The Lithiation of 1-(Phenylthiomethyl)benzimidazole and Related Compounds.[1]

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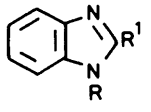
1-(Phenylthiomethyl)benzimidazole is lithiated initially at the 2-position and at low temperatures the 2-lithio derivative reacts with active electrophiles to form 2-substituted products. At higher temperatures rearrangement occurs to a rather unstable methylene-lithiated isomer, which can be trapped by weaker electrophiles. Lithiation can be directed exclusively to the methylene group by: (a) using the corresponding sulphoxide or sulphone, or (b) blocking the 2-position with a t-butyl or phenyl (not methyl) group.

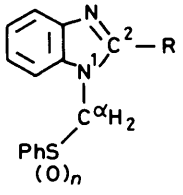
An azole ring can render acidic hydrogen atoms attached to carbon in at least four distinct environments: (a) ring :CH α to ring sulphur or nitrogen; (b) substituent :CHXY attached to a ring carbon α or γ to a pyridine-like ring nitrogen; (c) substituent :CHXY attached to a pyrrole-like ring nitrogen atom; (d) the *ortho* :CH of a phenyl group α to a pyridine-like ring nitrogen.

For X = Y = H, the order of kinetic acidity in imidazoles as found, *e.g.* by H/D exchange or in metallation reactions[2] is: a, b greater than c. 1-Methyl (**1**) and 1-benzylbenzimidazole (**2**) undergo lithiation at C-2.[3,4] 2-Methyl (**3**) and 2-benzylbenzimidazole (**4**) metallated with an excess of butyl-lithium react with various electrophiles at the C-2 methyl or C-2 methylene group.[5] In 2-phenylbenzimidazole (**5**) the *ortho* position of the phenyl substituent is lithiated.[6] In disubstituted compounds such as 1,2-dimethylbenzimidazole (**6**)[7] or 1,2-dimethylimidazole[8] metallation occurs exclusively at the C-2 methyl group. At higher temperatures, dimerizations are observed in some cases.[3]

In summary, it seems that both the C-2 position and C-2 alkyl substituents are more susceptible to metallation than a corresponding functionality at N-1.

The above order of acidity is expected to be modified if X,Y are not equal to H. Thus N–CH_2–SR groups are considerably more acidic than N–Me, and should be able to compete with deprotonation at ring positions *ortho* to a ring sulphur or nitrogen.





(1) R = Me	R^1 = H		(7) R = H	*n* = 0	
(2) R = $PhCH_2$	R^1 = H		(8) R = H	*n* = 1	
(3) R = H	R^1 = Me		(9) R = H	*n* = 2	
(4) R = H	R^1 = $PhCH_2$		(10) R = Me	*n* = 0	
(5) R = H	R^1 = Ph		(11) R = Bu^t	*n* = 0	
(6) R = Me	R^1 = Me		(12) R = Ph	*n* = 0	

We now describe work in the benzimidazole series designed to achieve regioselective lithiation of the N-1 methylene group. The introduction of various sulphur functionalities gave compounds (**7**), (**8**), and (**9**) with increased kinetic acidity of the adjacent methylene group. We have also tested various blocking groups at the C-2 positions in compounds (**10**), (**11**), and (**12**).

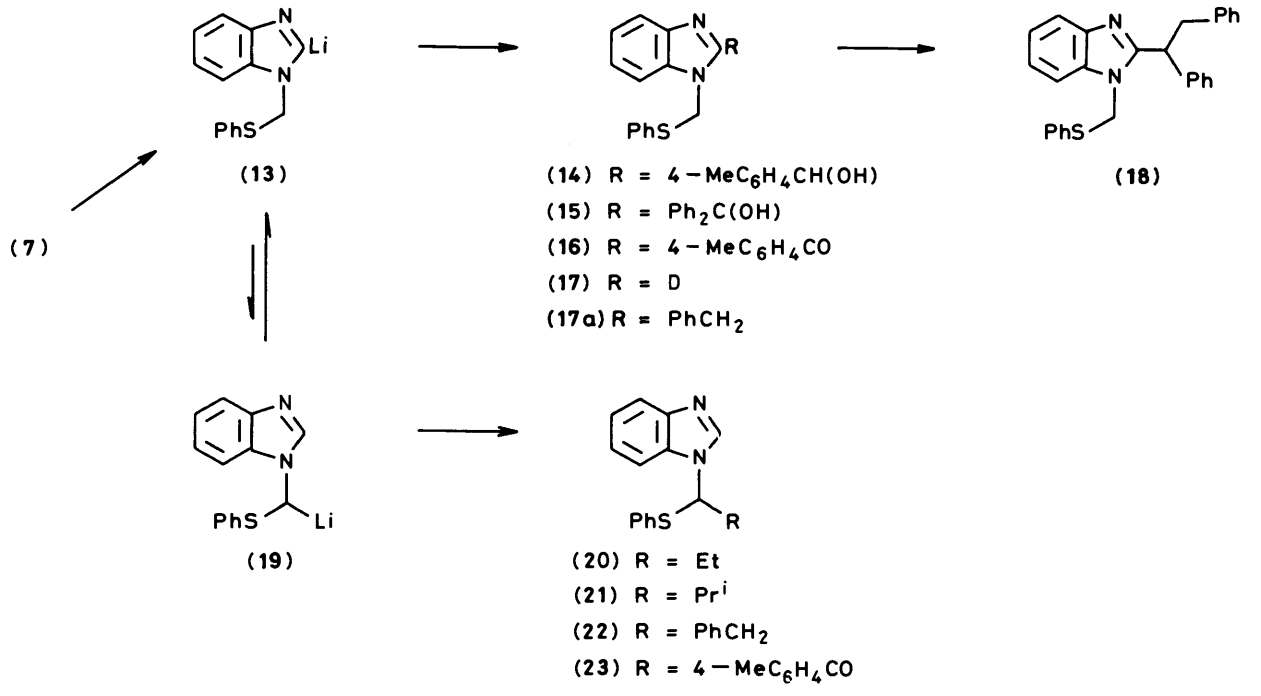
Preparation and Metallation of 1-(*Phenylthiomethyl*)*benzimidazole* (**1**).—The alkylation of the benzimidazole anion with phenylthiomethyl chloride as described by Russian authors[9] and in a patent[10] gives low yields or crude products needing purification by chromatography. We prepared the 1-(phenylthiomethyl)benzimidazoles (**7**), (**10**), (**11**), and (**12**), from the corresponding benzimidazole anions generated in NaH–DMF and obtained good yields even with the C-2 substituted examples (see Experimental section).

