excess of butyllithium is required to react also with the iodobutane generated in the reaction. Under these conditions 1-triphenylmethylimidazole-2-carbaldehyde (11%) and 1-triphenylmethylimidazole-4,5-dicarbaldehyde are present also in the crude product. When a stoichiometric amount of butyllithium is employed, the yield of 1-triphenylmethylimidazole-4-carbaldehyde is reduced to 50% and 1-triphenylmethylimidazole (19%), starting material (8%), 1-triphenylmethylimidazole-2-carbaldehyde (7%), and 4-iodo-1-triphenylmethylimidazole-2-carbaldehyde (16%) were detected also in the crude product.[124]

A similar study with 4-iodo-1-methylimidazole (**47**) gave 2,4-diiodo-1-methylimidazole (**51**) (Scheme 17) in a maximum yield of 40% when the reaction was quenched with iodine.[135] Starting material was recovered even



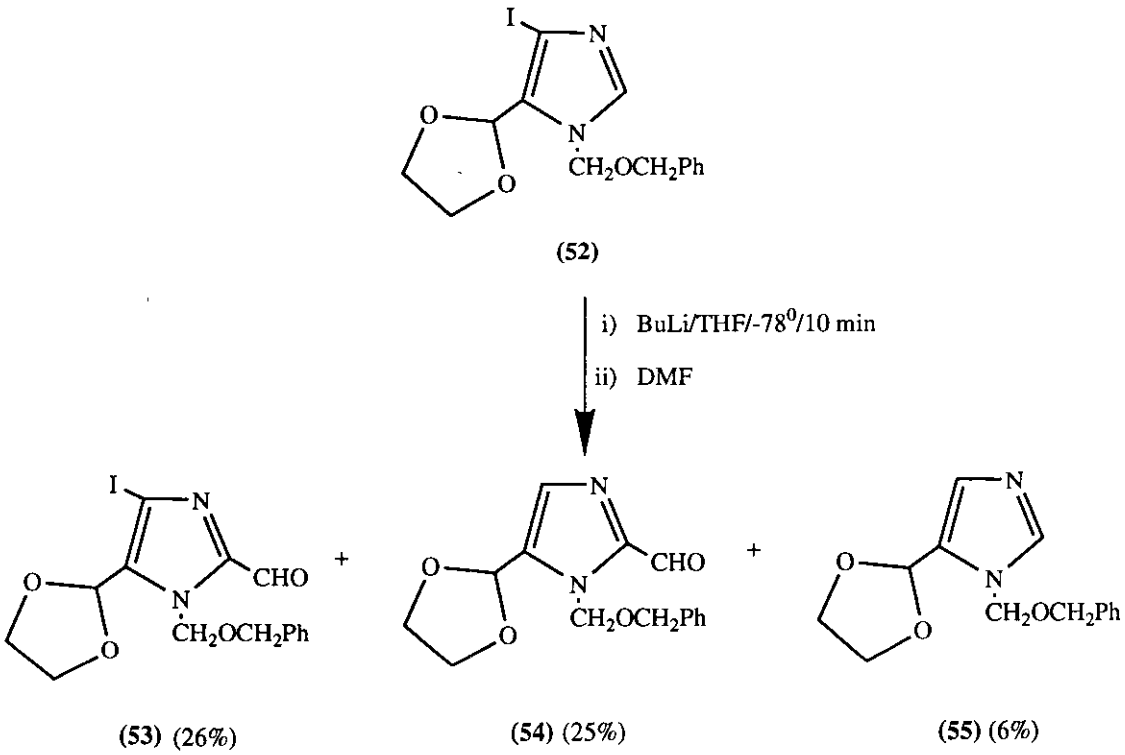
(47) (48) (49) (50)

(47) + (51)

Scheme 17

though three mol. equiv. of butyllithium was used. The lithiated derivatives (**48**)-(**50**) were believed to be present in the reaction mixture prior to quenching, suggesting that metallation in position-2 is significant in this case.

An intermediate similar to **50** has been trapped by Groziak's group,[60] who reported isolation of aldehyde (**53**) (26% yield) (Scheme 18) from treatment of the 4-iodoimidazole (**52**) with butyllithium (THF/-78 °C) followed

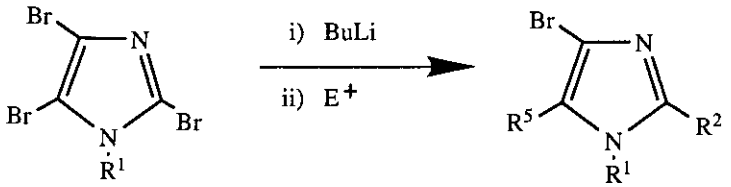


Scheme 18

by addition of DMF. Simultaneous formation of compound (**54**) is evidence of transmetallation to position-2. When the 2-lithiated derivative of compound (**52**) was quenched after 15 minutes with aqueous ammonium chloride, imidazole (**55**) was obtained (76%). The 2-deuteriated derivative of **55** was obtained with deuterium oxide as the quenching reagent, indicating transmetallation of the 4-lithiated intermediate to the 2-lithiated derivative. Similar results were obtained at -100 °C after 15 min.

However, when 5-diethoxymethyl-4-iodo-1-methylimidazole is treated successively with butyllithium (Et_2O/-30 °C), DMF, and acid, it yields a moderate yield (47%) of 1-methylimidazole-4,5-dicarbaldehyde *via* an intermediate 4-lithiated compound.[129]

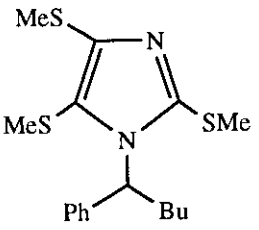
As hinted above *N*-protected 2,4,5-tribromoimidazoles (**31**) yield their 2,5-dilithiated derivatives (**56**; $R^2 = R^5 =$ Li) with two mol. equiv. of an organolithium reagent (Scheme 19). 4-Bromo-1-methylimidazole is obtained when the 2,5-dilithiated derivative (**56**; R^1 = Me, $R^2 = R^5$ = Li) of 2,4,5-tribromo-1-methylimidazole



(31) **(56)**

Scheme 19

(**31**; R^1 = Me) is quenched with water.[24] 1-Benzyl-2,4,5-tribromoimidazole (**31**; $R^1 = CH_2Ph$) (Scheme 19) similarly yields compound (**56**; $R^1 = CH_2Ph$; $R^2 = R^5$ = H) (71% yield).[126] When the quenching reagent is dimethyl disulfide, compound (**56**; $R^1 = CH_2Ph$, $R^2 = R^5$ = SMe) (72%) is the product. Attempts to prepare the 2,4,5-trilithiated derivative of compound (**31**; $R^1 = CH_2Ph$) with five mol. equiv. of butyllithium resulted in α-(or lateral)metallation in addition to bromine → lithium exchange and, after quenching with dimethyl disulfide,



(57)

afforded compound (**57**) (33% yield).[126] The butyl group is introduced by capture of the bromobutane generated by the initial bromine → lithium exchange reactions.

