

## METALLATION AND METAL-HALOGEN EXCHANGE REACTIONS OF IMIDAZOLES

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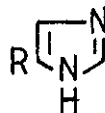
*Abstract - Imidazoles synthesised via organometallic derivatives, particularly organolithium derivatives prepared by metallation and metal-halogen exchange reactions, are reviewed.*

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1. INTRODUCTION

Despite the considerable industrial importance of imidazoles and the widespread interest in their chemistry<sup>1-4</sup> many simple imidazoles are not readily accessible. Thus, for example, 4(5)-methoxyimidazole (1) was unknown until recently<sup>5,6</sup> 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,

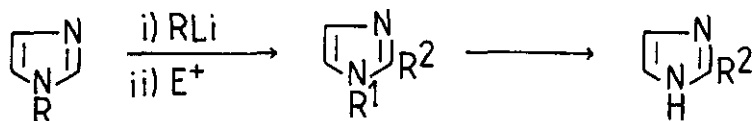
materials such as the parent ring system which, at the time of writing, costs around £12.50/kg (for small quantities).

Surprisingly, with the exception of imidazol-2-yl-lithium reagents, the use of organometallic derivatives of imidazoles in synthesis has not been exploited.<sup>7</sup> 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<sup>8</sup> in 1957 and Roe<sup>9</sup> 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

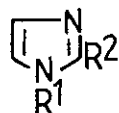
ease of removal have been discussed in a recent paper by Chadwick and Ngochindo.<sup>10</sup> Imidazoles not protected at the ring nitrogen atom are metallated in this position and the resulting 1-lithio-derivatives can be alkylated.<sup>11,12</sup>

1-Methylimidazole has been studied more than any other compound (Table 1), presumably because it is commercially available. The report<sup>8</sup> 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<sup>10</sup> 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.<sup>10</sup>


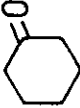
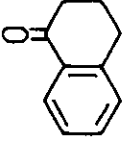
The claim made by Japanese workers<sup>13</sup> that 1-benzylimidazole metallates to a significant extent in the 5-position is probably a mistake.<sup>10</sup> The reaction mixture was quenched with 2,3:5,6-di-*O*-isopropylidene- $\beta$ -D-gulono-1,4-lactone, which gave two products; the major product (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.*<sup>14</sup> and Chadwick and Ngochindo<sup>10</sup> 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

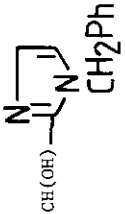
## SYNTHESIS OF 1,2-DISUBSTITUTED IMIDAZOLES VIA METALLATION OF 1-SUBSTITUTED IMIDAZOLES





R <sup>1</sup>	R <sup>2</sup>	Reagent	Yield (%)	Ref.
Me	Me	Me <sub>2</sub> SO <sub>4</sub>	68	15
Me	F	FCIO <sub>3</sub>	55	16
Me	Br	Br <sub>2</sub>	80	16
Me	I	I <sub>2</sub>	95, 69, 80	16, 17, 18
Me	SMe	Me <sub>2</sub> S <sub>2</sub>	24 <sup>a</sup>	19
Me	CO <sub>2</sub> H	CO <sub>2</sub>	32-39 <sup>b</sup>	8
Me	CO <sub>2</sub> Me	ClCO <sub>2</sub> Me	48 <sup>c</sup>	19
Me	CO <sub>2</sub> Et	ClCO <sub>2</sub> Et	10	8
Me	CHO	DMF	65	15
Me	CH(OH)Me	MeCHO	35	20
Me	C(OH)Ph <sub>2</sub>	Ph <sub>2</sub> CO	16 <sup>d</sup> , 86, 40-87 <sup>e</sup> , -	19, 8, 21, 22
Me	C(OH)MePh	PhCOMe	—	22
Me	C(OH)Bu <sup>n</sup> Ph	PhCOBu <sup>n</sup>	—	22
Me	C(OH)MeC <sub>6</sub> H <sub>13</sub> <sup>-n</sup>	MeCOC <sub>6</sub> H <sub>13</sub> <sup>-n</sup>	—	22
Me			—	22

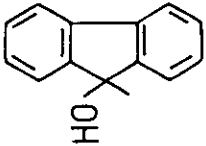
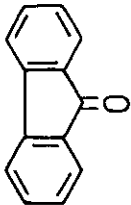
Me	CH(OH)pyrid-2-yl	$C_5H_4NCHO-2$	48	9
Me	CH(OH)pyrid-3-yl	$C_5H_4NCHO-3$	33	9
Me	CH(OH) $C_6H_3(OMe)_2-3,4$	$3,4-(MeO)_2C_6H_3CHO$	23	9
Me	CH(OH) $C_6H_4(-OCH_2O-)-3,4$	$3,4-(-OCH_2O-)C_6H_4CHO$	—	22
Me	CH(OH) $C_6H_4NMe_2-4$	$4-Me_2NC_6H_4CHO$	48	9
Me	CH(OH) $C_6H_{13}-n$	$n-C_6H_{13}CHO$	41, —	9, 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) <sup>f</sup>	$(mim)CHO^f$	43	23
Me	CH(OH)(mim) <sup>f</sup>	$HCO_2Et$	44	14
Me	C(OH)( $CH_2SH$ ) <sub>2</sub> <sup>g</sup>	$(EtOCH_2SCH_2)_2CO$	17	24