Lithiation of (**7**) with lithium di-isopropylamide (LDA) in THF at −78 °C and quenching the lithiated compound with *p*-tolualdehyde, benzophenone, or methyl 4-methylbenzoate gave the alcohols (**14**) and (**15**) and the ketone (**16**), indicating that the ring metallated carbanion (**13**) is formed under these conditions. Similarly, methyl iodide at −78 °C yielded the already characterized (*vide supra*) C-2 methylated product (**10**). With benzyl iodide at −78 °C, an approximately 1:1 mixture of starting material (**7**) and the complex C-2 substituted product (**18**) was obtained. Compound (**18**) arises by further benzylation of an initially C-2 benzylated intermediate: evidently there is rapid transmetallation from the C-2 lithiated species (**13**) to the initial C-2 benzylated intermediate (**17a**). Compound (**18**) displays (measured at 300 MHz) a narrow AB system at *ca.* 5.1 p.p.m. for the *S*-methylene group and an AMX pattern between 3.9 and 3.2 p.p.m. due to the C-2 substituent. The ^{13}C n.m.r. confirms this assignment with sp^3-C signals at 48.6 (t, CH_2S), 46.1 (d) and 41.6 (t).

However, benzyl bromide gave, under conditions as above, the α-C alkylated product (**22**) (70%, estimated from the integrated ^1H n.m.r.) after 3 h at −78 °C. Good yields of isolated (**22**) were achieved in raising the reaction temperature to −20 °C after the addition of benzyl bromide. Compound (**22**) is characterized in its ^1H n.m.r. spectrum by an A_2X pattern (triplet at 5.70, doublet at 3.60 p.p.m.). Similarly the α-C alkylated products (**20**) and (**21**) were formed by analogous reactions with ethyl iodide and isopropyl iodide.

Generation of the carbanion of (**7**) at −78 °C as above followed by addition of *p*-toluoylnitrile at −40 °C gave, after acidic work-up, a mixture of the two isomeric ketones: α-C acylated product (**23**) (44%) and the 2-acylated derivative (**16**) (33%) which were separated by flash chromatography.

In a second series of experiments, (**7**) was metallated in diethyl ether solution with phenyl-lithium at −78 °C. *p*-Tolualdehyde gave both at −78 °C and at −20 °C (entries 5 and 6 in Table 1) the alcohol (**14**) in high yields. Reaction of the carbanion at −78 °C or −20 °C with D_2O afforded the C-2 deuteriated compound (**17**): in each case, neither starting material (**7**) nor CH_2-deuteriated product was detected in the ^1H n.m.r. Reaction of benzyl bromide under analogous conditions at −78 °C gave unchanged starting material (**7**) (by



Scheme 1.

Table 1. Lithiation of (7) and reaction with *p*-tolualdehyde

Entry	Base–solvent	Method[a]	T_1	T_2 (°C)	T_3	Yield of (14)[b] %
1	LDA–THF	A	−78	−78	−78	90
2	LDA–THF	A	−78	−40	−78	15
3	LDA–Et_2O	A	−78	−20	−78	60
4	LDA–THF	B	−78	—	—	70
5	PhLi–Et_2O	C	−78	−78	−78	95
6	PhLi–Et_2O	C	−78	−20	−20	83
7	BuLi–TMEDA–Et_2O	C	−20	−20	−20	67

[a] Method A: (7) added to Li-base at T_1, kept reaction mixture at T_2 (for 1—2 h), then quenched at T_3. Method B: Li-base added to a mixture of (7) and *p*-tolualdehyde. Method C: Li-base added to (7) at T_1, then analogous to method A. [b] Yields from isolated products, difference to 100% recovered (7) or decomposition (entry 2), no α-C product isolated or detected (n.m.r.) in any case.

t.l.c.) after 2 h and even after a further 2 h at −40 °C. Finally, on raising the temperature, α-C alkylation was observed at −10 °C.

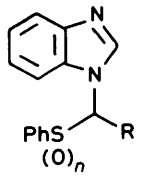
Table 1 summarizes our attempts to achieve reaction at the CH_2 of (7) with *p*-tolualdehyde as the electrophile. Even under conditions expected to favour the thermodynamically more stable carbanion intermediate (especially entry 6) no α-alcohol was isolated or detected in the ^1H n.m.r. of the crude product. The yields of (**14**) tended to decrease with increasing temperatures and with the use of THF instead of diethyl ether, indicating that the carbanion (**13**) is less stable under these conditions.

In view of this behaviour, we believe that the C-2 carbanion (**13**) is initially formed under all metallating conditions employed. At low temperatures this C-2 carbanion (**13**) is attacked at an appreciable rate only by highly reactive electrophiles, such as *p*-tolualdehyde or benzyl iodide. Elevated temperatures and solvents with a considerable Lewis base character promote rearrangement of (**13**) by transmetallation to the isomeric thermodynamically more stable carbanion (**19**). However, (**19**) is evidently kinetically unstable and decays quite rapidly. To obtain good yields of products derived from (**19**), it has to be trapped immediately by an electrophile already present. Consequently, selective alkyiation of the methylene group is observed with those alkyl halides which do not rapidly react with the isomeric carbanion (**13**).