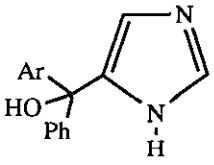
With two mol. equiv. of butyllithium (THF/-70 °C) 2,5-dibromo-1-methylimidazole gives the corresponding 2,5-dilithiated imidazole which can be quenched with 2 mol. equiv. of DMF or chlorotrimethylsilane, to give 1-

methylimidazole-5-carbaldehyde (48% yield; the major product is 1-methylimidazole) or 1-methyl-5-trimethylsilylimidazole (88%), respectively. The 2-substituent is lost on work-up (with aqueous NH_4Cl).[25]

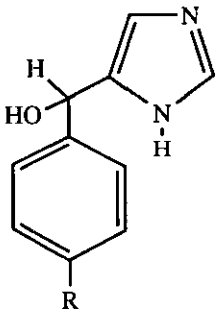
B N-*Un*protected imidazoles

Metallation of mono- or polyhalogenated imidazoles *un*substituted on the ring N-atom occurs initially to give the *N*-lithiated species[12,13,22,125] then, with an excess of the organolithium reagent, halogen → metal exchange is observed. With five mol. equiv. of butyllithium in THF 4(5)-bromoimidazole, e.g., yields a 1,4(5)-dilithiated derivative which affords imidazole or 4(5)-deuterioimidazole following addition of methanol or deuteriomethanol, respectively.[136] With lithium naphthalenide followed by quenching with benzophenone the same substrate affords carbinol (**58**; Ar = Ph) in yields of up to 64%.[22,125,137]

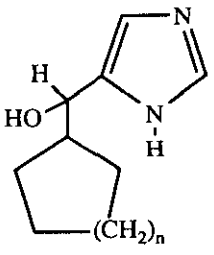
The yields of products derived from 4(5)-bromoimidazole are dependent on the base used, the time taken to generate the dilithiated species, and the quantity of electrophilic quenching reagent added.[22] Compounds (**58**)-(**61**) have all been prepared in this manner (22-64% yields) (*tert*-BuLi/THF/-78 °C).[22] The generation of compounds (**59**; R = H, Me, OMe, or Cl) is followed by their spontaneous aerial oxidation to the corresponding ketones (37-61% yield).[22] In a similar study the ketones derived by oxidation of carbinols [**59**; R = H (55%),



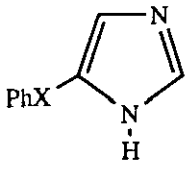
(58)
Ar = Ph (64%)
Ar = imidazol-4-yl (22%)



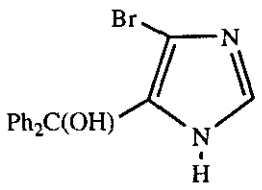
(59)



(60)
n = 1 (29%)
n = 2 (48%)



(61)
X = S (62.5%)
X = CONH (33%)



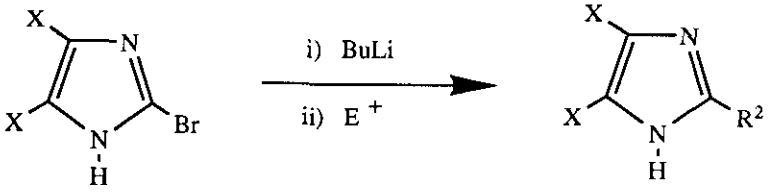
(62)

2-OMe (52%), 4-OMe (48%), 3,4-$(OMe)_2$ (63%)] were obtained by treatment of 4(5)-bromoimidazole with lithium naphthalenide followed by addition of the appropriate aldehyde.[138] Yields of ketones were much lower (17% and 24%, respectively, when R = H or 4-OMe) when the quenching electrophile was the corresponding benzonitrile.[138]

When 4,5-dibromoimidazole is allowed to react with two mol. equiv. of butyllithium and the resulting 1,5-dilithiated derivative is quenched with benzophenone, a disappointing yield (only 17%) of carbinol (**62**) is obtained.[125]

Various polysubstituted imidazoles are available through treatment of polyhalogenated imidazoles *un*protected on the ring *N*-atom with organolithium reagents followed by addition of suitable electrophiles (Scheme 20) (Table VII).[139]

With four mol. equiv. of butyllithium followed by addition of methanol 2,4,5-tribromoimidazole (**63**; X = Br) has been reported to give 4(5)-bromoimidazole,[136] again evidence of the greater resistance of the bromine atom



(63) **(64)**

Scheme 20

next to the pyridine-like *N*-atom to undergo bromine → lithium exchange compared with the other two bromine atoms ("ALP effect");[122-124] 4,5-dibromoimidazole (**64**; X = Br, R^2 = H) and 4(5)-bromo-5(4)-butylimidazole were obtained also.

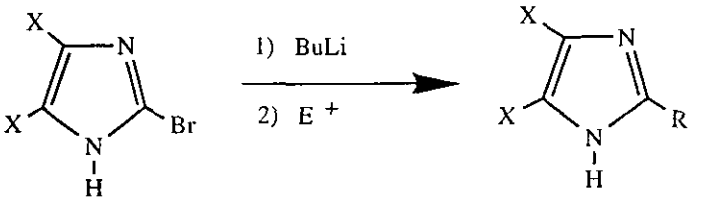
The yields of products obtained by bromine → lithium exchange of *N-un*substituted bromoimidazoles are lower than those obtained from the corresponding *N*-protected compounds. Thus, the synthetic utility of these procedures is limited currently although further work should be encouraged since protection and deprotection of imidazoles is wasteful of materials and time.

