METALLATION AND METAL-HALOGEN EXCHANGE REACTIONS OF IMIDAZOLES

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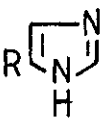
Abstract - Imidazoles synthesised via organometallic derivatives, particularly organolithium derivatives prepared by metallation and metal-halogen exchange reactions, are reviewed.

Contents:

1. INTRODUCTION

Despite the considerable industrial importance of imidazoles and the widespread interest in their chemistry[1-4] many simple imidazoles are not readily accessible. Thus, for example, 4(5)-methoxyimidazole (1) was unknown until recently[5,6] and a synthesis of imidazole-4(5)-thiol (2) has



(1) R = OMe

(2) R = SH

not been reported as far as we are aware. It appears to us, therefore, that there is a need for further versatile syntheses of imidazoles, preferably starting from cheap, commercially available,

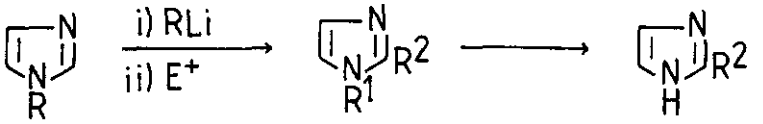
materials such as the parent ring system which, at the time of writing, costs around £12.50/kg (for small quantities).

Surprisingly, with the exception of imidazol-2-yl-lithium reagents, the use of organometallic derivatives of imidazoles in synthesis has not been exploited.[7] Thus, in order to promote the use of such reagents, we assemble here the already published literature. First we review organolithium reagents, then cover the sparse literature on other organometallic derivatives.

2. ORGANOLITHIUM DERIVATIVES

2.1 Monolithiated Derivatives Prepared by Metallation in the Ring

Since the early work of Shirley and Alley[8] in 1957 and Roe[9] in 1963 successive metallation of suitably 1-protected imidazoles and reaction of the resulting imidazol-2-yl-lithium compounds with a variety of electrophiles has yielded a range of 1,2-di- (Table 1) and poly-substituted imidazoles (Table 2) (Scheme 1). The advantages and disadvantages of the various protecting groups and their



SCHEME 1

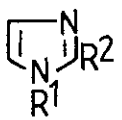
ease of removal have been discussed in a recent paper by Chadwick and Ngochindo.[10] Imidazoles not protected at the ring nitrogen atom are metallated in this position and the resulting 1-lithio-derivatives can be alkylated.[11,12]

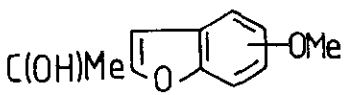
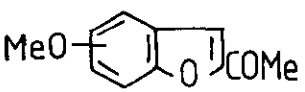
1-Methylimidazole has been studied more than any other compound (Table 1), presumably because it is commercially available. The report[8] that it metallates with n-butyl-lithium mainly in the 2-position but also to a minor extent (< 2%) in the 5-position was based on isolation of the two monocarboxylic acids following carbonation of the mixture. Chadwick and Ngochindo[10] have shown, however, that the 5-carboxylic acid arises by decarboxylation of the imidazole-2,5-dicarboxylic acid (see ref. 40; this refers also to the sensitivity of imidazole-2-carboxylic acids to decarboxylation) which arises by carbonation of a trace of the 2,5-dilithiated derivative. When the reaction mixture is treated with ethereal diazomethane prior to work-up, dimethyl 1-methylimidazole-2,5-dicarboxylate can be isolated.[10]

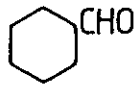
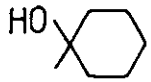
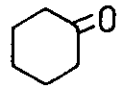
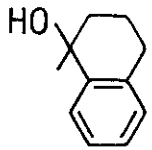
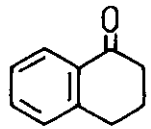
The claim made by Japanese workers[13] that 1-benzylimidazole metallates to a significant extent in the 5-position is probably a mistake.[10] The reaction mixture was quenched with 2,3:5,6-di-O-isopropylidene-L-gulono-1,4-lactone, which gave two products; the major product (30% yield) was derived from 1-benzylimidazol-2-yl-lithium whilst the other (12% yield) was assumed to be that (3) derived from 1-benzylimidazol-5-yl-lithium. However, Breslow et al.[14] and Chadwick and Ngochindo[10] have found that 1-benzylimidazole can metallate to a significant extent in its methylene group as well as in the 2-position; the extent of benzylic metallation increases with temperature and the

TABLE 1

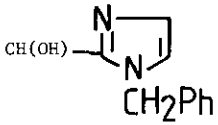
SYNTHESIS OF 1,2-DISUBSTITUTED IMIDAZOLES VIA METALLATION OF 1-SUBSTITUTED IMIDAZOLES

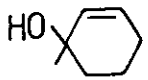
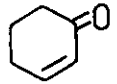
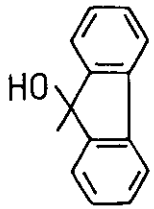
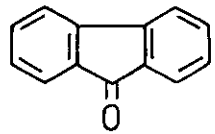
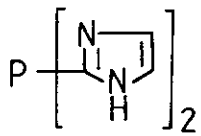


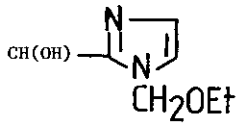
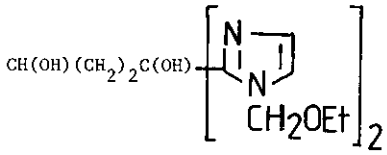
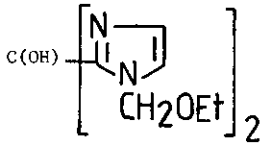
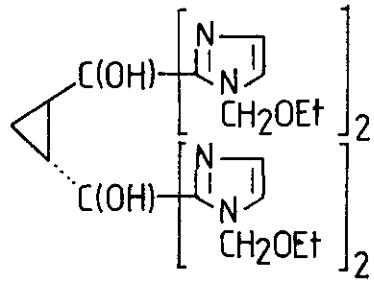
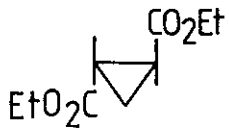
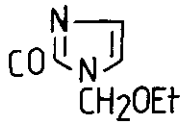
R^1	R^2	Reagent	Yield (%)	Ref.
Me	Me	Me_2SO_4	68	15
Me	F	$FClO_3$	55	16
Me	Br	Br_2	80	16
Me	I	I_2	95,69,80	16,17,18
Me	SMe	Me_2S_2	24[a]	19
Me	CO_2H	CO_2	32-39[b]	8
Me	CO_2Me	$ClCO_2Me$	48[c]	19
Me	CO_2Et	$ClCO_2Et$	10	8
Me	CHO	DMF	65	15
Me	*CH(OH)*Me	MeCHO	35	20
Me	$C(OH)Ph_2$	Ph_2CO	16[d],86,40-87[e],-	19,8,21,22
Me	C(OH)MePh	PhCOMe	—	22
Me	$C(OH)Bu^nPh$	$PhCOBu^n$	—	22
Me	$C(OH)MeC_6H_{13}$-n	$MeCOC_6H_{13}$-n	—	22
Me			—	22