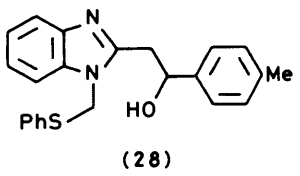
Preparation and Lithiation of the Sulphoxide (**8**) *and Sulphone* (**9**).—In an attempt to solve the problems of competitive α-C *vs.* C-2 attack which we have encountered in metallated derivatives of (**7**), we investigated the corresponding sulphoxide (**8**) and sulphone (**9**), which are expected to display a more kinetically acidic *N*-methylene group. The sulphoxide (**8**) and the sulphone (**9**) were readily obtained *via* oxidation of (**7**) with 1 or 2 mol equiv. of *m*-chloroperbenzoic acid (*m*-CPBA). Both (**8**) and (**9**) were metallated smoothly in LDA–THF at −78 °C and gave the expected α-C alkylated products in high yields: (**24**) and (**26**) with benzyl bromide and (**25**) and (**27**) with *p*-tolualdehyde.

The sulphoxides (**24**) and (**25**) proved to be less stable than the corresponding sulphide and sulphone derivatives. The benzylated sulphoxide (**24**) underwent decomposition even when recrystallization was attempted.

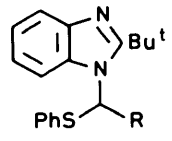
Lithiation of 2-Substituted 1-(Phenylthiomethyl)benzimidazoles.—We have also investigated the selectivity in the metal-

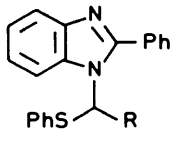


(24) R = $PhCH_2$ n = 1
(25) R = 4-$MeC_6H_4CH(OH)$ n = 1
(26) R = $PhCH_2$ n = 2
(27) R = 4-$MeC_6H_4CH(OH)$ n = 2



(28)





(29) R = $PhCH_2$
(30) R = 4-$MeC_6H_4CH(OH)$
(31) R = $PhCH_2$
(32) R = 4-$MeC_6H_4CH(OH)$
(33) R = 4-$MeC_6H_4C(Me)OH$

lation reactions of various analogues containing a blocking group at 2-position.

2-Methyl-1-(phenylthiomethyl)benzimidazole (**10**) undergoes lithiation in LDA–THF at −78 °C and reacts with *p*-tolualdehyde at the C-2 methyl group to give the alcohol (**28**). The ^{1}H n.m.r. spectrum rules out a structure arising from an attack at the *S*-methylene group, displaying a *S*-methylene singlet at 5.45 similar to that of the starting material (**10**) at 5.20 p.p.m. Additionally the expected A_2X pattern of the C-2 substituent is found at 5.25(t) and 2.75(d) p.p.m.

Consequently the 2-t-butyl analogue (**11**) was metallated with butyl-lithium–tetramethylenediamine (TMEDA) in diethyl ether. Trapping the carbanion of (**11**) with *p*-tolualdehyde after 1 h at −78 °C gave only 25% of (**30**) (besides mainly 1-phenylpentanol), but after 2 h at −20 °C 72% of (**30**) (in a 4:1 mixture of two diastereoisomers, *vide infra*). In a similar fashion, benzyl bromide was used as electrophile to furnish (**29**).

To examine also an aromatic blocking group, we chose the 2-phenyl derivative (**12**). Lithiation of (**12**) proceeded efficiently with either LDA–ether or butyl-lithium–TMEDA–ether at −78 °C. With all electrophiles employed, only the α-C alkylated products (**31**), (**32**), and (**33**) were formed. No products arising from lithiation at the *ortho* position of the 2-phenyl substituent were identified. All attempts to metallate (**12**) with butyl-lithium in diethyl ether at −78 °C, conditions which should favour lithiation at the C-*ortho* position (due to the complexing properties of the benzimidazole moiety), failed as after quenching with *p*-tolualdehyde only starting material (besides 1-phenylpentanol) was recovered.

Diastereoisomeric 2-Benzimidazol-1-ylethanols.—As mentioned above mixtures of diastereoisomeric benzimidazolylethanols were obtained in reactions of the various 1-(*S*-methyl)benzimidazole carbanions with *p*-tolualdehyde or 4-methylacetophenone. As is generally the case with diastereoisomeric reaction products, the *R**,*R** and the *R**.*S** isomers were produced in unequal amounts. The particular ratios of the 2-benzimidazol-1-ylethanols are reported in the Experimental section.

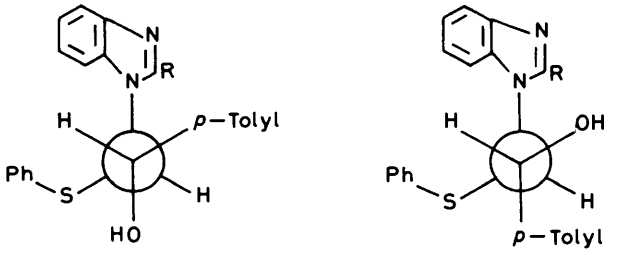
In the case of the 2-t-butyl (**30**) and the 2-phenyl (**32**) derivatives we separated the diastereoisomers by flash chromatography or by repeated recrystallization. Their relative stereochemistry was established based on their ^{1}H n.m.r. spectra (recorded at 300 MHz). The aromatic parts of the spectra were assigned by homonuclear decoupling experiments and comparison with literature data.[11]

Table 2. Metallation of (**12**) and reaction with *p*-tolualdehyde

Reaction conditions	(R*,S*)-(32) : (R*,R*)-(32)[a]	
LDA–Et_2O −78 °C reverse add.	3	4
BuLi–TMEDA–Et_2O −78 °C	1	1
BuLi–TMEDA–Et_2O −20 °C	7	3

[a] Determined from the integrated ^{1}H n.m.r. yields (sum of isomers) almost quantitatively.

As all four substituents of the ethane backbone are rather bulky, one of the possible three rotamers of both isomers (the two protons antiperiplanar, shown for *R**,*S** and *R**.*R** in Scheme 2 is assumed to predominate.[12] This assumption is supported by the large values of the vicinal proton coupling constants [for (**30**): 8.2 and 9.6 Hz, for (**32**): 9.5 and 8.3 Hz] observed for both configurations.



(30; *R**,*S**) R = Bu^t
(32; *R**,*S**) R = Ph
(30; *R**,*R**) R = Bu^t
(32; *R**,*R**) R = Ph

Scheme 2.