V LATERAL METALLATION

Some substituents on the imidazole ring, particularly 2-alkyl groups, are prone to α-(or lateral)metallation (Table VIII). Tertov's group reported[140] that 1,2-dimethylimidazole is metallated by butyllithium (at -10 °C) exclusively

TableVII

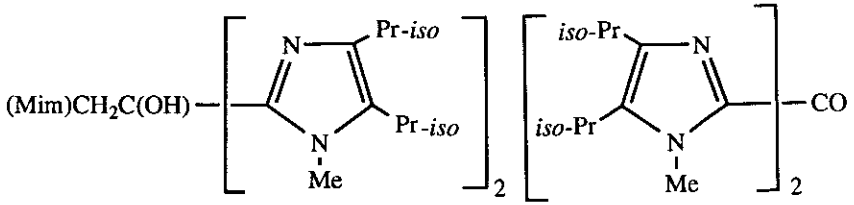
Exchange at Position-2 of 2,4,5-Trihalogenated Imidazoles with Butyllithium

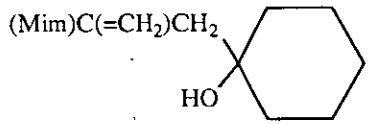
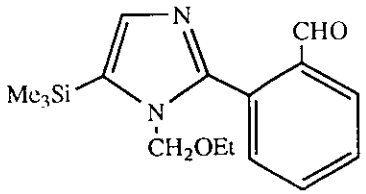
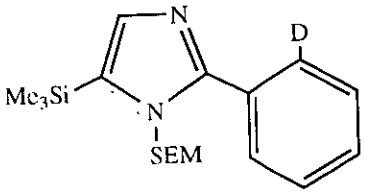


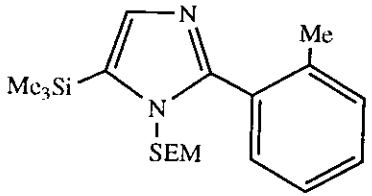
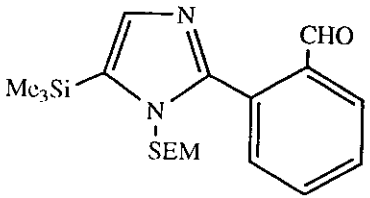
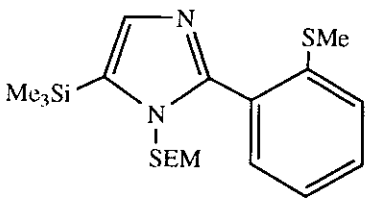
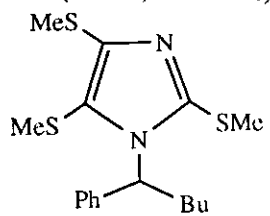
X	R	Reagent	Yield (%)	Ref.
Cl	CHO	DMF	52	125
Cl	CO_2H	CO_2	48	125
Cl	$CH(OH)C_6H_3(OMe)_2$-2,3	2,3-$(MeO)_2C_6H_3CHO$	44	139
Cl	$CH(OH)C_6H_3(OMe)_2$-2,5	2,5-$(MeO)_2C_6H_3CHO$	-	139
Cl	$CH(OH)C_6H_3(OMe)_2$-3,4	3,4-$(MeO)_2C_6H_3CHO$	-	139
Cl	SBu	S_8, BuI	42	125
Br	H	H_3O^+	40	125
Br	CHO	DMF	43	125
Br	CO_2H	CO_2	57	125
Br	SBu	S_8, BuI	40	125

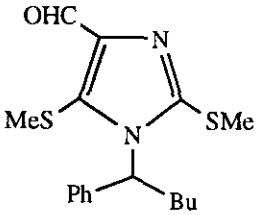
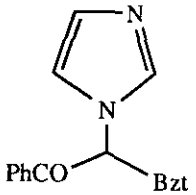
Table VIII

Imidazoles Synthesised *via* Lateral Metallation[a]

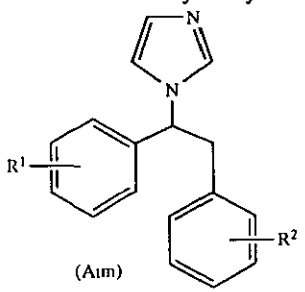
Substituent[b]	Product[c]	Reagent[c]	Yield (%)	Ref.
2-Me	(Mim)CH_2D	D_2O	84[d]	32
2-Me	(Dam)CH_2Ar[e]	$ArCH_2Cl$[e]	50-63	99
2-Me	(Mim)$CH_2CH(OH)C_6H_4Me$-4	4-MeC_6H_4CHO	82,70[f]	118
2-Me	(Mim)$CH_2CH(OH)$(2-py)	2-PyCHO	67	118
2-Me	(Mim)$CH_2C(OH)Ph_2$	Ph_2CO	54	118
2-Me	(Mim)$CH_2C(OH)(Mim)_2$	$(Mim)_2CO$	43	37
2-Me			63	141
2-Me	(Mim)$C(SMe)_3$	Me_2S_2	41	118
2-Me	(Mim)CH_2SiMe_3	Me_3SiCl	63	142
2-Me	(Eom)CH_2CO_2Et	$(EtO)_2CO$	23	116
2-Me	(Eom)$CH_2C(OH)(Eom)_2$	$(Eom)_2CO$	33.5	116
2-Me	$[(Eom)CH_2]_3P$	$^1/_3PCl_3$	46[g]	143

2-Bu	(Dam)CHPrBu	BuBr	27	21
2-CMe=CH_2	(Mim)C(=CH_2)(CH_2)$_2$OH	HCHO	41	40
2-CMe=CH_2	(Mim)C(=CH_2)CH_2CH(OH)-C_6H_3(OCH_2O)-3,4	3,4-(OCH_2O)C_6H_3CHO	32	40
2-CMe=CH_2		cyclohexanone	47	40
2-CMe=CH_2	(Mim)C(=CH_2)CH_2C(OH)CMePh	PhCOMe	43	40
2-CMe=CH_2	(Mim)C(=CH_2)CH_2C(OH)Ph_2	Ph_2CO	30	40
2-SMe	(Mom)CH_2Li	no derivatives mentioned		93
2-SCH_2R^h	(Mim)SCHRCH_2SnBu_3	Bu_3SnCH_2I	31	144
2-$SOCH_2$CHMeEt	(Mim)SOCH[CH(OH)Ph]CHMeEt^i	PhCHO	–	145
2-Ph		DMF	73	16
2-Ph		MeOD	38^i	16

