Electrophilic Substitution of Imidazo[2,1-*b*]thiazoles

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Fifteen imidazo[2,1-*b*]thiazoles containing a range of substituents at position 6 have been used in studies of electrophilic substitution at position 5. Acid-catalysed deuteriation was examined quantitively and, by making certain assumptions, values for the rate constants (k_1) of the deuteriation process were obtained. A 3-methyl group increases k_1 by a factor of *ca.* 3; for different 6-substituents the k_1-values are in the order Me > Bu^t ~ C_6H_4OMe-*p* > Ph. Bromination occurred preferentially at position 5 even with substrates containing 6-substituents (*e.g.*, 2-thienyl) which themselves have a reactive nucleus. Although 6-alkyl-5-nitrosoimidazothiazoles are unstable and cannot be prepared by the standard method (sodium nitrite and acetic acid), the 6-t-butyl compounds were obtained by a procedure in which the work-up involves very mild treatment. The 5-formyl derivatives show extensive mesomerism, and in solution they adopt the conformation having the carbonyl oxygen *syn* to N(4). In one compound, the 4,6-dimethyl-5-carbaldehyde, the *anti* rotamer is present as the minor component. Imidazo[2,1-*b*]thiazoles are easily converted into 5-trifluoroacetyl compounds and 5-thiocyanates.

Imidazo[2,1-*b*]thiazoles readily undergo electrophilic substitution at position 5. In the following summary references to the most recent substantial work are given, and these lead back to the earlier publications. The processes studied extensively are bromination[1,2], nitration[3–5] and nitrosation;[5,6] those less widely examined are thiocyanation[7,8] and formylation.[9] A range of substitutions has been carried out on 6-chloroimidazo[2,1-*b*]thiazole.[7] That substitution occurs at position 5 was established by chemical[1] and spectrometric[10] methods, and the chemical shifts of the protons at the various nuclear positions are now known.[11] Almost all the work has been concerned with imidazothiazoles having an aromatic, or aromatic heterocyclic, group or a halogen substituent at position 6. (Exceptions include the bromination[8] and formylation[9] of the 6-methyl compound.) The alkyl groups of the known imidazothiazoles (*i.e.*, not only those employed in substitution) appear to be limited almost exclusively to methyl and ethyl; the only t-butyl derivative was obtained in low yield (10%).[12] In the present work it was planned to investigate the effect of 6-substituents on the rate of 5-substitution, to extend the range of electrophilic reagents, and to examine the spectrometric features of some of the products.

Previously,[13] imidazothiazoles with (substituted) phenyl, 2-thienyl, and methyl groups at position 6 had been obtained, but for the present purposes there was an interest in studying substrates with a bulky 6-alkyl substituent. The use of 1-bromo-3,3-dimethylbutan-2-one **2** (R^3 = Bu^t) in the general sequence (Scheme 1) gave the 6-t-butyl compounds **3Ab** and **3Bb** in high overall yield (*ca.* 75%); thus, the t-butyl group does not inhibit intramolecular ring closure at the neighbouring position. Fifteen 6-substituted imidazothiazoles were used for the investigation of electrophilic attack. Acid-catalysed deuteriation, selected as the reaction most suitable for rate studies, is discussed first. Other reactions, leading to products of types **5**–**11** (Scheme 1), are covered in later sections. Interpretation of the results and assessment of their significance are greatly facilitated by reference to recent work[14] on the quantitative electrophilic reactivity of aromatic and heterocyclic systems.†