One isomer of both series (**30**) and (**32**) displays a significant upfield shift of the 2-t-butyl or the *ortho*-phenyl protons [in comparison to the unsubstituted (**11**) and (**12**)]. We attribute this effect to the *R**,*S** configuration. Here the tolyl group is *gauche* to the C-2 substituent and causes, due to its anisotropic effect, an upfield shift of the t-butyl group in (**30**; *R**,*S**) of 0.5 p.p.m. and of the *ortho* proton in (**32**; *R**,*S**) of 0.6 p.p.m. Additionally, the *ortho* and the *meta* protons of the tolyl group in (**32**; *R**,*S**) are also significantly shifted to higher field (by 0.2 and 0.4 p.p.m., as compared to 4-methylbenzyl alcohol[13]). By contrast, in the *R**,*R** configuration the C-2 substituent shifts are similar to those of the starting materials, except the *ortho* protons of the tolyl group in (**32**; *R**,*R**) experience a downfield shift (+0.2 p.p.m.) probably due to a perturbation caused by the phenylthio group in the *gauche* position.

The 2-benzimidazol-1-ylethanols (**30**; *R**,*R**) and (**32**; *R**,*R**) exhibit higher melting points and solubility, and lower R_f values than their *R**,*S** counterparts. This indicates that in the former the hydroxy group is more accessible for intermolecular hydrogen bonding; the latter may possess a weak intramolecular S–H–O hydrogen bond.

The ratio of the *R**,*S** and *R**,*R** isomers formed depends on the reaction condition employed (see Table 2). Higher temperatures favoured the *R**,*S** isomer, probably due to a S–Li–O complexation in the intermediate lithium alcoholate.

Experimental

M.p.s were determined with a Kofler hot-stage microscope and are uncorrected. Spectra were recorded with the following instruments: ^{1}H n.m.r. with a Varian Model EM 360 L or a Nicolet Model NT 300 spectrometer with Me_4Si as internal standard; ^{13}C n.m.r. with a JEOL Model JNM-FX 100, referring to the centre signal of $CDCl_3$ (77.0) and of [$^2H_6$]-DMSO (39.5), respectively; mass spectra with an AEI MS20 spectrometer. Elemental analyses were carried out by Dr. R. W. King.

Diethyl ether and THF were distilled from sodium benzophenone ketyl, di-isopropylamine and TMEDA refluxed over CaH_2, distilled and stored over 4 Å molecular sieves, *N,N*-dimethylformamide distilled (50 cm column) and stored over 3 Å molecular sieves. Flash chromatography was performed on silica gel (230—400 mesh), thin-layer chromatography on Kodak Chromagram sheets 13181.

All reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen.

The following compounds were prepared by literature methods: 2-methylbenzimidazole, m.p. 175 °C (lit.,[14] m.p. 172—174 °C); 2-t-butylbenzimidazole, m.p. 313—315 °C (Found: C, 75.85; H, 8.30; N, 16.05. $C_{11}H_{14}N_2$ requires C, 75.82; H, 8.10; N, 16.08%) (lit.,[15] m.p. 334 °C); 2-phenylbenzimidazole, m.p. 295 °C (lit.,[16] m.p. 294.5—295.5 °C); phenylthiomethyl chloride, b.p. 66 °C/2 mmHg (lit.,[17] b.p. 103—104 °C/12 mmHg).

General Procedure for the Preparation of 2-Substituted 1-(Phenylthiomethyl)benzimidazoles (**7**), (**10**), (**11**), *and* (**12**).—To a suspension of the 2-substituted benzimidazole (30 mmol) in dry DMF (30 ml), NaH (0.77 g, 32 mmol) was added in portions to give a cloudy solution after 1 h. After addition of phenylthiomethyl chloride (4.92 g, 31 mmol), the reaction mixture was stirred at 25 °C for 30 min, then at 50 °C for 2 h, cooled, and poured into water (600 ml). The crude material was filtered with suction [in the case of (**7**) and (**10**)] or extracted with Et_2O (3 × 150 ml). The combined extracts were dried ($MgSO_4$), and the solvents removed at reduced pressure (50 °C/15 mmHg, last traces of DMF at 80 °C/1 mmHg). The crude products were recrystallized from benzene–hexane mixtures. The following were thus prepared:

1-(*Phenylthiomethyl*)*benzimidazole* (**7**). Needles (95%), had m.p. 88—89 °C (lit.,[9] m.p. 89—90 °C); δ($CDCl_3$) 8.1—7.8 (1 H, m), 7.60 (1 H, s), 7.6—7.2 (8 H, m), and 5.40 (2 H, s).

2-*Methyl*-1-(*phenylthiomethyl*)*benzimidazole* (**10**). Needles (90%), had m.p. 118—120 °C (Found: C, 71.25; H, 5.7; N, 10.75. $C_{15}H_{14}N_2S$ requires C, 70.83; H, 5.55; N, 11.01%); δ($CDCl_3$) 7.9—7.6 (1 H, m), 7.5—7.1 (8 H, m), 5.20 (2 H, s), and 2.05 (3 H, s).

2-(1,1-*Dimethylethyl*)-1-(*phenylthiomethyl*)*benzimidazole* (**11**). Prisms (58%), had b.p. 150—160 °C/0.7 mmHg (bulb-to-bulb), m.p. 45—48 °C (Found: C, 72.55; H, 6.8; N, 9.25. $C_{18}H_{20}N_2S$ requires C, 72.93; H, 6.80; N, 9.45%); δ($CDCl_3$) 8.0—7.7 (1 H, m), 7.6—7.1 (8 H, m), 5.75 (2 H, s), and 1.50 (9 H, s).

2-*Phenyl*-1-(*phenylthiomethyl*)*benzimidazole* (**12**). Prisms (86%), had m.p. 67—69 °C (Found: C, 76.05; H, 5.1; N, 8.85. $C_{20}H_{16}N_2S$ requires C, 75.92; H, 5.10; N, 8.85%); δ($CDCl_3$) 8.1—7.7 (1 H, m), 7.6—7.1 (13 H, m), and 5.50 (2 H, s).