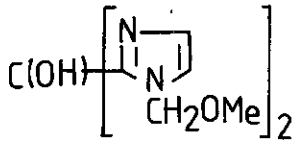
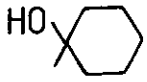
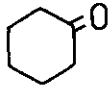
Me	CH(OH)pyrid-2-yl	C_5H_4NCHO-2	48	9
Me	CH(OH)pyrid-3-yl	C_5H_4NCHO-3	33	9
Me	$CH(OH)C_6H_3(OMe)_2$-3,4	$3,4-(MeO)_2C_6H_3CHO$	23	9
Me	$CH(OH)C_6H_4(-OCH_2O-)$-3,4	$3,4-(-OCH_2O-)C_6H_4CHO$	—	22
Me	$CH(OH)C_6H_4NMe_2$-4	$4-Me_2NC_6H_4CHO$	48	9
Me	$CH(OH)C_6H_{13}$-n	$n-C_6H_{13}CHO$	41,—	9,22
Me	$CH(OH)CH_2CHMe(CH_2)_2CH=CMe_2$	$Me_2C=CH(CH_2)_2CHMeCH_2CHO$	—	22
Me	$CH(OH)CH_2Ph$	$PhCH_2CHO$	44	9
Me	$CH(OH)C_6H_{11}$		—	22
Me			56	9
Me			—	22
Me	CH(OH)(mim)[f]	(mim)CHO[f]	43	23
Me	CH(OH)(mim)[f]	HCO_2Et	44	14
Me	$C(OH)(CH_2SH)_2$[g]	$(EtOCH_2SCH_2)_2CO$	17	24

Me	$C(OH)(mim)_2$[f]	$(EtO)_2CO$	30	14
Me	$C(OH)(mim)_2$[f] + (mim)CO	$(EtO)_2CO$	4 … 34	23 (see also ref. 25)
Me	$C(OH)(py)_2$[h]	$(py)_2CO$[h]	61,—	25,23
Me	$C(OH)(6\text{-D-py})_2$[h]	$(6\text{-D-py})_2CO$[h]	—	25
Me	$C(OH)(mim)_2$[f]	$(mim)_2CO$[f]	8	23
Me	C(OH)(mim)(py)[h]	(py)(mim)CO[f,h]	23	23
Me	C(OH)(mim)(py)[h]	$(py)CO_2Et$[h]	9	25
Me	CO(py)[h]	$(py)CO_2Et$[h]	51	23
Me	CO(mim)[f]	$(mim)CO_2Et$[f]	34	23
Me	NO_2	N_2O_4	—	26
Me	NHN=NPh	PhN_3	70[i]	27
Me	CONH(α-naphthyl)	α-naphthylNCO	66	8
Me	$SnMe_3$	$ClSnMe_3$	86	28
Me	$SiMe_3$	$ClSiMe_3$	—,56,20-30	29,30,31
Me	$SiMe_2Ph$	$ClSiMe_2Ph$	—	32
Me	$SiPh_3$	$ClSiPh_3$	—	32
Me	$SiMe_2(mim)$[f]	Cl_2SiMe_2	56	30
Bu^n	Me	MeI	—	33
Bu^t	$C(OH)Ph_2$	Ph_2CO	98	10
CH_2Ph	Me	Me_2SO_4	81	15
CH_2Ph	Me	MeI	69	10
CH_2Ph	CO_2H	CO_2	67,85	8 (see also ref. 14),34
CH_2Ph	CHO	DMF	68	15

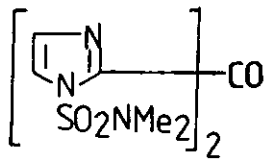
CH_2Ph	CH_2OH	HCHO	—	34
CH_2Ph	CH(OH)Me	MeCHO	22	9
CH_2Ph	CH(OH)Ph	PhCHO	48,—	9,35
CH_2Ph		HCO_2Et	22	9
CH_2Ph	quinol-2-yl	*quinoline*	29	8
CHMePh	Me	MeI	64	10
Ph	I	I_2	72	17
Ph	CO_2H	CO_2	60[b]	8
Ph	CO_2Et	$ClCO_2Et$	5	8
Ph	$C(OH)Ph_2$	Ph_2CO	76	8
Ph	CONHPh	PhNCO	39	8
Ph	NO_2	N_2O_4	—	26
CPh_3	Me	MeI	—,[j]95	10,36
CPh_3	Cl	NCS[k]	<5	36
CPh_3	Cl	Bu^tOCl	39	36
CPh_3	Br	NBS[k]	35	36
CPh_3	I	I_2	41	36
CPh_3	I	NIS[k]	40	36
CPh_3	CO_2Et	$ClCO_2Et$	90	36
CPh_3	CHO	DMF	98	36
CPh_3	NO_2	Pr^nONO_2	30	37

CPh_3	NO_2	$C(NO_2)_4$	—	37
CPh_3	NHN=NPh	PhN_3	95	36
quinol-3-yl	D	D_2O	82	38
quinol-3-yl	For an explanation of the preparation of compound (8) see text.		55	38,39
$CH(OEt)_2$[1]	Bu^n	Bu^nI	84	40
$CH(OEt)_2$[1]	CO_2H	CO_2	60	40
$CH(OEt)_2$[1]	COMe	$MeCONMe_2$	80	40
$CH(OEt)_2$[1]	CH(OH)Ph	PhCHO	77	40
$CH(OEt)_2$[1]	$C(OH)Ph_2$	Ph_2CO	72	40
$CH(OEt)_2$[1]			49	40
$CH(OEt)_2$[1]	$C(OH)Me(py)$[h]	(py)COMe[h]	64	40
$CH(OEt)_2$[1]			84	40
$CH(OEt)_2$[1]	$C(OH)(CH_2SH)_2$[g]	$(EtOCH_2SCH_2)_2CO$	20	24
$CH(OEt)_2$[1]	$C(OH)(CH_2SCH_2OEt)_2$	$(EtOCH_2SCH_2)_2CO$	36	40
$CH(OEt)_2$[1]		PCl_3	36	40