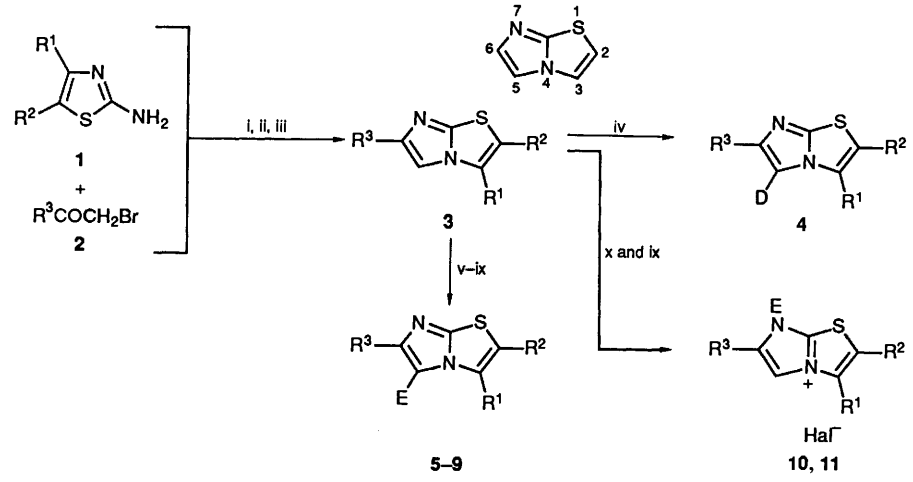
The imidazothiazoles were unaffected by treatment with deuterioethanol–deuterium oxide, but in deuterium chloride–deuterium oxide they underwent rapid substitution. Work-up after the uptake of 1 atom equiv. of deuterium gave 5-deuterio products (**4**) of high isotopic purity even from imidazothiazoles containing other potentially exchangeable protons (such as those in the *p*-methoxyphenyl and 2-thienyl groups). High reactivity is general for similar systems containing a bridgehead nitrogen because the transition state leading to the intermediate (as structure **13** in Scheme 2) is itself aromatic, and an approximate quantitative approach to the selectivity of deuteriation can be made by evaluating the σ^+-values of different positions.[14] [In this usage σ^+ is defined by $\log_{10}$ (partial rate factor) = $\rho\sigma^+$.] The 5-position of 6-methylpyrrolo[2,1-*b*]thiazole has a σ^+-value of −2.08:[14a] introduction of nitrogen at position 7, which gives the corresponding imidazothiazole system, may cause some lowering of reactivity by an inductive effect but the resonance possibilities are not affected and a σ^+-value of *ca.* −1.5 may be estimated for the 5-position of the parent imidazo[2,1-*b*]thiazole. In the deuteriation (ρ *ca.* −9) of 6-(2-thienyl)imidazo[2,1-*b*]thiazole **3Ag**, for example, the other potential site for substitution is position 5 of the thiophene nuclues (σ^+ *ca.* −0.9). The ratio $\log_{10}$ [*k*(imidazothiazole)/*k*(thiophene)] is then *ca.* 5.4.

Preparation of the 5-deuterio products involved treatment of the substrates with an excess of acid and in such solutions only small amounts of the free imidazothiazoles, the species undergoing substitution, are present. In the kinetic runs excesses of the imidazothiazoles were used with deuteriotrifluoroacetic acid in hexadeuterioacetone–deuterium oxide: this procedure gives reactions which are monitored without ambiguity and removes some uncertainties from the quantitative interpretation.

Scheme 2 summarises the kinetic work, and for brevity the symbols representing the various species shown there are used in the following discussion. The process monitored by ^{1}H NMR spectroscopy is $B_H \longrightarrow B_D$; plots of $-\ln[B_H]$ *versus* time gave good straight lines. In order to develop a simple rate equation for the series of reactions set out in Scheme 2 (where the acidic species may be regarded as D_3O^+) it is necessary to eliminate k_2 from the result of applying steady-state treatment to Int (the intermediate). As in a related study,[15a] a value of 2 (based on earlier work[15b]) was assumed for the isotope effect (k_2/k_{-1}) in the partitioning of Int between B_H and B_D. This led to equation (1). The acid strengths of CF_3CO_2D and B_HD^+ are so different

† We are grateful to Dr. R. Taylor of the University of Sussex for suggesting this comparison and calculating some relative reactivities.