1-(*Phenylsuphinylmethyl*)*benzimidazole* (**8**).—To (**7**) (2.4 g, 10.0 mmol) in chloroform (100 ml), was added *m*-CPBA (80%; 2.15 g, 10.0 mmol) in portions at −20 °C. The reaction mixture was stirred at −20 °C for 3 h, extracted with saturated aqueous $NaHCO_3$ (2 × 30 ml) and water (1 × 20 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure (50 °C/20 mmHg) and the crude material recrystallized from benzene to give the product (2.1 g, 89%), as prisms, m.p. 138—139 °C (Found: C, 65.30; H, 4.75; N, 10.80. $C_{14}H_{12}N_2OS$ requires C, 65.59; H, 4.72; N, 10.93%); δ([$^2H_6$]-DMSO) 8.10 (1 H, s), 7.8—7.1 (9 H, m), and 5.87 and 5.67 (2 H, AB, J_{AB} 14.4 Hz).

1-(*Phenylsuphonylmethyl*)*benzimidazole* (**9**).—To (**7**) (2.4 g, 10.0 mmol) in chloroform (150 ml), was added *m*-CPBA (80%; 4.7 g, 22.0 mmol) in portions at 0 °C and the reaction mixture stirred at 25 °C for 3 h. Further work-up as described above yielded needles (from benzene) (2.0 g, 73%), m.p. 148—150 °C (Found: C, 62.10; H, 4.35; N, 10.15. $C_{14}H_{12}N_2O_2S$ requires C, 61.75; 4.44; N, 10.29%); δ([$^2H_6$]-DMSO) 8.10 (1 H, s), 7.9—7.1 (9 H, m), and 6.25 (2 H, s).

Lithiation of (**7**) *in LDA–THF and Reaction with Electrophiles.*—The benzimidazole (**7**) (1.2 g, 5.0 mmol) in dry THF (50 ml) was added to LDA (prepared from di-isopropylamine [0.78 ml; 5.5 mmol) and butyl-lithium (2.4 M in hexane; 2.2 ml) in dry THF (30 ml)] at −78 °C and stirred for 2 h to form a pale yellow precipitate.

General Procedure for Reaction with Carbonyl Compounds.—To the suspension described above the carbonyl compound (5.2 mol) dissolved in dry THF (5 ml) was added. The reaction mixture was stirred at −78 °C for 30 min (with the aldehyde and ester) and for 3 h (with benzophenone). The reaction mixture was quenched with water (30 ml), the aqueous layer extracted with diethyl ether [the alcohol (**14**) was extracted with $CHCl_3$], and the combined organic extracts were washed with brine, dried ($MgSO_4$), and the solvents removed under reduced pressure (40 °C/20 mmHg). The following were thus prepared.

2-[*Hydroxy*-(p-*tolyl*)*methyl*]-1-(1-*phenylthiomethyl*)-*benzimidazole* (**14**). From *p*-tolualdehyde as carbonyl compound: needles (from EtOAc) (90%), m.p. 179—180 °C (Found: C, 72.90; H, 5.70; N, 7.40. $C_{22}H_{20}N_2OS$: C, 73.30; H, 5.59; N, 7.75%); δ($CDCl_3$—[$^2H_6$]-DMSO) 7.9—7.6 (1 H, m), 7.6—7.0 (12 H, m), 6.35 (1 H, d, *J* 4 Hz, exchanges with D_2O), 5.95 (1 H, d, *J* 4 Hz), 5.80 and 5.58 (2 H, AB, J_{AB} 12.6 Hz), and 2.35 (3 H, s).

2-[*Hydroxy*(*diphenyl*)*methyl*]-1-(1-*phenylthiomethyl*)-*benzimidazole* (**15**). From benzophenone as carbonyl compound: prisms (from benzene) (77%), m.p. 132 °C (Found: C, 76.95; H, 5.35; N, 6.55. $C_{27}H_{22}N_2OS$ requires C, 76.74; H, 5.25; N, 6.63%); δ($CDCl_3$) 8.0—7.7 (1 H, m), 7.6—6.9 (18 H, m), 5.45 (2 H, s), and 3.9 (1 H, br s).

2-(p-*Methylbenzoyl*)-1-(1-*phenylthiomethyl*)*benzimidazole* (**16**). From methyl 4-methylbenzoate as carbonyl compound: needles (from hexane–benzene) (87%), m.p. 101—102 °C (Found: C, 73.80; H, 5.05; N, 7.70. $C_{22}H_{18}N_2OS$ requires C, 73.72; H, 5.06; N, 7.81%); δ($CDCl_3$) 8.2—7.9 (4 H, m), 7.6—7.0 (9 H, m), 6.05 (2 H, s) and 2.45 (3 H, s).

Reaction with p-*Toluonitrile.*—To the suspension described above *p*-toluonitrile (5.2 mmol) in dry THF (5 ml) was added at 40 °C. The reaction mixture was stirred for 2 h at −40 °C, warmed to 0 °C, quenched with 2M- HCl (20 ml) and stirred overnight at 25 °C. Neutralisation of the mixture ($NaHCO_3$ aq.) preceded work-up as described above. Flash chromatography on silica gel eluting with hexane–EtOAc (3:1, v/v) yielded two isomeric ketones, (i) Compound (**16**), R_f = 0.6, (33%), identical with the compound described above. (ii) 1-[*Phenylthio*(p-*toluoyl*)*methyl*]*benzimidazole* (**23**), R_f = 0.15, (44%), m.p. 118—119% °C (Found: C, 74.00; H, 5.10; N, 7.45. $C_{22}H_{18}N_2OS$ requires C, 73.72; H, 5.06; N, 7.81%); δ($CDCl_3$) 8.30 (1 H, s), 8.2—7.7 (3 H, m), 7.5—7.1 (10 H, m), 7.05 (1 H, s), and 2.45 (3 H, s).

Reaction with Alkyl Halides at −78 °C.—To the suspension described above the alkyl halide (5.2 mmol) in dry THF (5 ml) was added. The reaction mixture was stirred at −78 °C for 3 h

(precipitate finally dissolved), quenched with water and work-up followed as described above. The following were thus prepared.

2-*Methyl*-1-(*phenylthiomethyl*)*benzimidazole* (**10**). From methyl iodide as alkyl halide: needles (from benzene–hexane) (76%), m.p. 119 °C, identical in other respects (^{1}H n.m.r. and ^{13}C n.m.r. with the sample prepared as described above.