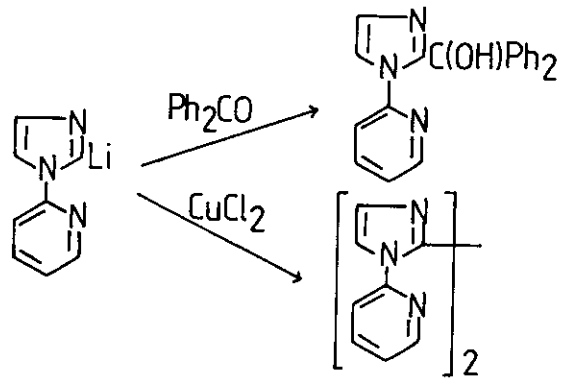
CH_2OEt	SPh	Ph_2S_2	—	14
CH_2OEt	$C(OH)Ph_2$	Ph_2CO	81	41
CH_2OEt	$C(OH)(py)_2$[h]	$(py)_2CO$[h]	36	25
CH_2OEt		$PhCOCO_2Et$	—	42
CH_2OEt		$MeO_2C(CH_2)_2CHO$	39.5	42
CH_2OEt		$(EtO)_2CO$	50–70	14
CH_2OEt			32	42
CH_2OEt		$(EtO)_2CO$	23	42

CH_2OMe	SMe	Me_2S_2	—	14
CH_2OMe	SPh	Ph_2S_2	—	14
CH_2OMe	CH(OH)Ph	PhCHO	45	9
CH_2OMe		$(EtO)_2CO$	—	14
SO_2Ph	D	D_2O	100	43
SO_2Ph	I	I_2	6.5	43
SO_2Ph	CH_2OH	HCHO	10	43
SO_2Ph	CH(OH)Ph	PhCHO	18	43
SO_2Ph			15	43
SO_2NMe_2	D	D_2O	25 (isolated)	10
SO_2NMe_2	Me	MeI or Me_2SO_4	82	10
SO_2NMe_2	CO_2Me^m	$ClCO_2Me$	—	10
SO_2NMe_2	CH_2CH_2OH		25	10
SO_2NMe_2	$C(OH)Ph_2$	Ph_2CO	60 (isolated)	10
$SiMe_3$	$SiMe_3$	$ClSiMe_3$	14	44

Footnotes: [a] 53% of 2,5-disubstituted compound formed also (see text). [b] Isolated as the copper(II) complex. [c] 19% 2,5-disubstituted compound formed also (see text). [d] 69% 2,5-disubstituted compound formed also (see text). [e] Lithium naphthalenide used also as the metallating reagent. [f] (mim) = 1-methylimidazol-2-yl. [g] After deprotection of product. [h] (py) = pyrid-2-yl; (mim).[f] [i] Yield quoted is that of the amine hydrochloride prepared by hydrolysis of the triazene with hydrochloric acid. [j] 2,5-Dimethyl derivative formed also, ratio 64:36 (mono:di). [k] NCS, NBS, and NIS are N-chloro-, N-bromo- and N-iodo-succinimide, respectively. [l] On work-up this labile protecting group was removed: yields quoted are for deprotected compound. [m] This reaction also yields the ketone (ratio 4:1):



ADDENDUM: The following reactions were discovered too late for inclusion into Table 1:



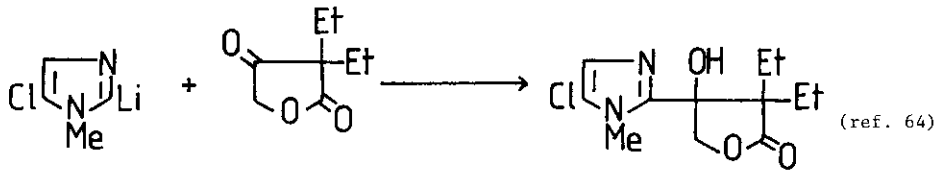
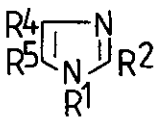
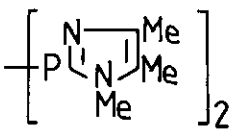
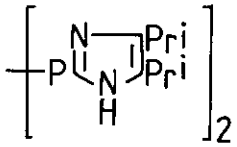
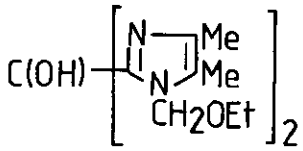
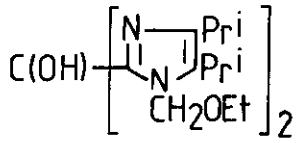


TABLE 2

SYNTHESIS OF POLYSUBSTITUTED IMIDAZOLES VIA METALLATION IN THE 2-POSITION

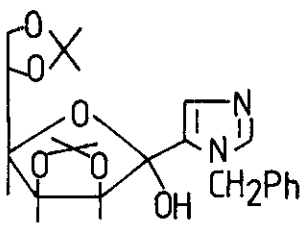


R^1	R^2	R^4	R^5	Reagent	Yield (%)	Ref.
Me	I	H	Cl	I_2	54,69	17,45
Me	CH(OH)Me	H	Me	MeCHO	30	20
Me	CH(OH)Me	H	Cl	MeCHO	64	20
Me	CH(OH)Me	Me	H	MeCHO	—	20
Me	CH(OH)Me	Ph	H	MeCHO	62	20
Me	CH(OH)Me	Cl	H	MeCHO	48	20
Me	CH(OH)Me	Br	H	MeCHO	—	20
Me	CH(OH)Me	Me	Me	MeCHO	24	20
Ph	I	H	Cl	I_2	54	17
CPh_3	NO_2	Me	H	Pr^nONO_2	50[a]	37
CPh_3	NO_2	CH_2OH	H	Pr^nONO_2	29[a]	37
$CH(OEt)_2$	CHO	Me	Me	DMF	82[b]	40
$CH(OEt)_2$		Me	Me	PCl_3	46[b]	40

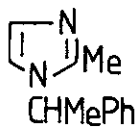
$CH(OEt)_2$		Pr^i	Pr^i	PCl_3	55[b]	40
CH_2OEt		Me	Me	$(EtO)_2CO$	50	25
CH_2OEt		Pr^i	Pr^i	$(EtO)_2CO$	62	25
Me[c]	CHO	Br	H	DMF	52	46
Me[c]	Br	Br	H	Br_2	87	16
Me[d]	I	I	H	I_2	53	16

Footnotes: [a] Yield quoted is after removal of trityl group with acid. [b] After deprotection of initial product. [c] In this case the starting material was 4,5-dibromo-1-methylimidazole. [d] In this case the starting material was 4,5-di-iodo-1-methylimidazole.