Me	$C(OH)(mim)_2 \frac{f}{2}$	$(EtO)_2CO$	30	14
Me	$\left[ \begin{array}{l} C(OH)(mim)_2 \frac{f}{2} \\ + \\ (mim)CO \end{array} \right]$	$(EtO)_2CO$	4 34	23 (see also ref. 25)
Me	$C(OH)(py)_2 \frac{h}{2}$	$(py)_2CO \frac{h}{2}$	61, —	25, 23
Me	$C(OH)(6-D-py)_2 \frac{h}{2}$	$(6-D-py)_2CO \frac{h}{2}$	—	25
Me	$C(OH)(mim)_2 \frac{f}{2}$	$(mim)_2CO \frac{f}{2}$	8	23
Me	$C(OH)(mim)(py) \frac{h}{2}$	$(py)(mim)CO \frac{f, h}{2}$	23	23
Me	$C(OH)(mim)(py) \frac{h}{2}$	$(py)CO_2Et \frac{h}{2}$	9	25
Me	$CO(py) \frac{h}{2}$	$(py)CO_2Et \frac{h}{2}$	51	23
Me	$CO(mim) \frac{f}{2}$	$(mim)CO_2Et \frac{f}{2}$	34	23
Me	$NO_2$	$N_2O_4$	—	26
Me	$NHN=NPh$	$PhN_3$	$70 \frac{f}{2}$	27
Me	$CONH(\alpha\text{-naphthyl})$	$\alpha\text{-naphthylNCO}$	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	$SiMe_2(mim) \frac{f}{2}$	$Cl_2SiMe_2$	56	30
Bu <sup>n</sup>	Me	MeI	—	33
Bu <sup>t</sup>	$C(OH)Ph_2$	$Ph_2CO$	98	10
CH <sub>2</sub> Ph	Me	$Me_2SO_4$	81	15
CH <sub>2</sub> Ph	Me	MeI	69	10
CH <sub>2</sub> Ph	$CO_2H$	$CO_2$	67, 85	8 (see also ref. 14), 34
CH <sub>2</sub> Ph	CHO	DMF	68	15


CH <sub>2</sub> Ph	CH <sub>2</sub> OH	RCHO	—	34
CH <sub>2</sub> Ph	CH(OH)Me	MeCHO	22	9
CH <sub>2</sub> Ph	CH(OH)Ph	PhCHO	48, —	9, 35
CH <sub>2</sub> Ph		HCO <sub>2</sub> Et	22	9
CH <sub>2</sub> Ph	quinol-2-yl	quinoline	29	8
CHMePh	Me	MeI	64	10
Ph	I	I <sub>2</sub>	72	17
Ph	CO <sub>2</sub> H	CO <sub>2</sub>	60 <sup>b</sup>	8
Ph	CO <sub>2</sub> Et	ClCO <sub>2</sub> Et	5	8
Ph	C(OH)Ph <sub>2</sub>	Ph <sub>2</sub> CO	76	8
Ph	CONHPh	PhNCO	39	8
Ph	NO <sub>2</sub>	N <sub>2</sub> O <sub>4</sub>	—	26
CPh <sub>3</sub>	Me	MeI	—, <sup>d</sup> 95	10, 36
CPh <sub>3</sub>	Cl	NCS <sup>k</sup>	<5	36
CPh <sub>3</sub>	Cl	Bu <sup>t</sup> OCl	39	36
CPh <sub>3</sub>	Br	NBS <sup>k</sup>	35	36
CPh <sub>3</sub>	I	I <sub>2</sub>	41	36
CPh <sub>3</sub>	I	NIS <sup>k</sup>	40	36
CPh <sub>3</sub>	CO <sub>2</sub> Et	ClCO <sub>2</sub> Et	90	36
CPh <sub>3</sub>	CHO	DMF	98	36
CPh <sub>3</sub>	NO <sub>2</sub>	Pr <sup>n</sup> ONO <sub>2</sub>	30	37

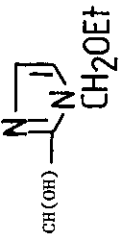
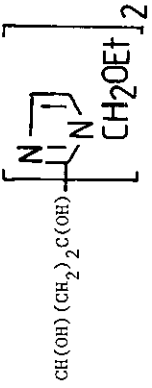
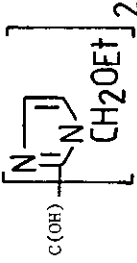
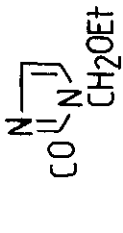
CPh <sub>3</sub>	NO <sub>2</sub>	C(NO <sub>2</sub> ) <sub>4</sub>	37
CPh <sub>3</sub>	NHN=NPh	PhN <sub>3</sub>	36
quino1-3-yl	D	D <sub>2</sub> O	38
quino1-3-yl	For an explanation of the preparation of compound (8) see text.		
CH(OEt) <sub>2</sub> <sup>1</sup> / <sub>2</sub>	Bu <sup>n</sup> I	Bu <sup>n</sup> I	40
CH(OEt) <sub>2</sub> <sup>1</sup> / <sub>2</sub>	CO <sub>2</sub> H	CO <sub>2</sub>	40
CH(OEt) <sub>2</sub> <sup>1</sup> / <sub>2</sub>	COME	MeCONMe <sub>2</sub>	40
CH(OEt) <sub>2</sub> <sup>1</sup> / <sub>2</sub>	CH(OH)Ph	PhCHO	40
CH(OEt) <sub>2</sub> <sup>1</sup> / <sub>2</sub>	C(OH)Ph <sub>2</sub>	Ph <sub>2</sub> CO	40
CH(OEt) <sub>2</sub> <sup>1</sup> / <sub>2</sub>			49

CH(OEt) <sub>2</sub> <sup>1</sup> / <sub>2</sub>	C(OH)Me(py) <sup>n</sup>	(py)COMe <sup>h</sup>	64
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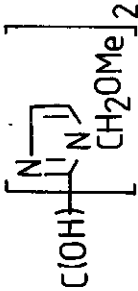