2-Ph		MeI	56[i]	16
2-Ph		DMF	52, 41[j]	16
2-Ph		Me_2S_2	52[i]	16
1-CH_2Ph	Aim ($R^1 = R^2 = H$)	$PhCH_2Br$	12[k]	54
1-CH_2Ph	Aim ($R^1 = R^2 = H$)	$PhCH_2Cl$	61, –	94, 54
1-CH_2Ph	Aim ($R^1 = R^2 = Cl$)	4-$ClC_6H_4CH_2Cl$	29, 7[k]	94, 54
1-CH_2Ph	Aim ($R^1 = H$, R^2 = 4-Me)	4-$MeC_6H_4CH_2Cl$	61	94
1-CH_2Ph		BuBr	33	126

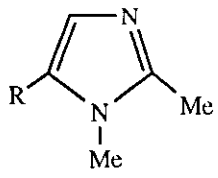
1-CH_2Ph		BuBr	46	126
1-$CH_2C_6H_4Cl$-4	Aim (R^1 = 4-Cl, R^2 = H)	$PhCH_2Cl$	48	94[l]
1-$CH_2C_6H_4Me$-4	Aim (R^1 = 4-Me, R^2 = H)	$PhCH_2Cl$	41	94
1-$CH_2C_6H_3Cl_2$-2,4	Aim ($R^1 = R^2$ = 2,4-Cl_2)	2,4-$Cl_2C_6H_3CH_2Cl$	45	94
1-$CH_2C_6H_3Cl_2$-2,4	Aim (R^1 = 2,4-Cl_2, R^2 = 4-Ph)	4-$PhC_6H_4CH_2Cl$	38	94
1-$CH_2C_6H_4Ph$-4	Aim (R^1 = Ph, R^2 = H)	$PhCH_2Cl$	64	94
1-CH_2Bzt[g]		$PhCO_2Et$	53	56

[a] *With BuLi unless stated otherwise.* [b] *Substituent laterally metallated.* [c] **ABBREVIATIONS USED**: Mim = 1-methylimidazol-2-yl; Mom = 1-methoxymethylimidazol-2-yl; Eom = 1-ethoxymethylimidazol-2-yl; Dam = 1-dimethylaminomethylimidazol-2-yl; Aim = (see formula)

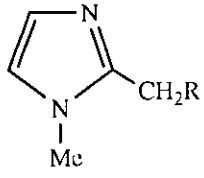


; 2-Py = pyrid-2-yl; Bzt = benzotriazol-1-yl; TMS = Me_3Si; SEM = $Me_3SiCH_2CH_2OCH_2$. [d] With LDA. [e] Ar = Ph, C_6H_4Br-2(or 4), C_6H_4Cl-4, C_6H_4OMe-4, $C_6H_3F_2$-2,4, $C_6H_3Cl_2$-2,4, or $C_6H_3(OMe)_2$-3,4. [f] With *tert*-BuOLi/KDA. [g] Yield after deprotection during which simultaneous oxidation at phosphorus occurs. [h] R = CH_2=$CMe(CH_2)_2$ CH=CMe_2 (product reacts further). [i] As a mixture of diastereomers. [j] Yields of products after removal of 1-SEM[c] and 5-TMS[c] protecting groups ("one-pot" reactions starting with 2-phenylimidazole). [k] Reaction carried out at ambient temperature. [l] 1-(4-Chlorobenzyl)-imidazole is metallated by butyllithium both at position-2 and in its N-C_α methylene group. The resulting anion has been quenched with 4-chloro- and 4-methoxybenzophenone.[18]

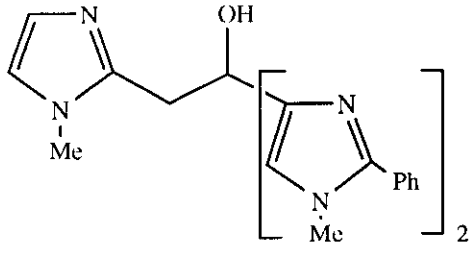
at position-5 to give, after addition of suitable quenching reagents, compounds [**65**; R = Br (26%), I (45%), CHO (20%), CH(OH)Ph (59.5%), $C(OH)Ph_2$ (73%)]. By contrast, others have reported the isolation of a mixture of compounds [**65**; R = CH(OH)Ph] and [**66**; R = CH(OH)Ph] following successive treatment of this substrate with butyllithium (at 0 °C)[140,146] or phenyllithium[147] and benzaldehyde. To further complicate the picture, exclusive α-(or lateral)metallation is suggested by the isolation of compounds [**66**; R = CH(OH)pyrid-2-yl] (66% yield) (BuLi/-15 °C, then pyrid-2-ylCHO) and (**67**) (19%) (BuLi also).[116] We have carried out a detailed investigation of the metallation of 1,2-dimethylimidazole with butyllithium and other reagents.[118] The results show that products arising from exclusive lateral metallation [**66**; R = $CH(OH)C_6H_4Me$-4 (82% yield) or



(**65**)



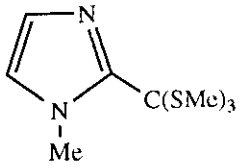
(**66**)



(**67**)

CH(OH)pyrid-2-yl (67%)] or exclusive metallation at position-5 [**65**; R = D (50% deuterium incorporation), $SiMe_3$ (72%), $SnMe_3$ (58%), $SnBu_3$ (difficult to purify)] may be obtained or mixtures of both types of product, (**65**) and (**66**) [R = SMe, $C(OH)Ph_2$], may be formed depending on the metallating agent, reaction conditions, and the quenching reagent. The product claimed to be compound [**65**; R = $C(OH)Ph_2$] by Tertov's group[140] was shown to be its isomer [**66**; R = $C(OH)Ph_2$].[118] The conditions best suited to lateral metallation in the 2-methyl group include the use of butyllithium in ether in the presence of TMEDA or in ether *but at -110 °C*, butyllithium in THF, or LDA in ether.[118] The results of this investigation suggest that the laterally metallated product is more stable than the 5-lithiated product. The 5-lithiated product can be obtained by treatment of 1,2-dimethyl-5-trimethylstannylimidazole with butyllithium in THF at -110 °C; with dimethyl disulfide or benzophenone added at this temperature the 5-substituted compounds [**65**; R = SMe (100%), $C(OH)Ph_2$ (94%)] are formed exclusively. However, if the reaction mixture is allowed to warm up (e.g. to -20 °C), the initially formed 5-lithiated compound equilibrates with the more stable laterally metallated species and, following addition of benzophenone, a mixture