2-(1,2-*Diphenylethyl*)-1-(*phenylthiomethyl*)*benzimidazole* (**18**). From benzyl iodide as alkyl halide: prisms (from benzene) (35%), m.p. 103—105 °C (Found: C, 79.90; H, 5.90; N, 6.60. $C_{28}H_{24}N_2S$ requires C, 79.96; H, 5.75; N, 6.66%), after flash chromatography on silica gel eluting with hexane–EtOAc (2:1, v/v); (**7**) (40%) was recovered; δ($CDCl_3$, 300 MHz) 7.86—7.83 (1 H, m), 7.37—7.03 (14 H, m), 6.92—6.88 (2 H, m), 6.83—6.80 (2 H, m), 5.06 and 4.99 (2 H, AB, J_{AB} 14.4 Hz), and 3.85, 3.58 and 3.30 (3 H, AMX, J_{AM} 5.6 Hz, J_{AX} 9.6 Hz; J_{MX} 13.4 Hz).

Reaction with Alkyl Halides at −20 °C.—To the suspension described above the alkyl halide (5.2 mmol) in dry THF (5 ml) was added. The reaction mixture was warmed to −15 °C over 30 min, kept at −20 °C for 2 h, quenched with water (50 ml), and extracted with Et_2O (1 × 100 ml, 2 × 50 ml). The combined extracts were washed with water (30 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure (40 °C/20 mmHg). The following were thus prepared.

1-[1-(*Phenylthio*)*propyl*]*benzimidazole* (**20**). From ethyl iodide as alkyl halide colourless oil (85%), after flash chromatography on silica gel eluting with hexane–EtOAc (2:1 v/v); δ($CDCl_3$) 8.0—7.1 (9 H, m), 7.80 (1 H, s), 5.45 (1 H, t *J* 7 Hz), 2.6—2.0 (2 H, m), 1.00 (3 H, t *J* 7 Hz) (Found: 268.103 4. Calc. for $C_{16}H_{16}N_2S$: M^+, 268.103 8.

1-[2-*Methyl*-1-(*phenylthio*)*propyl*]*benzimidazole* (**21**). From isopropyl iodide as alkyl halide: pale yellow oil (60%) after flash chromatography on silica gel eluting with hexane–EtOAc (2:1, v/v); δ($CDCl_3$) 8.1—7.1 (9 H, m), 7.90 (1 H, s), 5.25 (1 H, d *J* 9 Hz), 2.9—2.3 (1 H, m), 1.30 (3 H, d *J* 7 Hz), and 0.90 (3 H, d *J* 7 Hz) (Found: 282.118 3. Calc. for $C_{17}H_{18}N_2S$: M^+, 282.119 0).

1-[2-*Phenyl*-1-(*phenylthio*)*ethyl*]*benzimidazole* (**22**). From benzyl bromide as alkyl halide fine needles (from benzene–hexane) (85%), m.p. 103—104 °C (Found: C, 75.90; H, 5.30; N, 8.20. $C_{21}H_{18}N_2S$ requires C, 76.33; H, 5.49; N, 8.48%); δ($CDCl_3$) 7.9—7.7 (1 H, m), 7.65 (1 H, s) 7.5—6.9 (16 H, m), 5.70 (1 H, t, *J* 7 Hz), and 3.60 (2 H, d, *J* 7 Hz).

Lithiation of (**7**) *with Phenyl-lithium–Diethyl Ether and Reaction with Electrophiles.*—To a suspension of (**7**) (1.2 g, 5.0 mmol) in dry diethyl ether (50 ml) phenyl-lithium (2 M in cyclohexane–ether; 2.6 ml) was added at −78 °C. The reaction mixture was (i) stirred at −78 °C for 1 h or (ii) additionally kept at −20 °C for 1 h to give a yellow, cloudy solution.

1-(*Phenylthiomethyl*)*benzimidazol*-2-*yl*(p-*tolyl*)*methanol* (**14**).—To the solution described above following (i) or (ii) *p*-tolualdehyde (0.55 g, 5.2 mmol) in dry diethyl ether (5 ml) was added and after 20 min the reaction mixture was quenched with water (10 ml). The product was precipitated and was filtered off with suction to give (**14**) in 95% yield following (*i*) or 83% following (ii). The spectroscopic and analytical data were identical with those of the sample prepared as described above.

1-(*Phenylthiomethyl*)[2-^{2}H$_1$]*benzimidazole* (**17**).—The solution described above following (i) or (ii) was quenched with D_2O (0.3 ml), and after being stirred for a further 30 min was extracted with water (20 ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure (40 °C/20 mmHg) left crude material which was recrystallized from benzene–hexane to give 85% and 80% of (**17**), m.p. 81 °C; δ($CDCl_3$) 8.1—7.8 (1 H, m), 7.7—7.1 (8 H, m), and 5.40 (2 H, s).

1-[2-*Phenyl*-1-(*phenylthio*)*ethyl*]*benzimidazole* (**22**).—To the solution described above following (i), benzyl bromide (0.90 g, 5.3 mmol) in dry diethyl ether (5 ml) was added. The reaction mixture was stirred at −78 °C for 2 h, at −40 °C for 2 h, and then at −10 °C for a further 2 h. After quenching with water (20 ml) work-up was analogous to that described above to yield needles (from benzene–hexane) (78%). Analytical and spectroscopic data were identical with those of the sample prepared as described above.

Lithiation of the Sulphoxide (**8**) *or the Sulphone* (**9**) *in LDA–THF and Reaction with Electrophiles: General Procedure.*—(i) The sulphoxide (**8**) (0.77 g, 3 mmol) or (ii) the sulphone (**9**) (0.82 g, 3 mmol) in dry THF (50 ml) was added to LDA [prepared from di-isopropylamine (0.47 ml, 3.3 mmol) and butyl-lithium (2.4 M in hexane; 1.3 ml)] in dry THF (20 ml) at −78 °C and stirred for 1 h to give a clear yellow solution. The carbanion was quenched with 1.1 equiv. of the electrophile and kept at −78 °C for 1 h in the case of benzyl bromide and 15 min in the case of *p*-tolualdehyde. Water (30 ml) and diethyl ether (50 ml) were added, the separated aqueous layer was extracted with ether (2 × 20 ml), and the combined organic extracts were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated under reduced pressure. The following were thus prepared.