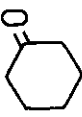

CH(OEt) <sub>2</sub> <sup>1</sup> / <sub>2</sub>			84
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CH(OEt) <sub>2</sub> <sup>1</sup> / <sub>2</sub>	C(OH)(CH <sub>2</sub> SH) <sub>2</sub> <sup>g</sup>	(EtOCH <sub>2</sub> SCH <sub>2</sub> ) <sub>2</sub> CO	24
CH(OEt) <sub>2</sub> <sup>1</sup> / <sub>2</sub>	C(OH)(CH <sub>2</sub> SCH <sub>2</sub> OEt) <sub>2</sub>	(EtOCH <sub>2</sub> SCH <sub>2</sub> ) <sub>2</sub> CO	40

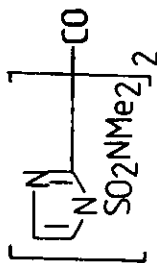
CH(OEt) <sub>2</sub> <sup>1</sup> / <sub>2</sub>		PCl <sub>3</sub>	40
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$\text{CH}_2\text{OEt}$	SPR	$\text{Ph}_2\text{S}_2$	—	14
$\text{CH}_2\text{OEt}$	$\text{C(OH)Ph}_2$	$\text{Ph}_2\text{CO}$	81	41
$\text{CH}_2\text{OEt}$	$\text{C(OH)(py)}_2^{\text{h}}$	$(\text{py})_2\text{CO}^{\text{h}}$	36	25
$\text{CH}_2\text{OEt}$		$\text{PhCOCO}_2\text{Et}$	—	42
$\text{CH}_2\text{OEt}$	$\text{CH(OH)(CH}_2)_2\text{C(OH)}$	$\text{MeO}_2\text{C(CH}_2)_2\text{CHO}$	39, 5	42
$\text{CH}_2\text{OEt}$		$(\text{EtO})_2\text{CO}$	50-70	14
$\text{CH}_2\text{OEt}$		$(\text{EtO})_2\text{CO}$	32	42
$\text{CH}_2\text{OEt}$		$(\text{EtO})_2\text{CO}$	23	42



CH <sub>2</sub> OMe	SMe	Me <sub>2</sub> S <sub>2</sub>	—	14
CH <sub>2</sub> OMe	SPh	Ph <sub>2</sub> S <sub>2</sub>	—	14
CH <sub>2</sub> OMe	CH(OH)Ph	PhCHO	45	9
CH <sub>2</sub> OMe		(EtO) <sub>2</sub> CO	—	14
SO <sub>2</sub> Ph	D	D <sub>2</sub> O	100	43
SO <sub>2</sub> Ph	I	I <sub>2</sub>	6.5	43
SO <sub>2</sub> Ph	CH <sub>2</sub> OH	HCHO	10	43
SO <sub>2</sub> Ph	CH(OH)Ph	PhCHO	18	43
SO <sub>2</sub> Ph			15	43
SO <sub>2</sub> NMe <sub>2</sub>	D	D <sub>2</sub> O	25 (isolated)	10
SO <sub>2</sub> NMe <sub>2</sub>	Me	MeI or Me <sub>2</sub> SO <sub>4</sub>	82	10
SO <sub>2</sub> NMe <sub>2</sub>	CO <sub>2</sub> Me <sup>m</sup>	ClCO <sub>2</sub> Me	—	10
SO <sub>2</sub> NMe <sub>2</sub>	CH <sub>2</sub> CH <sub>2</sub> OH		25	10
SO <sub>2</sub> NMe <sub>2</sub>	C(OH)Ph <sub>2</sub>	Ph <sub>2</sub> CO	60 (isolated)	10
SiMe <sub>3</sub>	SiMe <sub>3</sub>	CISiMe <sub>3</sub>	14	44

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



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

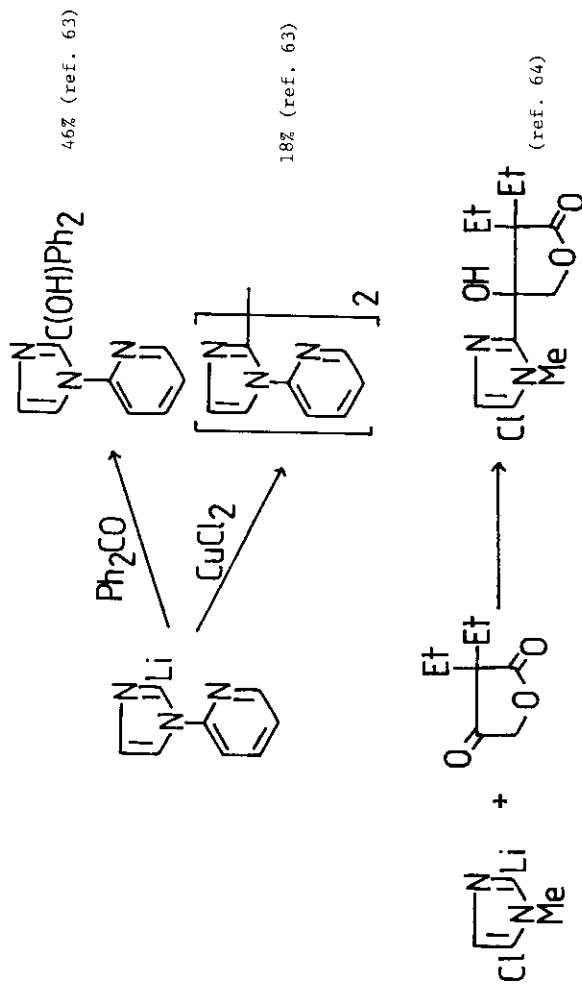
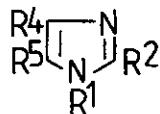