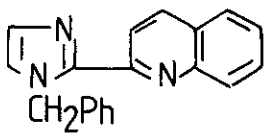
amount of n-butyl-lithium used.* At 20°C and with a ratio of n-butyl-lithium to imidazole of 2.0:1 compound (4) (64% yield) can be isolated after addition of iodomethane.[10] 1-Benzylimidazol-2-yl-lithium reacts with quinoline in the expected manner, to give the product (5) arising from initial azomethine bond addition.[8]



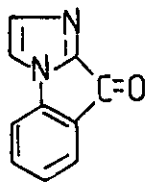
(3)



(4)



(5)



(6)

1-Phenylimidazole is metallated normally in the 2-position with one mol. equiv. of n-butyl-lithium (Table 1) but, with three mol. equiv. of this reagent, metallation occurs both in the 2-position and in the ortho-position of the substituent, as shown by isolation of a low yield (5%) of compound (6) following successive treatment of the product with carbon dioxide and acid.[8]

n-Butyl-lithium is the reagent most often used to metallate 1-substituted imidazoles but other organolithium reagents, such as methyl-lithium, have been employed. Lithium di-isopropylamide (LDA) metallates 1-(quinol-3-yl)imidazole in the 2-position in tetrahydrofuran (THF).[38,39] However, the initially generated 2-lithio-derivative undergoes azomethine bond addition with the starting material, to give an intermediate (7) (Scheme 2) which is metallated further in the vacant imidazole 2-position. This is followed by intramolecular azomethine bond addition and isolation of the racemic macrocyclic dimer (8) following hydrolysis of the resulting dilithium compound with water and oxidation of the product with potassium permanganate.[38,39]

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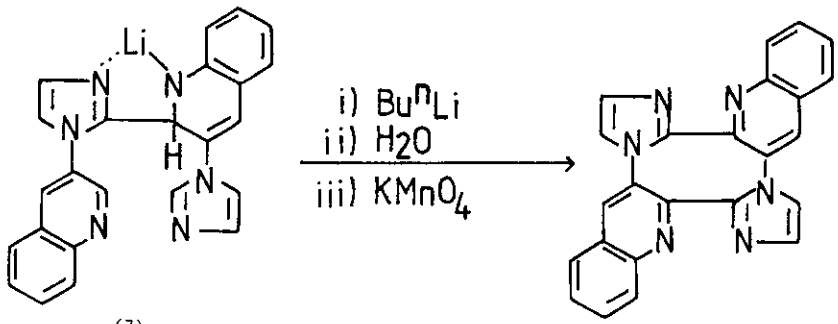
*1-Benzylpyrazoles are metallated faster in the benzylic methylene group but the products rearrange: A.R. Katritzky, C. Jayaram, and S.N. Vassilatos, Tetrahedron, 1983, 39, 2023; see also A.R. Katritzky, A.E. Abdel-Rahman, D.E. Leahy, and O.A. Schwarz, Tetrahedron, 1983, 39, 4133.

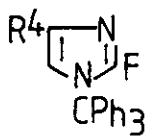


(7) (8)

SCHEME 2

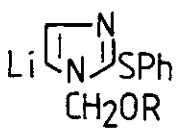
Tertov and Morkovnik[21] used lithium naphthalenide to metallate 1-methylimidazole and trapped the 2-lithio-derivative with benzophenone (Table 1). 1-Phenylimidazole, by contrast, was not metallated by this reagent, nor with sodium naphthalenide.[21]

Interestingly, and presumably because of steric hindrance from the 1-substituent, 2-fluoro-1-triphenylmethylimidazole is metallated directly in the 4-position by t-butyl-lithium in THF, even at -75°C! The resulting imidazol-4-yl-lithium compound (9) reacts with NN-dimethylformamide (DMF) to give a good yield of the aldehyde (10).[47]



(9) R^4 = Li

(10) R^4 = CHO



(11) R = Me

(12) R = Et

Literature claims to the synthesis of 1-benzyl- and 1-methyl-imidazol-5-yl-lithium have been mentioned already in this Section; in the next Section we refer to 1,2-dimethylimidazol-5-yl-lithium. The two imidazol-5-yl-lithium compounds (11) and (12) have been prepared by Breslow and coworkers[14] by direct metallation of 1-methoxy(or ethoxy)methyl-2-phenylthioimidazole with LDA; use of n-butyl- or t-butyl-lithium was reported by this group to result in C-S bond cleavage. However, we have used n-butyl-lithium to prepare these lithium compounds without becoming aware of this problem.[12,41] 1-Ethoxymethyl-2-phenylimidazole is metallated similarly in the 5-position with n-butyl-lithium in THF.[42] Several 1,2,5-trisubstituted imidazoles (Table 3) have been prepared from these imidazol-5-yl-lithium compounds.

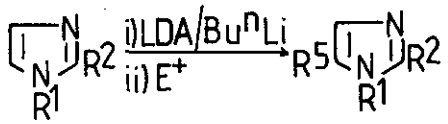
Monolithiated imidazoles are available also *via* metal-halogen exchange reactions (Section 2.4).

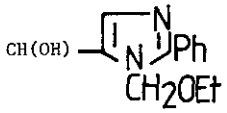
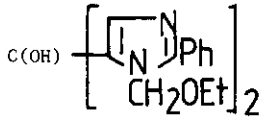
2.2 Lateral Metallation

In 1967, Tertov *et al.*[48] reported that 1,2-dimethylimidazole is metallated exclusively in the

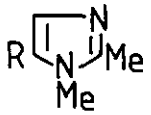
TABLE 3

SYNTHESIS OF 1,2,5-TRISUBSTITUTED IMIDAZOLES BY METALLATION OF 1,2-DISUBSTITUTED IMIDAZOLES

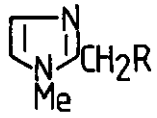


R^1	R^2	R^5	Reagent	Yield (%)	Ref.
CH_2OMe	SPh	CH(OH)Ph	PhCHO	38	14
CH_2OMe	SPh	$C(OH)(im)_2$[a]	$(EtO)_2CO$	70	14
CH_2OMe	SPh	CH(OH)(im)[a]	HCO_2Et	—	14
CH_2OEt	Ph	CH_2OH	HCHO	—	42
CH_2OEt	Ph	CO_2Et	$ClCO_2Et$	—	42
CH_2OEt	Ph		HCO_2Me	70	42
CH_2OEt	Ph		$(EtO)_2CO$	85-92	42
CH_2OEt	SPh	CO_2H	CO_2	99	12,41
CH_2OEt	SPh	SMe	Me_2S_2	83	12,41
CH_2OEt	SPh	SPh	Ph_2S_2	100	12,41
CH_2OEt	SPh	$SCH_2CH(OEt)_2$	$[(EtO)_2CHCH_2S]_2$	31	12,41
CH_2OEt	SPh	$CH(OH)C_6H_4Me$-4	$4\text{-}MeC_6H_4CHO$	62	12,41
CH_2OEt	SPh	$C(OH)(im)CONMe_2$[a]	$EtO_2C.CONMe_2$	—	14