1-[2-*Phenyl*-1-(*phenylsulphinyl*)*ethyl*]*benzimidazole* (**24**). From benzyl bromide following (i): fine powder (after triturating with cyclohexane: recrystallization led to decomposition) (83%), m.p. 132—133 °C (Found: C, 71.75; H, 5.25; N, 7.70. $C_{21}H_{18}N_2OS$ + 1.5% inorganic material requires C, 71.73; H, 5.16; N, 7.97%); δ($CDCl_3$) 8.30 (1 H, s), 7.9—6.6 (14 H, m), and 5.30, 3.95, and 3.64 (3 H, ABX, J_{AB} 16 Hz, J_{AX} 4.7 Hz, J_{BX} 8.3 Hz).

1-[2-*Hydroxy*-(p-*tolyl*)*ethyl*]-1-(1-*phenylsulphinyl*)*benzimidazole* (**25**). From *p*-tolualdehyde following (i): fine needles (from EtOAc–benzene) (73%), m.p. 210—214 °C (Found: C, 69.95; H, 5.50; N, 7.30. $C_{22}H_{20}N_2O_2S$ requires C, 70.19; H, 5.35; N, 7.44%); δ($CDCl_3$/[$^2H_6$]-DMSO) 8.7—8.3 (1 H, m), 8.0—6.6 (13 H, m), 5.6—5.2 (2 H, m), 2.35 (1.5 H, s), and 2.15 (1.5 H, s).

1-[2-*Phenyl*-1-(*phenylsulphonyl*)*ethyl*]*benzimidazole* (**26**). From benzyl bromide following (i): needles (from benzene) (68%), m.p. 215—217 °C (Found: C, 69.55; H, 5.05; N, 7.60. $C_{21}H_{18}N_2OS$ requires C, 69.59; H, 5.01; N, 7.73%); δ($CDCl_3$) 8.2—7.9 (1 H, m), 7.8—6.9 (14 H, m), and 5.47, 4.07 and 3.78 (ABX, J_{AB} 14.5 Hz, J_{AX} 4.5 Hz, J_{BX} 11.0 Hz).

1-[2-*Hydroxy*-(p-*tolyl*)*ethyl*]-1-(1-*phenylsulphonyl*)*benzimidazole* (**27**). From *p*-tolualdehyde following (ii): fine needles (from EtOAc) (55%), m.p. 201—204 °C (Found: C, 67.15: H. 5.25; N, 6.70. $C_{22}H_{20}N_2O_3S$ requires C, 67.31; H, 5.14; N, 7.14%); δ($CDCl_3$–TFA) 8.0—6.9 (14 H, m), 6.5—6.0 (2 H, m), and 2.20 (3 H, s).

Lithiation of (**10**): *Preparation of* 1-[2-*Hydroxy*-1-(*phenylthiomethyl*)-2-(p-*tolyl*)*ethyl*]*benzimidazole* (**28**).—Compound (**10**) (1.27 g, 5 mmol) in dry THF (30 ml) was added to LDA [prepared from di-isopropylamine (0.78 ml; 5.5 mmol) and butyl-lithium (2.4 M in hexane 2.2 ml)] in dry THF (50 ml) at −78 °C to give an orange solution. After 1 h, *p*-tolualdehyde (0.66 g, 5.5 mmol) in dry THF (5 ml) was added. The reaction mixture was kept at −78 °C for 30 min and then quenched with water (30 ml) and diethyl ether (30 ml). The aqueous layer was extracted with diethyl ether (2 × 20 ml) and the combined organic extracts were dried ($MgSO_4$) and concentrated. Prisms from cyclohexane–benzene (1.05 g, 51%), m.p. 124—126 °C (Found: C, 74.05; H, 6.05; N, 7.60. $C_{23}H_{22}N_2OS$ requires C, 73.77; H, 5.92; N, 7.48%); δ($CDCl_3$) 7.9—7.6 (1 H, m), 7.5—7.1

(12 H, m), 5.45 (2 H, s), 5.25 (1 H, t, *J* 6 Hz), 2.75 (2 H, d, *J* 6 Hz), and 2.50 (3 H, s).

Lithiation of Compounds (**11**) *and* (**12**) *in Butyl-lithium–TMEDA–Ether and Reaction with Electrophiles: General Procedure.*—To (i) compound (**11**) (0.89 g, 3 mmol) or (ii) compound (**12**) (0.95 g, 3 mmol) in dry diethyl ether (50 ml) was added a mixture of butyl-lithium–TMEDA [prepared by adding butyl-lithium (2.4 M in hexane; 1.3 ml) to TMEDA (0.5 ml, 3.3 mmol) in dry diethyl ether (5 ml) at 25 °C] at (i) −20 °C or (ii) −78 °C. In both cases the carbanions gave yellow suspensions. The electrophile (3.3 mmol) dissolved in dry diethyl ether (10 ml) was added and the reaction mixture kept at (i) −20 °C or (ii) −78 °C for 0.5—1 h and then quenched with water (30 ml). The aqueous layer was separated, extracted with ether (2 × 20 ml) and the combined ethereal extracts dried ($MgSO_4$) and concentrated. The following were thus prepared.

2-(1,1-*Dimethylethyl*)-1-[2-*phenyl*-1-(*phenylthio*)-*ethyl*]-*benzimidazole* (**29**). From benzyl bromide following (i) needles (from cyclohexane) (86%), m.p. 121—122 °C (Found: C, 77.50; H, 6.70; N, 7.10. $C_{25}H_{26}N_2S$ requires C, 77.68; H, 6.78; N, 7.25%); δ($CDCl_3$) 8.3—8.0 (1 H, m), 7.9—7.7 (1 H, m), 7.5—6.9 (12 H, m), 6.12, 3.78 and 3.51 (3 H, ABX, J_{AB} 14.4 Hz, J_{AX} 8.5 Hz, J_{BX} 6.9 Hz), and 1.00 (9 H, s).