Scheme 1 Reactions of imidazo[2,1-*b*]thiazoles with electrophiles



A: $R^1 = R^2 = H$, B: $R^1 = Me$, $R^2 = H$, C: $R^1 = H$, $R^2 = Et$
a: $R^3 = Me$, b: $R^3 = Bu^t$, c: $R^3 = Ph$, d: $R^3 = C_6H_4OMe\text{-}p$, e: $R^3 = C_6H_4F\text{-}p$, f: $R^3 = C_6H_4NO_2\text{-}p$, g: R^3 = 2-Thienyl

The imidazothiazoles **3Ab**, **3Bb** and **3Bd** are new; references to the others are in the Discussion section.

Derivatives prepared (refs. are given to known compounds)

E / Reagents	4 D iv		5 Br v	6 SCN vi		7 NO vii	8 CF_3CO viii	9 CHO ix		E(Hal^-)		10 Me(I^-) x		11 $PhCOCH_2(Br^-)$ xi	
4	**Aa**	**Ab**	**Ac**	**Ad**	**Ae**	**Af**	**Ag**		**Bb**		**Bd**			**Ca**	**Cc**
5	**Aa**[a]	**Ab**			**Ae**	**Af**[b]		**Ba**[a]				**Bf**		**Ca**	**Cc**
6		**Ab**					**Ag**	**Ba**					**Bg**		
7[b]		**Ab**		**Ad**	**Ae**		**Ag**		**Bb**				**Bg**		
8	**Aa**		**Ac**					**Ba**		**Bc**					
9	**Aa**[c]	**Ab**	**Ac**[c]	**Ad**	**Ae**	**Af**[d]		**Ba**		**Bc**	**Bd**			**Ca**	**Cc**
10	**Aa**		**Ac**		**Ae**			**Ba**		**Bc**				**Ca**	**Cc**
11								**Ba**		**Bc**					

[a] Ref. 8. [b] Ref. 24. [c] Ref. 9. [d] Ref. 25

Reagents and conditions: i, Me_2CO, 20 °C; ii, EtOH, 78 °C; iii, Na_2CO_3; iv, DCl–D_2O, 70 °C; v, Br_2–CH_2Cl_2, 0 °C (Br_2–DMF, 80 °C for **5Af**); vi, Br_2–NH_4SCN; vii, i-$C_5H_{11}ONO$–CH_2Cl_2, 45 °C, or $NaNO_2$–AcOH (see text); viii, TFAA–$CHCl_3$; ix, $POCl_3$–DMF; x, MeI, 20 °C; xi, $PhCOCH_2Br$–Me_2CO, 20 °C.