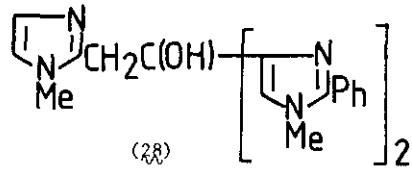
Footnote: [a] (im) = *1-ethoxy(or methoxy)-2-phenylthioimidazol-5-yl.*



(13) R = $C(OH)Ph_2$
(14) R = CH(OH)Ph
(15) R = CHO
(16) R = I
(17) R = Br
(18) R = D
(19) R = SMe
(20) R = $SiMe_3$
(21) R = $SnMe_3$
(22) R = $SnBu^n_3$



(23) R = $C(OH)Ph_2$
(24) R = CH(OH)Ph
(25) R = CH(OH)pyrid-2-yl
(26) R = $CH(OH)C_6H_4Me$-4
(27) R = SMe

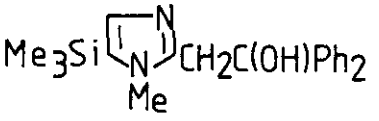


(28)

5-position (a similar claim was made for its reaction with phenylsodium; Section 4); they reacted the product with benzophenone (73% yield of product), benzaldehyde (59.5%), DMF (20%), iodophenylacetylene (48%), and N-bromodiethylamine (26%), to give what they claimed to be compounds (13)-(17), respectively, in the yields, indicated. However, in 1974 and 1975, respectively Noyce et al.[49] (using n-Bu^nLi in Et_2O) and Godefroi et al.[50] (using PhLi in C_6H_6) showed, using benzaldehyde as the trapping reagent, that the picture was not quite so clear cut; both groups isolated different mixtures of the two alcohols (14) and (24), depending on the organolithium reagent used and the reaction conditions. To further complicate matters, a report[51] appeared in 1979 that metallation of 1,2-dimethylimidazole with n-butyl-lithium in ether at -15°C and reaction of the product with pyridine-2-carbaldehyde gave only the alcohol (25) arising from exclusive lateral metallation. Similarly, lateral metallation of 1,2-dimethylimidazole with n-butyl-lithium in THF and condensation of the product with di(1-methyl-2-phenylimidazol-4-yl) ketone is claimed[42] to give exclusively compound (28) (19% yield).

We[52] have studied the metallation of 1,2-dimethylimidazole under a variety of reaction conditions and shown that, after quenching reaction mixtures with suitable reagents, single products may arise from lateral metallation in the 2-methyl group [e.g. compounds (25) and (26)] or from metallation in the 5-position [e.g. compounds (18) and (20)-(22)] or mixtures of both products [e.g. mixtures of compounds (13) and (23) or (19) and (27)] may arise, depending on the metallating reagent and reaction conditions. The nature of the product appears to be related to the "hardness" or "softness" of the quenching reagent.[52] The product isolated by Tertov et al.[48] using benzophenone as the trapping reagent and believed to be alcohol (13) was shown[52] to be alcohol (23) (both alcohols are produced and are separable by fractional crystallisation). Exclusive lateral metallation in the 2-methyl group is possible under a variety of reaction conditions (Bu^nLi/TMEDA*/Et_2O; Bu^nLi/THF; LDA/Et_2O; Bu^nLi/Et_2O but only at -110°C!; or PhNa/Et_2O - see Section 4).

1,2-Dimethyl-5-trimethylsilylimidazole (20) is metallated exclusively by n-butyl-lithium in its 2-methyl group, as shown by quenching the product with benzophenone, which gives only alcohol (29).[52] When the corresponding tin compound (21) is subjected to the same reaction conditions,



(29)

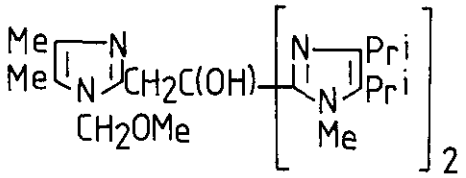
however, the only isolable product is alcohol (23). This suggested to us that the initially generated 1,2-dimethylimidazol-5-yl-lithium undergoes transmetallation reactions at this temperature

*TMEDA is NNN'N'-tetramethylethylenediamine.

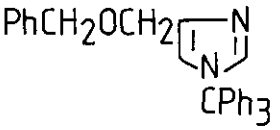
prior to addition of the quenching reagent. When the tin compound (21) was treated with n-butyl-lithium in ether but at -110°C, then quenched with benzophenone or dimethyl disulphide, it gave only compound (13) or (19), respectively.[52] If the solution of the lithium compound was allowed to warm up prior to quenching with benzophenone, then a mixture of alcohols (13) and (23) was obtained.

We consider that 1,2-dimethylimidazole is metallated faster in the 2-methyl group than in the 5-position and that transmetallation reactions occur *if the initially generated lithium compound is* allowed to stand, especially at higher temperatures.

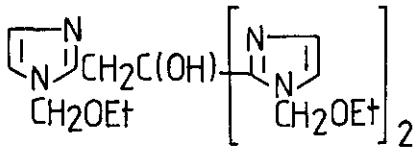
1-Methoxymethyl-2,4,5-trimethylimidazole is metallated exclusively in its 2-methyl group and the resulting lithium derivative reacts with di(4,5-di-isopropyl-1-methylimidazol-2-yl) ketone to give compound (30) following hydrolysis of the mixture.[25] Compound (31) may be prepared similarly (33.5% yield) via lateral metallation of 1-ethoxymethyl-2-methylimidazole with n-butyl-lithium in THF and condensation of the product with di(1-ethoxymethylimidazol-2-yl) ketone.[42] Reaction of 1-ethoxymethyl-2-lithiomethylimidazole with diethyl carbonate is claimed[42] to give ethyl 2-(1-ethoxymethylimidazol-2-yl)acetate (23% yield). 1-Methoxymethyl-2-methylthioimidazole is metallated in its 2-methylthio-group[14] whilst 4-benzyloxymethyl-1-triphenylmethylimidazole (32) is metallated



(30)



(32)



(31)

in the methylene group attached to the ring at C-4.[37] We have referred already (Section 2.1) to metallation of 1-benzylimidazole in its benzylic methylene group.