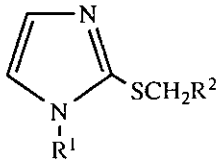
of carbinols (**65**) and (**66**) [R = $C(OH)Ph_2$] is formed instead.[118] Repeated lateral metallation of 1,2-dimethylimidazole in its 2-methyl group (Et_2O/ambient temperature) and quenching with dimethyl disulfide leads to compound (**68**) (41% yield).[118]



(68)

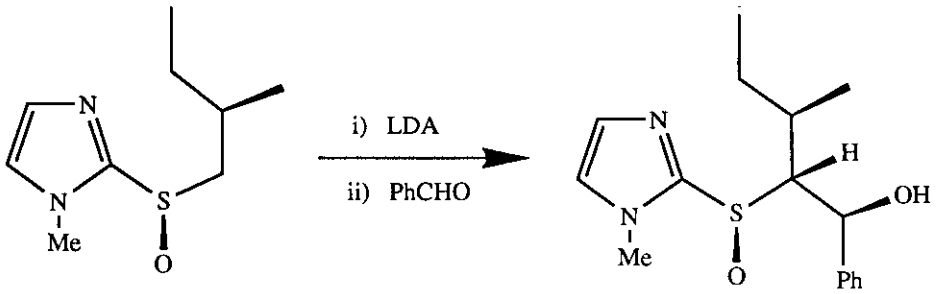
1-Dimethylaminomethyl-2-methylimidazole is laterally metallated with butyllithium (THF/-78 °C) in its 2-methyl group and the resulting anion can be quenched with benzyl chloride and a number of its derivatives (Table VIII) to give the corresponding 2-arylethyl derivative.[99]

A 2-(1-propen-2-yl)-substituent has been reported[40] to undergo lateral metallation with butyllithium in THF at -78 °C in the presence of HMPA and triethylaluminium and the resulting anion has been trapped with various carbonyl compounds.



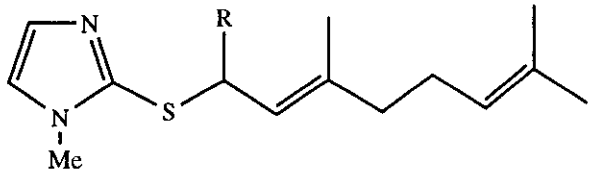
(69)

Lateral metallation has been reported for the 2-methylthio group in compound (**69**; $R^1 = CH_2OMe$, $R^2 = H$).[93] Similar metallation of compound (**70**) (Scheme 21) with LDA gives a lithium derivative whose lithium atom is chelated with the ring N-atom; reaction with benzaldehyde is stereocontrolled as a consequence and a 5:1 mixture of the diastereoisomers of compound (**71**) is obtained.[145] Compound (**72**; R = H) reacts with butyllithium (THF/-78 °C) to give, after quenching the resulting anion with tributylstannylmethyl iodide, what is believed to be compound (**72**; $R = CH_2SnBu_3$).[144] The initially generated anion reacts further with this compound as it forms to give compound (**72**; $R = SnBu_3$) (31% yield) and the lithium salt of 1-methylimidazole-2-thiol, which is captured by the added tributylstannylmethyl iodide to produce compound (**69**; $R^1 = Me$, $R^2 = SnBu_3$) (43% yield). Starting material (**72**; R = H) (14%) is recovered whilst the major product is the eliminated 4,8-dimethylnona-1,3,7-triene (45%).



(70) (71)

Scheme 21



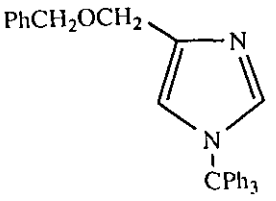
(72)

The 2-phenyl groups in 1-ethoxymethyl- and 1-trimethylsilylethoxymethyl-2-phenyl-5-trimethylsilylimidazole are *ortho*-lithiated by butyllithium (THF/-78 °C) and the resulting anions can be quenched with various electrophiles (MeOD, MeI, Me_2S_2, DMF) (Table VIII).[16] Starting with 2-phenylimidazole the 1- and 5-protecting groups can be introduced, the substituent introduced into the phenyl ring, and both protecting groups removed all in one pot (38-41% overall yields). 1-Ethoxymethyl-2-phenylimidazole is dilithiated with an excess of butyllithium (THF/-20 °C) in position-5 and in the *ortho*-position of the phenyl ring; quenching with an excess of DMF yields the corresponding dialdehyde in good yield but addition of one mol. equiv. of DMF also yields the dialdehyde together with starting material.[16] A monoaldehyde is not available *via* this route.

The C-4 methylene group in 4-benzyloxymethyl-1-triphenylmethylimidazole (**73**) is laterally metallated.[70] Noteworthy are the fluoride ion desilylation reactions of compounds (**74**; R = H)[148] and (**74**; R = SMe)[149] which give stabilised N-C_α anions that react with various reagents, e.g. aldehydes and ketones to give compounds (**75**; R^1 = H, SMe; R^2 = Ph, C_6H_4Cl-4; R^3 = H, Me, Ph) (22-89% yields).