TABLE 2

## SYNTHESIS OF POLYSUBSTITUTED IMIDAZOLES VIA METALLATION IN THE 2-POSITION

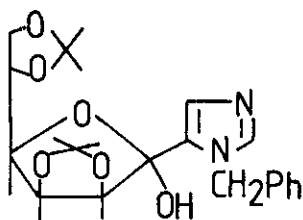


R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>	R <sup>5</sup>	Reagent	Yield (%)	Ref.
Me	I	H	Cl	I <sub>2</sub>	54,69	17,45
Me	CH(OH)Me	H	Me	MeCHO	30	20
Me	CH(OH)Me	H	Cl	MeCHO	64	20
Me	CH(OH)Me	Me	H	MeCHO	—	20
Me	CH(OH)Me	Ph	H	MeCHO	62	20
Me	CH(OH)Me	Cl	H	MeCHO	48	20
Me	CH(OH)Me	Br	H	MeCHO	—	20
Me	CH(OH)Me	Me	Me	MeCHO	24	20
Ph	I	H	Cl	I <sub>2</sub>	54	17
CPh <sub>3</sub>	NO <sub>2</sub>	Me	H	Pr <sup>n</sup> ONO <sub>2</sub>	50 <sup>a</sup>	37
CPh <sub>3</sub>	NO <sub>2</sub>	CH <sub>2</sub> OH	H	Pr <sup>n</sup> ONO <sub>2</sub>	29 <sup>a</sup>	37
CH(OEt) <sub>2</sub>	CHO	Me	Me	DMF	82 <sup>b</sup>	40
CH(OEt) <sub>2</sub>		Me	Me	PCl <sub>3</sub>	46 <sup>b</sup>	40

$\text{CH}(\text{OEt})_2$	$\left[ \begin{array}{c} \text{N} \text{---} \text{Pri} \\ \diagup \quad \diagdown \\ \text{P} \text{---} \text{N} \text{---} \text{Pri} \\ \diagdown \quad \diagup \\ \text{H} \end{array} \right]_2$	$\text{Pr}^i$	$\text{Pr}^i$	$\text{PCl}_3$	55 <sup>b</sup>	40
$\text{CH}_2\text{OEt}$	$\left[ \begin{array}{c} \text{N} \text{---} \text{Me} \\ \diagup \quad \diagdown \\ \text{C}(\text{OH}) \text{---} \text{N} \text{---} \text{Me} \\ \diagdown \quad \diagup \\ \text{CH}_2\text{OEt} \end{array} \right]_2$	$\text{Me}$	$\text{Me}$	$(\text{EtO})_2\text{CO}$	50	25
$\text{CH}_2\text{OEt}$	$\left[ \begin{array}{c} \text{N} \text{---} \text{Pri} \\ \diagup \quad \diagdown \\ \text{C}(\text{OH}) \text{---} \text{N} \text{---} \text{Pri} \\ \diagdown \quad \diagup \\ \text{CH}_2\text{OEt} \end{array} \right]_2$	$\text{Pr}^i$	$\text{Pr}^i$	$(\text{EtO})_2\text{CO}$	62	25
$\text{Me}^c$	$\text{CHO}$	$\text{Br}$	$\text{H}$	$\text{DMF}$	52	46
$\text{Me}^c$	$\text{Br}$	$\text{Br}$	$\text{H}$	$\text{Br}_2$	87	16
$\text{Me}^d$	$\text{I}$	$\text{I}$	$\text{H}$	$\text{I}_2$	53	16

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

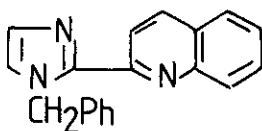
amount of n-butyl-lithium used.\* At 20°C and with a ratio of n-butyl-lithium to imidazole of 2.0:1 compound (4) (64% yield) can be isolated after addition of iodomethane.<sup>10</sup> 1-Benzylimidazol-2-yl-lithium reacts with quinoline in the expected manner, to give the product (5) arising from initial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



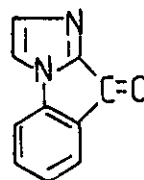
(3)



(4)



(5)

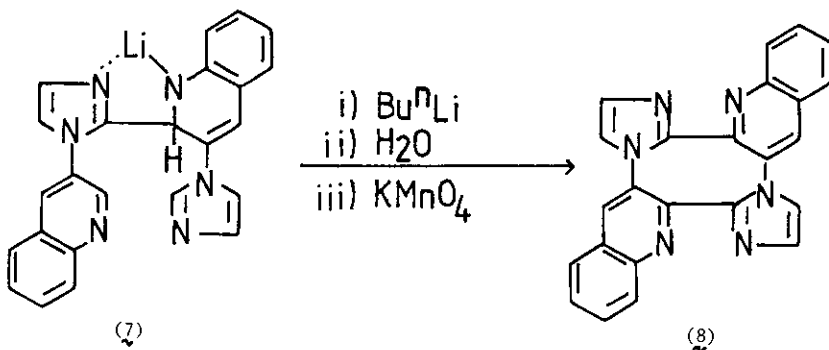


(6)

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.<sup>8</sup>

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).<sup>38,39</sup> 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.<sup>38,39</sup>

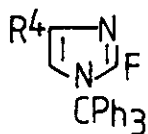
\* 1-Benzylpyrazoles are metallated faster in the benzylic methylene group but the products rearrange: A.R. Katritzky, C. Jayaram, and S.N. Vassilatos, *Tetrahedron*, 1983, **39**, 2023; see also A.R. Katritzky, A.E. Abdel-Rahman, D.E. Leahy, and O.A. Schwarz, *Tetrahedron*, 1983, **39**, 4133.