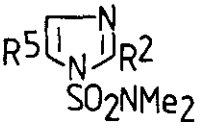
2.3 Dilithiated Derivatives Prepared by Metallation in the Ring

The first dilithiated derivative of imidazole, reported in 1973, was prepared by metallation of 1-methylimidazole with two mol. equiv. of n-butyl-lithium; addition of chlorotrimethylsilane gave a low yield (32%) of 1-methyl-2,5-bis(trimethylsilyl)imidazole.[30] Chadwick's group at Liverpool have studied in detail 2,5-dilithiation of 1-methyl-,[19] 1-triphenylmethyl-,[10] and 1-methoxymethyl-imidazole,[10] and NN-dimethylimidazole-1-sulphonamide (33; $R^2 = R^5 = H$)[10] (see Table 4, which illustrates the synthetic usefulness of these reactions).

With 1-methylimidazole, 1,2,5-trisubstituted products can be obtained following addition of suitable quenching reagents, by using a 5:1 mole ratio of n-butyl-lithium to 1-methylimidazole,

ether or hexane as the solvent, preferably with addition of TMEDA, and a temperature in excess of 20°C.[19] In most cases (Table 4) mixtures of 1,2,5-tri- and 1,2-di-substituted products are obtained; deuterium oxide, however, gives a 90-98% yield of 2,5-dideuterio-1-methylimidazole, which suggests that the mixtures obtained in the other reactions arise through incomplete reaction of the 2-anion.[19] 1-Methylimidazole-2,5-dicarboxylic acid readily decarboxylates in the 2-position (Section 2.1) whilst 1-methyl-2,5-bis(trimethylsilyl)imidazole is hydrolysed readily by water on work-up, to give 1-methyl-5-trimethylsilylimidazole.[19]

By contrast to the reaction conditions necessary to dimetallate 1-methylimidazole[19] and other 1-substituted imidazoles[10] (Table 4) with n-butyl-lithium, NN-dimethylimidazole-1-sulphonamide



(33)

(33; $R^2 = R^5 = H$) is dimetallated by the same reagent in 15 min. in dimethoxyethane (DME) at temperatures < -15°C and in the absence of TMEDA. Addition of a suitable electrophile allows the preparation of the corresponding 1,2,5-trisubstituted imidazole (Table 4). Whilst this 1-protecting group is stable to cold acid it can be removed by hot 2M-aqueous hydrochloric acid thus giving rise to a route to 2,5-disubstituted imidazoles (33).[10]

If only one mol. equiv. of the quenching electrophile is added to the 2,5-dilithiated compound (33; $R^2 = R^5 = Li$) and the product hydrolysed, then only the 5-mono-substituted compound (33; $R^2 = H$) is isolated.[10] Removal of the protecting group thus provides a route to 4(5)-mono-substituted imidazoles. The 2,5-dilithiated species (33 ; $R^2 = R^5 = Li$) reacts considerably faster with electrophiles in the 5-position than in the 2-position.

Further work is necessary on 1-protecting groups. It is doubtful whether the same protecting group will be useful under all circumstances and the choice of the protecting group will probably depend on the sequence of reactions to be followed in each case.

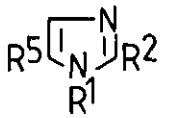
Di- and tri-lithiated imidazoles are also available via metal-halogen exchange reactions (next Section).

2.4 Mono- and Poly-Lithiated Derivatives Prepared by Metal-Halogen Exchange Reactions

A number of 2-substituted imidazoles have been prepared via replacement of a 2-bromine (or iodine) atom with lithium and reaction of the resulting imidazol-2-yl-lithium compound with a suitable electrophile (Table 5); halogen-metal exchange reactions are usually carried out at low temperatures (-50 to -110°C).

TABLE 4

SYNTHESIS OF 1,2,5-TRISUBSTITUTED IMIDAZOLES BY 2,5-DILITHIATION OF 1-SUBSTITUTED IMIDAZOLES



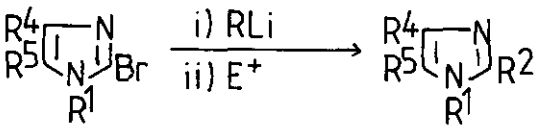
R^1	R^2	R^5	Reagent	Yield (%)	Ref.
Me	D	D	D_2O	90-98	19
Me	I	I	I_2	59	16
Me	CO_2H	CO_2H	CO_2	9	19
Me	CO_2Me	CO_2Me	$ClCO_2Me$	19[a]	19
Me	$C(OH)Ph_2$	$C(OH)Ph_2$	Ph_2CO	69[b]	19
Me	SMe	SMe	Me_2S_2	53[c]	19
Me	$SiMe_3$	$SiMe_3$	$ClSiMe_3$	32,-[d]	30,19
CPh_3	Me	Me	MeI	64[e]	10
CH_2OMe	D	D	D_2O	65-92	10
CH_2OMe	Me	Me	MeI	86	10
CH_2OMe	CH(OH)Ph	CH(OH)Ph	PhCHO	84	10
CH_2OMe	$COCMe_3$	$COCMe_3$	Me_3COCl	81	10
SO_2NMe_2	D	D	D_2O	90-98	10
SO_2NMe_2	Me	Me	MeI	53	10
SO_2NMe_2	CH_2CH_2OH	CH_2CH_2OH		61[f]	10

Footnotes: [a] 48% methyl 1-methylimidazole-2-carboxylate formed also by 2-monolithiation. [b] 16% 2-monolithiation. [c] 24% 2-monolithiation. [d] Not isolated; converted by hydrolysis into 1-methyl-5-trimethylsilylimidazole (58% yield). [e] 36% 2-methyl-1-triphenylmethylimidazole obtained also. [f] 39% product from 5-monolithiation (ratio by ^1H n.m.r. spectroscopic analysis).

A free ring NH— group, if present, is metallated first. Thus, when we[11,12] reacted 4(5)-bromoimidazole with one or two mol. equiv. of n-butyl-lithium in ether or THF and quenched the resulting mixture with dimethyl sulphate, only a mixture of 4- (34) and 5-bromo-1-methylimidazole (35) (ratio 1:2) (Scheme 3) was isolated in high yield. 2,4,5-Tribromoimidazole can be methylated similarly on nitrogen.[11]

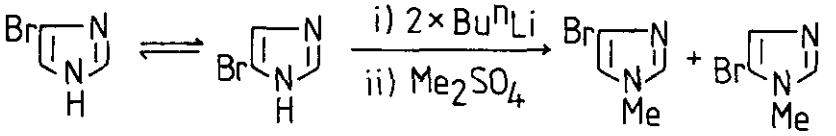
TABLE 5

2-SUBSTITUTED IMIDAZOLES PREPARED BY METAL HALOGEN EXCHANGE REACTIONS[a]