1-[2-*Hydroxy*-2-(p-*tolyl*)-1-(*phenylthio*)*ethyl*]-2-t-*butylbenzimidazole* (**30**). From *p*-tolualdehyde following (i); a mixture of two diastereoisomers separated by flash chromatography on silica gel eluting with hexane–EtOAc (9:1, v/v): *R*,S* isomer* (R_f = 0.2, less soluble): fine needles (from hexane–benzene) (58%) m.p. 181—182 °C (Found: C, 74.95; H, 6.85; N, 6.50. $C_{26}H_{28}N_2OS$ requires C, 74.96; H, 6.77; N, 6.72%); δ($CDCl_3$, 300 MHz) 8.01—7.98 (1 H, m), 7.80—7.77 (1 H, m), 7.36—7.19 (7 H, m), 6.96 and 6.91 (4 H, AB, J_{AB} 8.25 Hz, tolyl), 5.95 (1 H, d, *J* 8.2 Hz), 5.64 (1 H, dd, *J* 8.2 Hz, *J* 2.6 Hz), 3.55 (1 H, br s, exchanges with D_2O), 2.24 (3 H, s), and 0.78 (9 H, s); *R*,R* Isomer* (R_f = 0.14, more soluble) fine needles (from cyclohexane) (14%), m.p. 207—209 °C (Found: C, 75.20; H, 7.0; N, 6.40. $C_{26}H_{28}N_2OS$ requires C, 74.96; H, 6.77; N, 6.72%; δ($CDCl_3$, 300 MHz) 8.01—7.98 (1 H, m), 7.83—7.80 (1 H, m), 7.47 (2 H, d, *J* 8.1 Hz, tolyl), 7.34—7.26 (4 H, m), 7.21—7.16 (1 H, m, *p*-H PhS), 7.07—7.02 (2 H m, *m*-H PhS), 6.82—6.79 (2 H, m, *o*-H PhS), 6.08 (1 H, d, *J* 9.6 Hz), 5.50 (1 H, dd, *J* 9.6 Hz, *J* 3.3 Hz), 2.42 (3 H, s), 2.22 (1 H, br s, exchanges with D_2O), and 1.24 (9 H, s).

2-*Phenyl*-1-[2-*phenyl*-1-(*phenylthio*)*ethyl*]*benzimidazole* (**31**). From benzyl bromide following (ii): colourless oil [by flash chromatography on silica gel eluting with CH_2Cl_2–hexane (3:1, v/v)] (62%) (Found: C, 79.60; H, 5.50; N, 6.80. $C_{27}H_{22}N_2S$ requires C, 79.76; H, 5.46; N, 6.89%); δ($CDCl_3$) 8.4—8.2 (1 H, m), 8.1—7.8 (1 H, m), 7.6—6.6 (14 H, m), 6.3—6.1 (2 H, m), and 5.63, 3.78 and 3.34 (3 H, ABX, J_{AB} 14.0 Hz, J_{AX} 11.4 Hz, J_{BX} 4.4 Hz).

1-[2-*Hydroxy*-1-(*phenylthio*)-2-(p-*tolylethyl*]-2-*phenylbenzimidazole* (**32**). From *p*-tolualdehyde following (ii): mixture of two diastereoisomers [separated by flash chromatography on silica gel eluting with CH_2Cl_2]: *R*,S* isomer* (R_f = 0.5, less soluble): fine needles (from EtOAc) (48%), m.p. 188—189 °C (Found: C, 76.90; H, 5.65; N, 6.55. $C_{28}H_{24}N_2OS$ requires C, 77.03; H, 5.54; N, 6.42%); δ($CDCl_3$, 300 MHz) 8.10—8.07 (1 H, m), 7.77—7.74 (1 H, m), 7.43—7.32 (3 H, m), 7.26—7.19 (5 H, m, PhS), 7.03 (2 H, m, *m*-H 2-Ph), 6.83 (2 H, d, *J* 8 Hz, tolyl), 6.58 (2 H, d, *J* 8 Hz, tolyl), 6.08—6.05 (2 H, m), 5.53 and 5.42 (2 H, AB, J_{AB} 9.5 Hz), 3.50 (1 H, br s, exchanges with D_2O), and 2.25 (3 H, s). *R*,R* Isomer* (R_f = 0.1, more soluble): needles (from EtOAc–benzene) (44%), m.p. 189—192 °C (Found: C, 77.00; H, 5.70; N, 6.35. $C_{28}H_{24}N_2OS$ requires C, 77.03; H, 5.54; N, 6.42%); δ ($CDCl_3$, 300 MHz) 8.18—8.15 (1 H, m), 7.68—7.65 (1 H, m), 7.37—7.30 (3 H, m), 7.25—7.14 (7 H, m, tolyl + PhS), 6.99—6.94 (2 H, m, *m*-H 2-Ph), 6.92—6.89 (2 H, m, tolyl), 6.71—6.67 (2 H, m, *o*-H 2-Ph), 5.74 and 5.46 (AB, J_{AB} 8.3 Hz), 3.35 (1 H, br s, exchanges with D_2O), and 2.40 (3 H, s).

1-[2-*Hydroxy*-2-(p-*tolyl*)-1-(*phenylthio*)*propyl*]-2-*phenylbenzimidazole* (**33**). From 4-methylacetophenone following (ii) a 3:2 mixture of diastereoisomers (78%), m.p. 204—205 °C (Found: C, 77.65; H, 5.85; N, 6.05. $C_{29}H_{26}N_2OS$ requires C, 77.30; H, 5.85; N, 6.20%); δ($CDCl_3$) 8.8—8.4 (1 H, m), 8.1—7.8(1 H, m), 7.7—6.5 (*ca.* 15 H, m), 6.3—6.1 (0.8 H, m), 5.75 (0.6 H, s), 5.60 (0.4 H, s), 2.85 (0.6 H, br s), 2.70 (0.4 H, br s), 2.40 (1.8 H, s), 2.25 (1.2 H, s), 1.90 (1.2 H, s), and 1.20 (1.8 H, s).

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