SCHEME 2

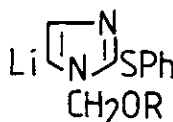
Tertov and Morkovnik<sup>21</sup> used lithium naphthalenide to metallate 1-methylimidazole and trapped the 2-lithio-derivative with benzophenone (Table 1). 1-Phenylimidazole, by contrast, was not metallated by this reagent, nor with sodium naphthalenide.<sup>21</sup>

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).<sup>47</sup>



(9) R<sup>4</sup> = Li

(10) R<sup>4</sup> = 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<sup>14</sup> 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.<sup>12,41</sup> 1-Ethoxymethyl-2-phenylimidazole is metallated similarly in the 5-position with *n*-butyl-lithium in THF.<sup>42</sup> Several 1,2,5-trisubstituted imidazoles (Table 3) have been prepared from these imidazol-5-yl-lithium compounds.

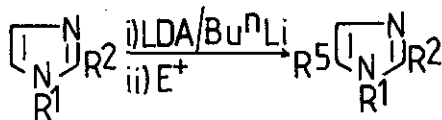
Monolithiated imidazoles are available also via metal-halogen exchange reactions (Section 2.4).

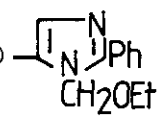

## 2.2 Lateral Metallation

In 1967, Tertov et al.<sup>48</sup> reported that 1,2-dimethylimidazole is metallated exclusively in the

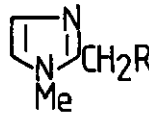
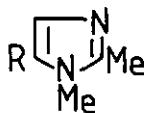
TABLE 3

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



R <sup>1</sup>	R <sup>2</sup>	R <sup>5</sup>	Reagent	Yield (%)	Ref.
CH <sub>2</sub> OMe	SPh	CH(OH)Ph	PhCHO	38	14
CH <sub>2</sub> OMe	SPh	C(OH)(im) <sub>2</sub> <sup>a</sup>	(EtO) <sub>2</sub> CO	70	14
CH <sub>2</sub> OMe	SPh	CH(OH)(im) <sup>a</sup>	HCO <sub>2</sub> Et	—	14
CH <sub>2</sub> OEt	Ph	CH <sub>2</sub> OH	HCHO	—	42
CH <sub>2</sub> OEt	Ph	CO <sub>2</sub> Et	ClCO <sub>2</sub> Et	—	42
CH <sub>2</sub> OEt	Ph	CH(OH) 	HCO <sub>2</sub> Me	70	42
CH <sub>2</sub> OEt	Ph	C(OH) 	(EtO) <sub>2</sub> CO	85-92	42
CH <sub>2</sub> OEt	SPh	CO <sub>2</sub> H	CO <sub>2</sub>	99	12,41
CH <sub>2</sub> OEt	SPh	SMe	Me <sub>2</sub> S <sub>2</sub>	83	12,41
CH <sub>2</sub> OEt	SPh	SPh	Ph <sub>2</sub> S <sub>2</sub>	100	12,41
CH <sub>2</sub> OEt	SPh	SCH <sub>2</sub> CH(OEt) <sub>2</sub>	[(EtO) <sub>2</sub> CHCH <sub>2</sub> S] <sub>2</sub>	31	12,41
CH <sub>2</sub> OEt	SPh	CH(OH)C <sub>6</sub> H <sub>4</sub> Me-4	4-MeC <sub>6</sub> H <sub>4</sub> CHO	62	12,41
CH <sub>2</sub> OEt	SPh	C(OH)(im)CONMe <sub>2</sub> <sup>a</sup>	EtO <sub>2</sub> C.CONMe <sub>2</sub>	—	14

Footnote: <sup>a</sup> (im) = 1-ethoxy (or methoxy)-2-phenylthioimidazol-5-yl.



(13) R = C(OH)Ph<sub>2</sub>

(18) R = D

(23) R = C(OH)Ph<sub>2</sub>

(26) R = CH(OH)C<sub>6</sub>H<sub>4</sub>Me-4

(14) R = CH(OH)Ph

(19) R = SMe

(24) R = CH(OH)Ph

(27) R = SMe

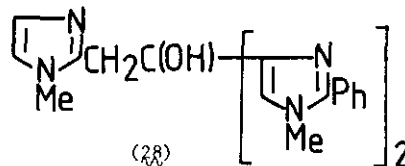
(15) R = CHO

(20) R = SiMe<sub>3</sub>

(25) R = CH(OH)pyrid-2-yl

(16) R = I

(21) R = SnMe<sub>3</sub>



(17) R = Br

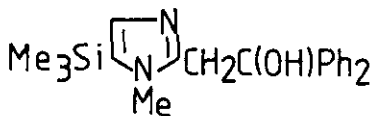
(22) R = SnBu<sub>3</sub><sup>n</sup>

(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.*<sup>49</sup> (using *n*-Bu<sup>n</sup>Li in Et<sub>2</sub>O) and Godefroi *et al.*<sup>50</sup> (using PhLi in C<sub>6</sub>H<sub>6</sub>) 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<sup>51</sup> 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<sup>42</sup> to give exclusively compound (28) (19% yield).