R^1	R^2	R^4	R^5	Reagent	Yield (%)	Ref.
H[b]	$CH(OH)C_6H_3(OMe)_2$-2,3	Cl	Cl	ArCHO	44	53
H[b]	$CH(OH)C_6H_3(OMe)_2$-2,5	Cl	Cl	ArCHO	—	53
H[b]	$CH(OH)C_6H_3(OMe)_2$-3,4	Cl	Cl	ArCHO	—	53
Me	H	H	Br	H_2O	—	16
Me(I)	H	H	I	H_2O	90	16
Me(I)	F	H	I	$FClO_3$	49	16
Me	CHO	H	Br	DMF	57	46
Me	NO_2	H	Pr^i	N_2O_4	—	54
Me	H	Br	H	H_2O	—	16
Me	H	Br	Br	H_2O	—	16
Me(I)	H	I	I	H_2O	—	16
Me	CHO	Br	Br	DMF	60	46
CH_2OEt	SPh	Br	Br	Ph_2S_2	67	11

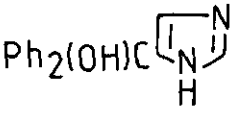
Footnotes: [a] Bromine exchange unless otherwise indicated. [b] Two equivalents of organolithium reagent used to generate 1,2-dilithiated species.



SCHEME 3

(34) (35)

Stensiö et al.,[55] however, prepared 4(5)-deuterioimidazole by treating 4(5)-bromoimidazole in THF successively with almost five mol. equiv. of n-butyl-lithium, deuteriomethanol, and acid. Use of methanol in place of deuteriomethanol gave an almost quantitative yield of imidazole.

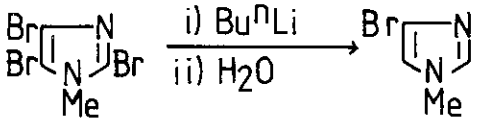


(36)

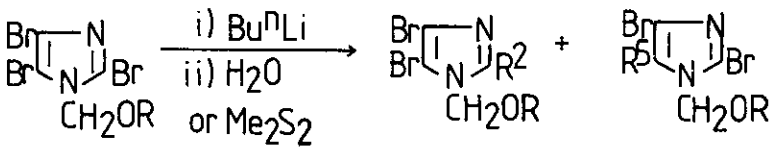
Treatment of 4(5)-bromoimidazole with two mol. equiv. of lithium naphthalenide followed by quenching the product with benzophenone yields alcohol (36) (60% yield).[56] We confirmed this result but failed to synthesise other 4(5)-substituted imidazoles by this route.

2-Bromo-4,5-dichloroimidazole undergoes successive metallation and metal-halogen exchange with two mol. equiv. of n-butyl-lithium and the resulting 1,2-dilithio-derivative condenses with various aldehydes, to give the corresponding 2-substituted 4,5-dichloroimidazole (Table 5).[53]

Stensiö et al.[55] converted 2,4,5-tribromoimidazole into 4(5)-bromoimidazole by treating it successively with four mol. equiv. of n-butyl-lithium and methanol. Small amounts of 4(5)-bromo-5-(4)-n-butylimidazole and 4,5-dibromoimidazole were formed also. 2,4,5-Tribromo-1-methylimidazole reacts similarly (Scheme 4) to give, after hydrolysis of the intermediate 2,5-dilithio-derivative, 4-bromo-1-methylimidazole.[16] We[57] have not achieved such regioselectivity in our reactions of 2,4,5-tribromo-1-ethoxy(or methoxy)methylimidazole with one mol. equiv. of n-butyl-lithium at -70°C (see also refs. 11 and 12) (Scheme 5). After quenching the reaction mixture with water, a mixture

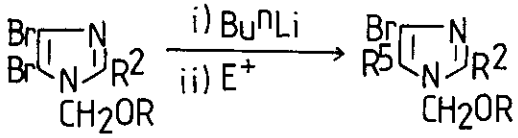


SCHEME 4



SCHEME 5

of compounds (37) and (38) ($R^2 = R^5 = H$) was obtained. Quenching of a similar reaction mixture with dimethyl disulphide gave a mixture of compounds (37) and (38) ($R^2 = R^5 = SMe$).[57] Compounds

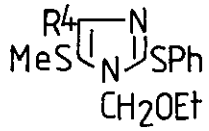


SCHEME 6

(37: R = Me, Et; R^2 = H, SMe, SPh) do react regioselectively with one mol. equiv. of n-butyl-lithium, however, and the resulting imidazol-5-yl-lithium compounds can be quenched with a number of electrophiles [e.g. R^5 = CHO, $Ph_2C(OH)$, etc.].[57]

Until recently imidazol-4-yl-lithium reagents were unknown. In 1978 Breslow's group[14] reported that "all attempts to make organometallic reagents from N-protected 4(5)-bromoimidazole failed,

leading either to reduction or to C-2 metallated derivatives". More recently, however, they reported the synthesis of 1-methyl-2-phenylimidazol-4-yl-lithium from 4-bromo-1-methyl-2-phenylimidazole (n-BuLi/THF/-78°C) and its reaction with diethylcarbonate, to give ethyl 1-methyl-2-phenylimidazole-4-carboxylate.[42] 4-Bromo-1-methylimidazole is metallated in the 2-position (even at -80°C!); 4-bromoimidazol-2-yl-lithiumcan be quenched with acetaldehyde (Table 2).[20] However, reaction of the 4-bromoimidazole (40) with n-butyl-lithium in ether at -70°C generates the

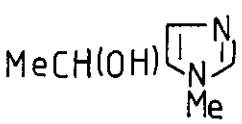


(40) R^4 = Br (43) R^4 = CHO

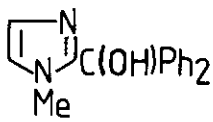
(41) R^4 = Li (44) R^4 = SMe

(42) R^4 = CO_2H

imidazol-4-yl-lithium compound (41), which can be trapped with carbon dioxide, DMF, or dimethyl disulphide to give high yields of compounds (42)-(44), respectively (see also Section 2.1).[12,41] A Russian group[58] treated 4-iodo-1-methylimidazole with three mol. equiv. of n-butyl-lithium and, after addition of iodine, isolated a 40% yield of 2,4-di-iodoimidazole. They considered that 1-methylimidazol-4-yl-lithium, 4-iodo-1-methylimidazol-2-yl-lithium, and 2,4-dilithio-1-methylimidazole were present prior to quenching. Unlike its 4-bromo-isomer, which metallates in the 2-position with n-butyl-lithium, 5-bromo-1-methylimidazole is reported to react with the same reagent by metal-halogen exchange (see also ref. 11); after addition of acetaldehyde the alcohol (45) can be isolated.[20]