Lateral metallation of an *N*-benzyl group has been mentioned in Section II.A in connection with the isolation of compound (**12**) and in Section IV.A in connection with the formation of compound (**57**). The *N*-benzyl

protecting group possesses this disadvantage as an *N*-protecting group and its lateral metallation is probably responsible for non-quantitative 2-metallation of such protected compounds and the low to moderate yields of



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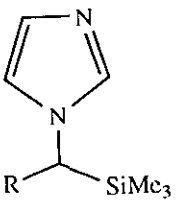

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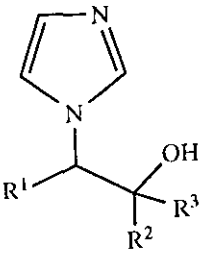
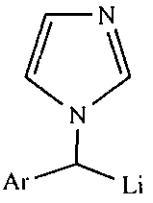


(75)

products given in Table VIII. It has been suggested[54] that the 2-lithiated derivatives (**76**) are more favoured both kinetically and thermodynamically than their laterally metallated isomers (**77**) but the mechanism of equilibration,

(76)



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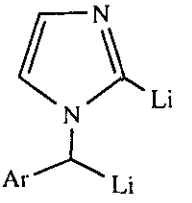
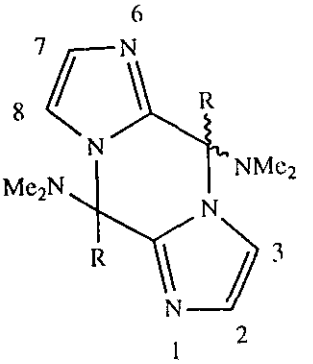


(78)

(**76**) (**77**), is unknown. The dilithiated derivatives (**78**) are readily generated in the presence of a slight excess of butyllithium[19] (but see also ref. 94).

ortho-Lithiation of 1-phenylimidazole has been mentioned in Section II.A.

Dilithiation (three mol. equiv. *tert*-BuLi/THF/-65 °C) of the diimidazopyrazine (**79**; R = H) is 85% complete after



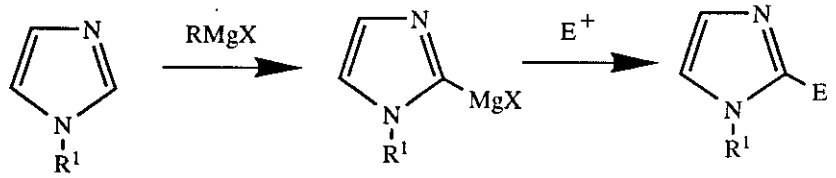
(79)

30 minutes with no further change, as shown by a deuterium oxide quench.[150] Compounds {(**79**): R = Me (MeI/54% yield); R = Pr (PrBr/53%) (PrI/72%); R = *iso*-Pr (*iso*-PrI/49%); R = $(CH_2)_4Me$ [$Me(CH_2)_4Br$/71%] [$Me(CH_2)_4I$/74%]; and R = CH_2Ph ($PhCH_2Br$/23%) ($PhCH_2I$/25%)} are obtained following addition of the appropriate alkyl halide and these are hydrolysed in hot aqueous sodium hydrogencarbonate solution to give the corresponding 2-alkanoyl(COR)imidazole.[150]

With sodium hydride in DMF, lateral metallation of the 2-methyl group occurs in 1,2,3-trimethylimidazolium iodide. In the presence of iodomethane the 2-ethyl derivative is formed, then the 2-isopropyl derivative.[102] Steric factors apparently prevent further alkylation of the latter product.

VI OTHER ORGANOMETALLIC DERIVATIVES

N-Protected imidazoles are metallated in position-2 in hot THF with ethylmagnesium bromide[36,151-153] or chloride (Scheme 22).[154]



Scheme 22

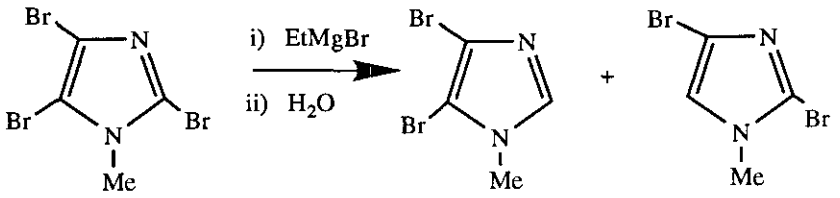
4- And 5-chloro-1-methylimidazoles fail to react with magnesium[155] unless the entrainment technique is used,[152] e.g.with dibromoethane in hot THF. Use of bromoethane results in competition between formation of the Grignard compound at position-4 or -5 and metallation in position-2.[152] In ether or cold THF the magnesium bromide or ethylmagnesium bromide formed initially gives insoluble co-ordination complexes with the imidazole which screen the surface of the magnesium, thus inhibiting the reaction.[152] For the formation of 4- and 5-trimethylsilylimidazoles it is preferable to bring together the chloro(or bromo)imidazole, magnesium, and chlorotrimethylsilane in a "one pot" procedure.[121]

There is evidence that the formation of 1-methylimidazol-4(or 5)-ylmagnesium bromides is accompanied by a transmetallation process with position-2 of the starting material. Following quenching with a suitable electrophile a mixture of 4(or 5)-substituted 1-methylimidazole and the corresponding 2-substituted 4(or 5)-chloro-1-methylimidazole is obtained.[152] However, treatment of *N*-protected 4-iodoimidazoles with ethylmagnesium

bromide in dichloromethane[156,157] or ether[129,134] generates the corresponding Grignard derivative which can be quenched with various electrophilic reagents (Table IX). There was no evidence in these reactions for rearrangement of the initially generated imidazol-4-yl anion.

A note has appeared[156] which proposes that the reactivity of *N*-protected imidazol-4-ylmagnesium salts can be modified by addition of other metal salts (e.g. $ZnCl_2$, CuCN).

N-Protected 2,4,5-tribromoimidazoles also react with ethylmagnesium bromide in ether, THF, or benzene at position-2;[22,125,130] hydrolysis of the resulting Grignard compound usually leads to the corresponding *N*-protected 4,5-dibromoimidazole. However, choice of solvent can be important.

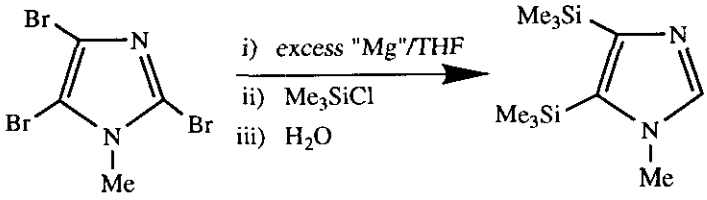


(80) **(81)**

Scheme 23

Thus, whilst 2,4,5-tribromo-1-methylimidazole reacts with ethylmagnesium bromide in ether at ambient temperature to give, after hydrolysis, exclusively 4,5-dibromo-1-methylimidazole (**80**) (Scheme 23) (80% yield), in THF the same procedure yields a 1:1 mixture of compound (**80**) and its isomer (**81**).[130]

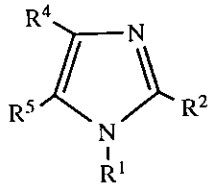
4,5-Dibromo-1-methylimidazole (**80**) reacts with 2.5 mol. equivs. of "activated magnesium" in HMPA to give, after addition of chlorotrimethylsilane, 4-bromo-1-methyl-5-trimethylsilylimidazole (77% yield).[121] A 4,5-*bis*(silylated) derivative has been prepared similarly (Scheme 24).