We<sup>52</sup> 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.<sup>52</sup> The product isolated by Tertov *et al.*<sup>48</sup> using benzophenone as the trapping reagent and believed to be alcohol (13) was shown<sup>52</sup> 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<sup>n</sup>Li/TMEDA\*/Et<sub>2</sub>O; Bu<sup>n</sup>Li/THF; LDA/Et<sub>2</sub>O; Bu<sup>n</sup>Li/Et<sub>2</sub>O but only at -110°C!; or PhNa/Et<sub>2</sub>O - 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).<sup>52</sup> 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

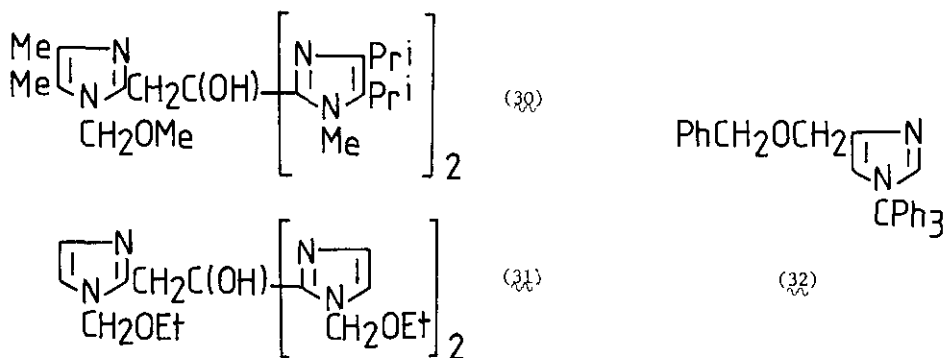
\* TMEDA is *NNN'*'-tetramethylethylenediamine.



prior to addition of the quenching reagent. When the tin compound (21) was treated with n-butyl-lithium in ether but at  $-110^{\circ}\text{C}$ , then quenched with benzophenone or dimethyl disulphide, it gave only compound (13) or (19), respectively.<sup>52</sup> 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.<sup>25</sup> 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.<sup>42</sup> Reaction of 1-ethoxymethyl-2-lithiomethylimidazole with diethyl carbonate is claimed<sup>42</sup> to give ethyl 2-(1-ethoxymethylimidazol-2-yl)acetate (23% yield). 1-Methoxymethyl-2-methylthioimidazole is metallated in its 2-methylthio-group<sup>14</sup> whilst 4-benzyloxymethyl-1-triphenylmethylimidazole (32) is metallated



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

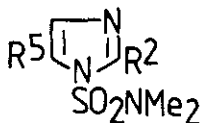
### 2.3 Dilithiated Derivatives Prepared by Metallation in the Ring

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.<sup>30</sup> Chadwick's group at Liverpool have studied in detail 2,5-dilithiation of 1-methyl-,<sup>19</sup> 1-triphenylmethyl-,<sup>10</sup> and 1-methoxymethyl-imidazole,<sup>10</sup> and NN-dimethylimidazole-1-sulphonamide (33;  $\text{R}^2 = \text{R}^5 = \text{H}$ )<sup>10</sup> (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.<sup>19</sup> 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.<sup>19</sup> 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.<sup>19</sup>

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



(33)

(33; R<sup>2</sup> = R<sup>5</sup> = 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).<sup>10</sup>

If only one mol. equiv. of the quenching electrophile is added to the 2,5-dilithiated compound (33; R<sup>2</sup> = R<sup>5</sup> = Li) and the product hydrolysed, then only the 5-mono-substituted compound (33; R<sup>2</sup> = H) is isolated.<sup>10</sup> Removal of the protecting group thus provides a route to 4(5)-mono-substituted imidazoles. The 2,5-dilithiated species (33; R<sup>2</sup> = R<sup>5</sup> = 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.

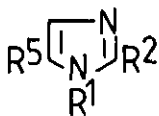
Di- and tri-lithiated imidazoles are also available via metal-halogen exchange reactions (next Section).

#### 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



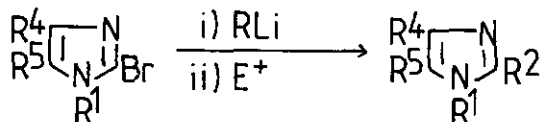
R <sup>1</sup>	R <sup>2</sup>	R <sup>5</sup>	Reagent	Yield (%)	Ref.
Me	D	D	D <sub>2</sub> O	90-98	19
Me	I	I	I <sub>2</sub>	59	16
Me	CO <sub>2</sub> H	CO <sub>2</sub> H	CO <sub>2</sub>	9	19
Me	CO <sub>2</sub> Me	CO <sub>2</sub> Me	ClCO <sub>2</sub> Me	19 <sup>a</sup>	19
Me	C(OH)Ph <sub>2</sub>	C(OH)Ph <sub>2</sub>	Ph <sub>2</sub> CO	69 <sup>b</sup>	19
Me	SMe	SMe	Me <sub>2</sub> S <sub>2</sub>	53 <sup>c</sup>	19
Me	SiMe <sub>3</sub>	SiMe <sub>3</sub>	ClSiMe <sub>3</sub>	32, - <sup>d</sup>	30, 19
CPh <sub>3</sub>	Me	Me	MeI	64 <sup>e</sup>	10
CH <sub>2</sub> OMe	D	D	D <sub>2</sub> O	65-92	10
CH <sub>2</sub> OMe	Me	Me	MeI	86	10
CH <sub>2</sub> OMe	CH(OH)Ph	CH(OH)Ph	PhCHO	84	10
CH <sub>2</sub> OMe	COCMe <sub>3</sub>	COCMe <sub>3</sub>	Me <sub>3</sub> COCl	81	10
SO <sub>2</sub> NMe <sub>2</sub>	D	D	D <sub>2</sub> O	90-98	10
SO <sub>2</sub> NMe <sub>2</sub>	Me	Me	MeI	53	10
SO <sub>2</sub> NMe <sub>2</sub>	CH <sub>2</sub> CH <sub>2</sub> OH	CH <sub>2</sub> CH <sub>2</sub> OH		61 <sup>f</sup>	10

Footnotes: <sup>a</sup> 48% methyl 1-methylimidazole-2-carboxylate formed also by 2-monolithiation.