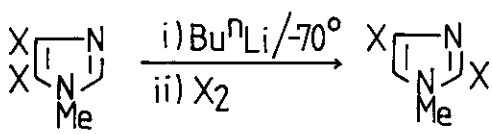
(45)



(46)

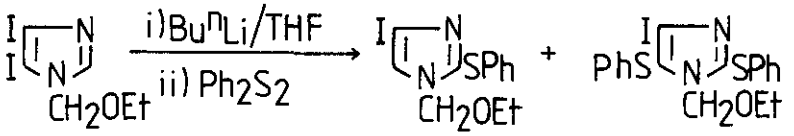
5-Chloro-1-methylimidazole reacts with lithium or sodium naphthalenide to give alcohol (46) (88% and 73% yield, respectively) after addition of benzophenone to the product, presumably by conversion of 1-methyl-imidazol-5-yl-lithium into its 2-isomer.[21]

4,5-Dibromo(or di-iodo)-1-methylimidazole reacts successively with n-butyl-lithium (at -70°C) and water to give 4-bromo(or iodo)-1-methylimidazole.[16] However, if the initially generated



SCHEME 7

imidazol-5-yl-lithium reagent is allowed to warm up, a transmetallation reaction occurs to give the corresponding 4-halogenoimidazol-2-yl-lithium reagent which, on quenching with elemental bromine or iodine yields either 2,4-dibromo- or 2,4-di-iodo-1-methylimidazole (Scheme 7).[16] When we[11] treated 1-ethoxymethyl-4,5-di-iodoimidazole (47) with one mol. equiv. of n-butyl-lithium in THF at -70°C and quenched the reaction mixture with diphenyl disulphide (Scheme 8), a mixture of compounds (48) and (49) (ratio 74:16) was obtained. We proposed that the initially generated imidazol-5-yl-lithium compound underwent transmetallation reactions and that 1-ethoxymethyl-4-iodo-imidazol-2-yl-lithium and 1-ethoxymethyl-4-iodo-2,5-dilithioimidazole were present prior to quenching.

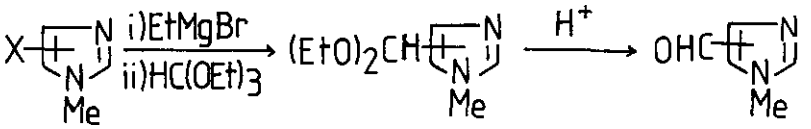


(47) (48) (49)

SCHEME 8

3. GRIGNARD DERIVATIVES

Surprisingly, Grignard derivatives of imidazole were unknown until 1981, when an Egyptian group[46] reported the reactions of 2-, 4-, and 5-bromo-1-methylimidazole and the corresponding iodo-



SCHEME 9

compounds with ethylmagnesium bromide; these reactions were carried out initially in refluxing ether, then the ether was replaced by benzene and heating continued to ensure their completion. The resulting Grignard derivatives were reacted with triethyl orthoformate (Scheme 9), to give acetals (48-87% yields) which, on hydrolysis with hot aqueous acid, give 1-methylimidazole-2- (72% yield), 4- (95%), and 5-carbaldehyde (93%), respectively. 2,4,5-Tribromo-1-ethoxy(and methoxy)-methylimidazole[57] react similarly with ethylmagnesium bromide and the resulting Grignard compound can be hydrolysed by water, to give the 1-substituted 4,5-dibromoimidazole in high yield.

Presumably Grignard derivatives of imidazole can be prepared by addition of magnesium salts to the corresponding organolithium compounds, although there are no literature reports of their preparation in this way.

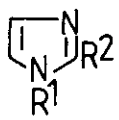
4. OTHER ORGANOMETALLIC DERIVATIVES

Phenylsodium (prepared from chlorobenzene and sodium in toluene) metallates 1-methylimidazole

and its 5-chloro-derivative and 1-benzyl- and 1-phenylimidazole in the 2-position and the resulting 2-sodio-derivatives can be trapped with DMF, aromatic aldehydes, benzophenone,[59,60] or phenyl azide[27] (Table 6). Hydrolysis with acid of the triazenes obtained using phenyl azide provides one of the best routes to 2-aminoimidazoles.[27] Tertov et al.[59,60] reported that 1,2-dimethylimidazole metallated with phenylsodium exclusively in its 5-position to give, after addition of benzophenone

TABLE 6

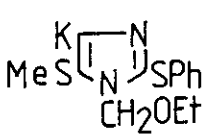
SYNTHESIS OF 1,2-DISUBSTITUTED IMIDAZOLES VIA METALLATION OF 1-SUBSTITUTED IMIDAZOLES WITH PHENYLSODIUM[27,59,60]



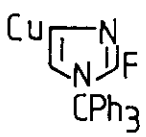
R^1	R^2	Reagent	Yield (%)
Me	CHO	DMF	35
Me	CH(OH)Ph	PhCHO	80
Me	$C(OH)Ph_2$	Ph_2CO	85
Me	$CH(OH)C_6H_3(OMe)_2$-3,4	$3,4-(MeO)_2C_6H_3CHO$	77
CH_2Ph	$C(OH)Ph_2$	Ph_2CO	66
CH_2Ph	NHN=NPh	PhN_3	—
Ph	CH(OH)Ph	PhCHO	61
Ph	$C(OH)Ph_2$	Ph_2CO	72
Ph	NHN=NPh	PhN_3	—
Me(5-Cl)	$C(OH)Ph_2$	Ph_2CO	80

or benzaldehyde, the alcohols (13) (70%) and (14) (63%), respectively. However, in our hands benzophenone gave only a low (8%) yield of the product (23) derived from lateral metallation (see also Section 2.2).[52]

1-Ethoxymethyl-5-methylthio-2-phenylthioimidazole cannot be metallated with n-butyl-lithium



(50)



(51)

or LDA under a variety of conditions, but it can be metallated with potassium di-isopropylamide-lithium t-butoxide (KDA) in THF at -78°C, as shown by trapping the 4-potassio-derivative (50) with

dimethyl disulphide.[12,41]

2-Fluoro-1-triphenylmethylimidazol-4-yl-lithium (Section 2.1) is converted by reaction with copper(I) iodide into the organocopper derivative (51) which reacts normally with allyl bromide, to give the 4-allyl derivative.[47]

Imidazole is mercuriated in the 4(5)-position and its 4(5)-alkyl derivatives are mercuriated adjacent to the alkyl group.[61,62] These mercurio-derivatives react with $^{211}At/I_2$ to give ^{211}At-astato-imidazoles.

In Section 2.2 we referred to silicon, e.g. (20), and tin derivatives, (21) and (22), of imidazole.

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