Scheme 24

Table IX

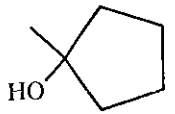
Imidazoles Prepared *via* Grignard Intermediates[a,b]



R^1	R^2	R^4	R^5	Solvent	Reagent	Yield (%)	Ref.
H	H (Br)	Br	Br	THF	H_3O^+	67	125
Me	COPh (H)	H	H	–	PhCN	60	36
Me	CO(4-Py)[c] (H)	H	H	–	4-PyCN[c]	30	36
Me	CH(OH)Ph (H)	H	H	THF	PhCHO	85	151
Me	$CH(OH)C_6H_4Cl$-2 (H)	H	H	THF	$2\text{-}ClC_6H_4CHO$	–	153
Me	$CH(OH)C_6H_4Me$-2 (H)	H	H	THF	$2\text{-}MeC_6H_4CHO$	–	153
Me[d]	$CH(OH)C_6H_3NO_2Cl$-2,5 (H)	H	H	THF	$2,5\text{-}(O_2N)ClC_6H_3CHO$	43	154
Me	$CH(OEt)_2$ (Br)	H	H	Et_2O/C_6H_6	$HC(OEt)_3$	56	134
Me	$CH(OEt)_2$ (I)	H	H	Et_2O/C_6H_6	$HC(OEt)_3$	65	134
Me	CH(OH)Ph (H)	Cl	H	THF	PhCHO	77, 9.5	151, 152
Me	CH(OH)Ph (H)	H	Cl	THF	PhCHO	87, 7.5	151, 152

Me	$C(OH)Ph_2$ (H)	H	Cl	THF	Ph_2CO	82	151
Me	H (Br)	Br	Br	C_6H_6	H_2O	48	22
Me	H (Br)	Br	Br	Et_2O	H_2O	80	130
Me	H	CH(OH)Ph (Cl)	H	THF	PhCHO	26.5	152
Me	H	$C(OH)Ph_2$ (Cl)	H	THF	Ph_2CO	10	152
Me	H	$SiMe_3$ (Cl)	H	THF	Me_3SiCl	58	121
Me	H	$CH(OEt)_2$ (Br)	H	Et_2O/C_6H_6	$HC(OEt)_3$	48	134
Me	Br	$SiMe_3$ (Br)	$SiMe_3$ (Br)	THF	MeSiCl	63	121
Me	H	$CH(OEt)_2$ (I)	H	Et_2O/C_6H_6	$HC(OEt)_3$	57	134
Me	H	$CH(OEt)_2$ (I)	$CH(OEt)_2$	CH_2Cl_2	$HC(OEt)_3$	58	129
Me	H	H	CH(OH)Ph (Cl)	THF	PhCHO	41	152
Me	H	H	$C(OH)Ph_2$ (Cl)	THF	Ph_2CO	17	152
Me	H	H	$SiMe_3$ (Cl)	THF	Me_3SiCl	81	121
Me	H	Br	H (Br)	–	H_2O	–	121
Me	H	H	$CH(OEt)_2$ (Br)	Et_2O/C_6H_6	$HC(OEt)_3$	60	134
Me	H	Br	$SiMe_3$ (Br)	HMPT	Me_3SiCl	77	121
Me	H	H	$CH(OEt)_2$ (I)	Et_2O/C_6H_6	$HC(OEt)_3$	87	134
Me	H	I	$CH(OEt)_2$ (I)	Et_2O	$HC(OEt)_3$	68	129
CH_2Ph	H (Br)	Br	Br	Et_2O	aq. NH_4Cl	80	125
$CH_2C_6H_4OMe$-4	H (Br)	Br	Br	THF	aq. NH_4Cl	73	125
$CH_2C_6H_4OMe$-4	$C(OH)Ph_2$ (Br)	Br	Br	Et_2O	Ph_2CO	83	125

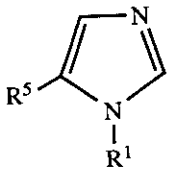
$CH_2C_6H_3(OMe)_2$-3,4	H (Br)	Br	Br	THF	aq. NH_4Cl	72	125
CH_2OMe	H (Br)	Br	Br	Et_2O	aq. NH_4Cl	73	125
CH_2OMe	SCH_2Ph	Br	H (Br)	Et_2O	aq. NH_4Cl	81	125
CH_2OEt	H (Br)	Br	Br	Et_2O	aq. NH_4Cl	80	125
CPh_3	H	$CH_2CH=CH_2$	H	THF	$CH_2=CHCH_2Br$	91[f]	158
CPh_3	H	2-Py	H	CH_2Cl_2	2-PyBr	66[g]	158
CPh_3	H	COPh	H	CH_2Cl_2	PhCN	54	158
CPh_3	H	CONHPh	H	CH_2Cl_2	*PhNCO*	82	158
CPh_3	H	CH(OH)Me (I)	H	THF	MeCHO	66	156
CPh_3	H	CH(OH)Me (I)	H	CH_2Cl_2	MeCHO	83	156
CPh_3	H	$CH(OH)(CH_2)_3CO_2Me$ (I)	H	CH_2Cl_2	$MeO_2C(CH_2)_3CHO$	63	156
CPh_3	H	$CH(OH)CH=CH_2$ (I)	H	CH_2Cl_2	$CH_2=CHCHO$	60	156
CPh_3	H	$CH(OH)CF=C(SMe)_2$ (I)	H	CH_2Cl_2	$(MeS)_2C=CFCHO$	72	157
CPh_3	H	CH(OH)Ph (I)	H	CH_2Cl_2	PhCHO	79	156
CPh_3	H	$C(OH)(C_6H_4Cl\text{-}4)_2$ (I)	H	THF	$(4\text{-}ClC_6H_4)_2CO$	53	156
CPh_3	H	$C(OH)(C_6H_4Cl\text{-}4)_2$ (I)	H	CH_2Cl_2	$(4\text{-}ClC_6H_4)_2CO$	69	156
CPh_3	H	$SiMe_3$	H	CH_2Cl_2	$Me_3SiOSO_2CF_3$	58	158
CPh_3	H	SePh	H	CH_2Cl_2	PhSeCl	86	158
CPh_3	H	tetrahydropyran-2-yl	H	CH_2Cl_2	phenyl tetrahydro-pyran-2-yl sulfone	53	158