<sup>b</sup> 16% 2-monolithiation. <sup>c</sup> 24% 2-monolithiation. <sup>d</sup> Not isolated; converted by hydrolysis into 1-methyl-5-trimethylsilylimidazole (58% yield). <sup>e</sup> 36% 2-methyl-1-triphenylmethylimidazole obtained also. <sup>f</sup> 39% product from 5-monolithiation (ratio by <sup>1</sup>H n.m.r. spectroscopic analysis).

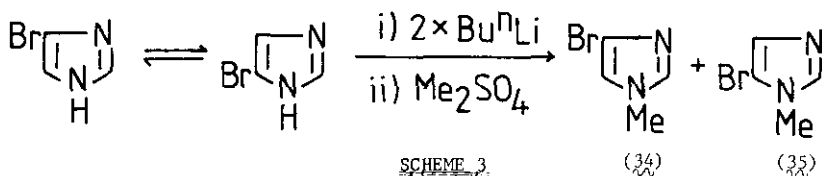
A free ring NH-group, if present, is metallated first. Thus, when we<sup>11,12</sup> reacted 4(5)-bromoimidazole with one or two mol. equiv. of n-butyl-lithium in ether or THF and quenched the resulting mixture with dimethyl sulphate, only a mixture of 4- (34) and 5-bromo-1-methylimidazole (35) (ratio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

TABLE 5

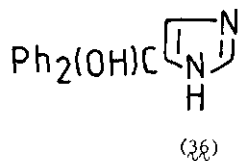
2-SUBSTITUTED IMIDAZOLES PREPARED BY METAL HALOGEN EXCHANGE REACTIONS<sup>a</sup>

R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>	R <sup>5</sup>	Reagent	Yield (%)	Ref.
H <sup>b</sup>	CH(OH)C <sub>6</sub> H <sub>3</sub> (OMe) <sub>2</sub> -2,3	Cl	Cl	ArCHO	44	53
H <sup>b</sup>	CH(OH)C <sub>6</sub> H <sub>3</sub> (OMe) <sub>2</sub> -2,5	Cl	Cl	ArCHO	—	53
H <sup>b</sup>	CH(OH)C <sub>6</sub> H <sub>3</sub> (OMe) <sub>2</sub> -3,4	Cl	Cl	ArCHO	—	53
Me	H	H	Br	H <sub>2</sub> O	—	16
Me(I)	H	H	I	H <sub>2</sub> O	90	16
Me(I)	F	H	I	FC10 <sub>3</sub>	49	16
Me	CHO	H	Br	DMF	57	46
Me	NO <sub>2</sub>	H	Pr <sup>i</sup>	N <sub>2</sub> O <sub>4</sub>	—	54
Me	H	Br	H	H <sub>2</sub> O	—	16
Me	H	Br	Br	H <sub>2</sub> O	—	16
Me(I)	H	I	I	H <sub>2</sub> O	—	16
Me	CHO	Br	Br	DMF	60	46
CH <sub>2</sub> OEt	SPh	Br	Br	Ph <sub>2</sub> S <sub>2</sub>	67	11

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



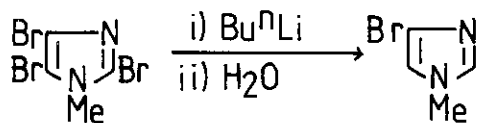
Stensiö *et al.*,<sup>55</sup> however, prepared 4(5)-deuterioimidazole by treating 4(5)-bromoimidazole in THF successively with almost five mol. equiv. of n-butyl-lithium, deuteriomethanol, and acid. Use of methanol in place of deuteriomethanol gave an almost quantitative yield of imidazole.



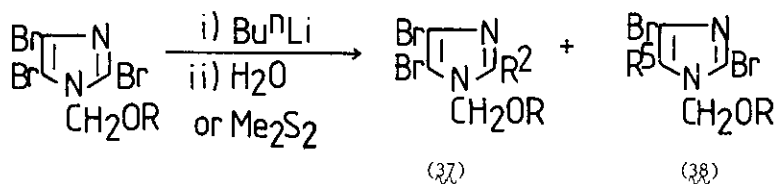
Treatment of 4(5)-bromoimidazole with two mol. equiv. of lithium naphthalenide followed by quenching the product with benzophenone yields alcohol (36) (60% yield).<sup>56</sup> We confirmed this result but failed to synthesise other 4(5)-substituted imidazoles by this route.

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).<sup>53</sup>

Stensiö *et al.*,<sup>55</sup> 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.<sup>16</sup> We<sup>57</sup> 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

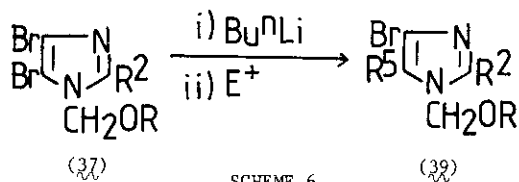


SCHEME 4



SCHEME 5

of compounds (37) and (38) ( $R^2 = R^5 = \text{H}$ ) was obtained. Quenching of a similar reaction mixture with dimethyl disulphide gave a mixture of compounds (37) and (38) ( $R^2 = R^5 = \text{SMe}$ ).<sup>57</sup> Compounds

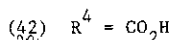
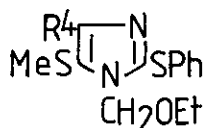