CPh_3	H	*N*-formylpiperidin-2-yl	H	CH_2Cl_2	*N*-formylpiperidin-2-yl phenyl sulfone	65	158
Ph	COPh (H)	H	H	–	PhCN	85	36
Ph	CO(4-Py)[c] (H)	H	H	–	4-PyCN[c]	50-60	36
SEM[c]	H	CH(OH)Ph (I)	H	CH_2Cl_2	PhCHO	66	156
SO_2NMe_2	H	CH(OH)Me (I)	H	CH_2Cl_2	MeCHO	80	156
SO_2NMe_2	H	$CH(OH)(CH_2)_2CH{=}CMe_2$ (I)	H	CH_2Cl_2	$Me_2C{=}CH(CH_2)_2CHO$	83	156
SO_2NMe_2	H	 (I)	H	CH_2Cl_2	cyclopentanone	77	156
SO_2NMe_2	H	$CH_2CH(OH)Ph$[h]	H	CH_2Cl_2	2-phenyloxirane	26[h]	158
SO_2NMe_2	H	CH(OH)Ph (I)	H	CH_2Cl_2	PhCHO	83	156
SO_2NMe_2	H	$C(OH)Ph_2$(I)	H	CH_2Cl_2	Ph_2CO	82	156
SO_2NMe_2	H	$CH(OEt)_2$	H	CH_2Cl_2	$PhOCH(OEt)_2$	97	158

[a] With EtMgBr unless stated otherwise. [b] (H) or (Br) means metallation or halogen → metal exchange at the position indicated. [c] **ABBREVIATIONS USED**: 4-Py = pyrid-4-yl; SEM = $Me_3SiCH_2CH_2OCH_2$. [d] With EtMgCl. [e] With Mg. [f] Grignard reagent converted to cuprate through addition of CuCN.2LiCl. [g] Grignard reagent converted to zincate through addition of $ZnBr_2$; coupling with pyrid-2-ylBr required a catalytic quantity of $Pd(PPh_3)_4$. [h] Isomer with 4-substituent = $CHPhCH_2OH$ (41% yield) formed also.

Apart from this paper, however, there have been no other reports to date of polymetallation of imidazoles *via* the use of or formation of Grignard reagents. Table IX lists the imidazoles that have been prepared from Grignard reagents.

Imidazoles (**82**; R^1 = Me, CH_2Ph, Ph; R^5 = H, Cl) are metallated by phenylsodium in toluene in position-2[119,159] and the resulting sodio derivatives can be quenched with various electrophiles. Similar results are obtained with sodium naphthalenide.[134] A report[140] (see also ref. 119) that 1,2-dimethylimidazole is metallated exclusively in position-5 with phenylsodium has been shown to be incorrect; lateral metallation occurs instead in the 2-methyl group (Section V).[118]



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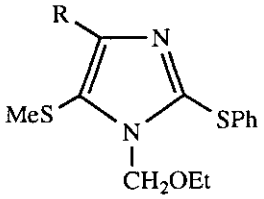
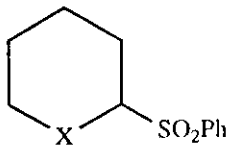


(83)

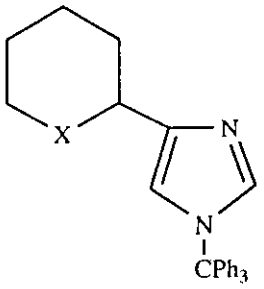
Potassium diisopropylamide-lithium *tert*-butoxide (KDA) (THF/-78 °C) metallates compound (**83**; R = H) in position-4; the resulting imidazol-4-yl anion was quenched with dimethyl disulfide, to give the tetrasubstituted imidazole (**83**; R = SMe).[12,117]

4-Allyl-1-triphenylmethylimidazole (91% yield) can be prepared by successive addition of CuCN.2LiCl (THF in this case) and allyl bromide to 1-triphenylmethylimidazol-4-ylmagnesium bromide (see below).[158] Addition of zinc chloride to the Grignard compound to give the 4-zincate, followed by addition of tetrahydropyranyl (**84**) or



(**84**) X = O

(**85**) X = NCHO

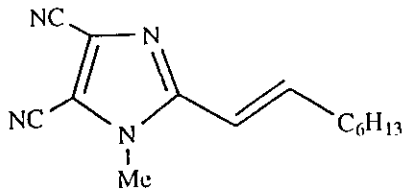


(**86**) X = O

(**87**) X = NCHO

piperidyl sulfone (**85**), gave the corresponding derivative (**86**; 53%) or (**87**; 65%), respectively.[158] Addition of zinc bromide followed by a catalytic quantity of $Pd(PPh_3)_4$, then 2-bromopyridine gave 4-pyrid-2-yl-1-triphenylmethylimidazole (66% yield).[158]

The presence of two cyano groups in 2-bromo-4,5-dicyano-1-methylimidazole allows insertion of zinc into the C-Br bond.[160] The resulting organozinc bromide can be coupled with 1-iodooct-1-ene using *bis*(benzylidene-acetone)palladium(0) [$Pd(dba)_2$] and triphenylphosphine as catalyst, to give the alkene (**88**) (41% yield).



(**88**)

2-Fluoro-1-triphenylmethylimidazol-4-ylcopper has been synthesised by reacting the corresponding lithium derivative with cuprous iodide and quenching with allyl bromide (see previously in this Section).[105]

Imidazole is mercurated in the 4(5)-position and its 4(5)-alkyl derivatives are mercurated adjacent to the alkyl group.[161,162] These mercurated derivatives react with $^{211}At/I_2$ to give ^{211}Atastatoimidazoles.

We have referred throughout this review to the synthesis and application of various silicon and tin derivatives of imidazole.

ACKNOWLEDGEMENTS

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† 19 References not covered in this review can be found in the Tables of our earlier review.[8]

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