SCHEME 6

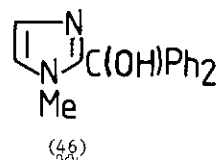
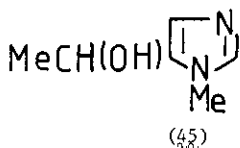
(37:  $R = \text{Me, Et}$ ;  $R^2 = \text{H, SMe, SPh}$ ) do react regioselectively with one mol. equiv. of n-butyl-lithium, however, and the resulting imidazol-5-yl-lithium compounds can be quenched with a number of electrophiles [e.g.  $R^5 = \text{CHO, Ph}_2\text{C(OH), etc.}$ ].<sup>57</sup>

Until recently imidazol-4-yl-lithium reagents were unknown. In 1978 Breslow's group<sup>14</sup> 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.<sup>42</sup> 4-Bromo-1-methylimidazole is metallated in the 2-position (even at -80°C!); 4-bromoimidazol-2-yl-lithium can be quenched with acetaldehyde (Table 2).<sup>20</sup> However, reaction of the 4-bromoimidazole (40) with n-butyl-lithium in ether at -70°C generates the

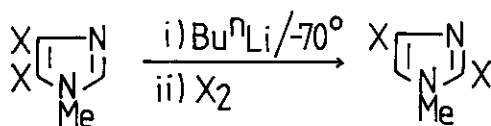


imidazol-4-yl-lithium compound (41), which can be trapped with carbon dioxide, DMF, or dimethyl disulphide to give high yields of compounds (42)-(44), respectively (see also Section 2.1).<sup>12,41</sup> A Russian group<sup>58</sup> treated 4-iodo-1-methylimidazole with three mol. equiv. of n-butyl-lithium 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.<sup>20</sup>



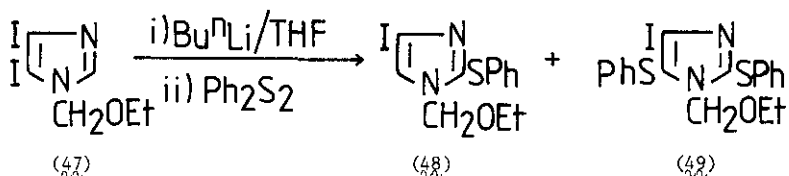
5-Chloro-1-methylimidazole reacts with lithium or sodium naphthalenide to give alcohol (46) (88% and 73% yield, respectively) after addition of benzophenone to the product, presumably by conversion of 1-methyl-imidazol-5-yl-lithium into its 2-isomer.<sup>21</sup>

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.<sup>16</sup> However, if the initially generated



SCHEME 7

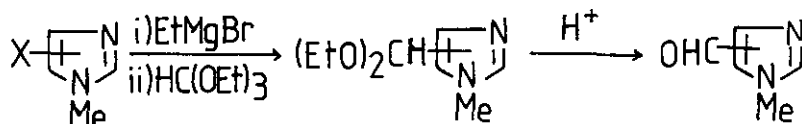
imidazol-5-yl-lithium reagent is allowed to warm up, a transmetallation reaction occurs to give the corresponding 4-halogenoimidazol-2-yl-lithium reagent which, on quenching with elemental bromine or iodine yields either 2,4-dibromo- or 2,4-di-iodo-1-methylimidazole (Scheme 7).<sup>16</sup> When we<sup>11</sup> 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-iodoimidazol-2-yl-lithium and 1-ethoxymethyl-4-iodo-2,5-dilithioimidazole were present prior to quenching.



SCHEME 8

### 3. GRIGNARD DERIVATIVES

Surprisingly, Grignard derivatives of imidazole were unknown until 1981, when an Egyptian group<sup>46</sup> 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<sup>57</sup> 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.

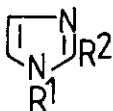
### 4. OTHER ORGANOMETALLIC DERIVATIVES

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,<sup>59,60</sup> or phenyl azide<sup>27</sup> (Table 6). Hydrolysis with acid of the triazenes obtained using phenyl azide provides one of the best routes to 2-aminoimidazoles.<sup>27</sup> Tertov *et al.*<sup>59,60</sup> reported that 1,2-dimethylimidazole metallated with phenylsodium exclusively in its 5-position to give, after addition of benzophenone

TABLE 6

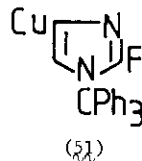
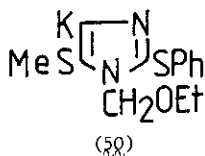
SYNTHESIS OF 1,2-DISUBSTITUTED IMIDAZOLES VIA METALLATION OF 1-SUBSTITUTED IMIDAZOLES WITH PHENYLSODIUM<sup>27,59,60</sup>



R <sup>1</sup>	R <sup>2</sup>	Reagent	Yield (%)
Me	CHO	DMF	35
Me	CH(OH)Ph	PhCHO	80
Me	C(OH)Ph <sub>2</sub>	Ph <sub>2</sub> CO	85
Me	CH(OH)C <sub>6</sub> H <sub>3</sub> (OMe) <sub>2</sub> -3,4	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CHO	77
CH <sub>2</sub> Ph	C(OH)Ph <sub>2</sub>	Ph <sub>2</sub> CO	66
CH <sub>2</sub> Ph	NHN=NPh	PhN <sub>3</sub>	—
Ph	CH(OH)Ph	PhCHO	61
Ph	C(OH)Ph <sub>2</sub>	Ph <sub>2</sub> CO	72
Ph	NHN=NPh	PhN <sub>3</sub>	—
Me(5-Cl)	C(OH)Ph <sub>2</sub>	Ph <sub>2</sub> CO	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).<sup>52</sup>

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



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.<sup>12,41</sup>

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.<sup>47</sup>

Imidazole is mercuriated in the 4(5)-position and its 4(5)-alkyl derivatives are mercuriated adjacent to the alkyl group.<sup>61,62</sup> These mercurio-derivatives react with <sup>211</sup>At/I<sub>2</sub> to give <sup>211</sup>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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