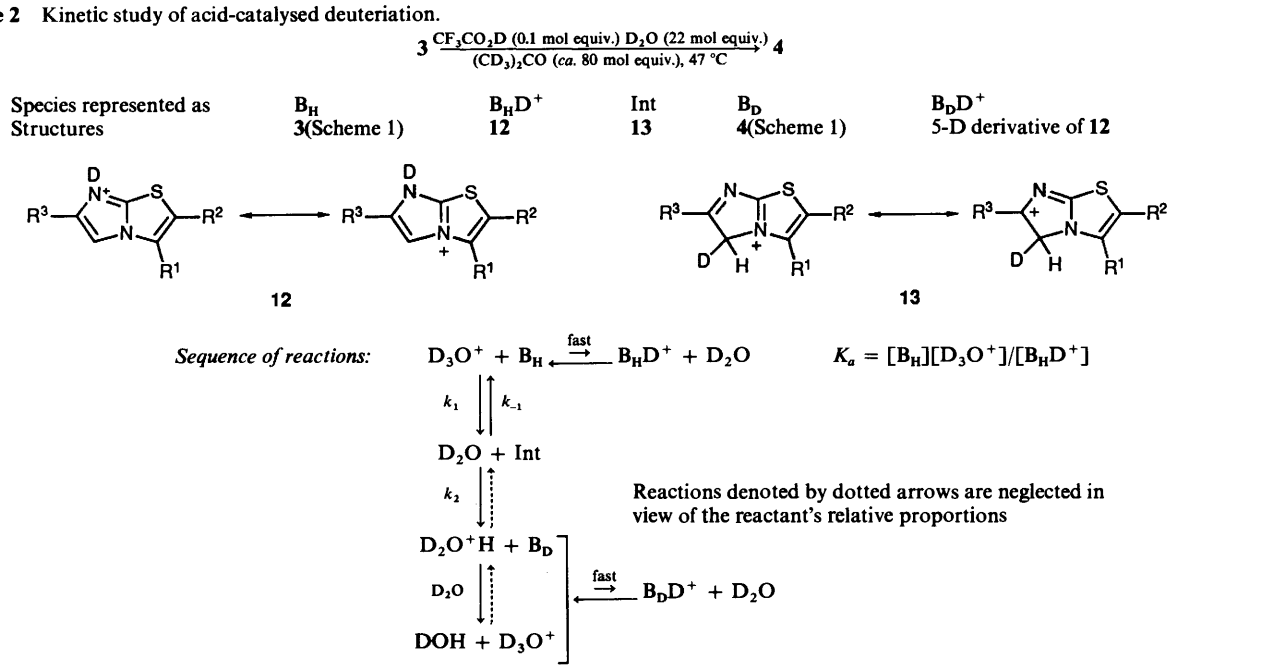
(*ca.* 7 pK_a units) that the amount of B_H removed as B_HD^+ in the initial fast equilibrium may be taken as equal to the amount of CF_3CO_2D used. If B_HD^+ and B_DD^+ have equal acid strengths [D_3O^+] remains constant during the deuteriation process and is given by equation (2). Substitution in equation (1) gives the final equation (3).

The main feature to emerge is that the observed rates of deuteriation (which are directly proportional to the k_1K_a-values) do not necessarily represent the reactivity of the substrates; a rapid deuteriation may arise from high reactivity (large k_1) or low basicity (large K_a). Figures for the pK_a-values of imidazothiazoles are not available, and those in Scheme 2 are estimates based on data for imidazoles[16] and 2-aminothiazoles.[17] For calculating relative k_1-values only the changes in pK_a-values are required, and these can be assessed with reasonable confidence. (For example, changing the 6-substituent from methyl to phenyl may be expected to lower the pK_a-value by at least one unit.) The k_1-figures so derived, although only approximate, are a better measure of the substituents' effects on the deuteriation process than are the observed rates. Compound **3Ad**, with the highest rate but a k_1-figure below the average, exemplifies the point.

Structure **12** for B_HD^+ is based on the known protonation of imidazo[2,1-*b*]thiazole at position 7.[18] The carbenium ion form will make only a minor contribution to the structure of the intermediate **13**; in the major, iminium ion, form the electronic effects of the substituents on the positive nitrogen centre should operate in the order R^3 (effect relayed by conjugation) > R^1 (at a neighbouring position which is not conjugated) > R^2 (more remote). The influence of the R^1 and R^2 groups on the k_1-values is then explained simply. Introduction of the R^2 (Et) group has little effect, as evidenced by the pairs **3Aa**/**3Ca** and **3Ac**/**3Cc**, but introduction of the R^1 (Me) group leads to a consistent enhancement (**3Aa**/**3Ba**, **3Ab**/**3Bb**, **3Ac**/**3Bc**). Of the substrates with different 6-substituents those with R^3 = Me have the highest values. The lower values of the compounds with R^3 = Bu^t arise from steric hindrance which, from related work,[14b] is known to operate by inhibiting solvation of the charged intermediate rather than addition of the deuteron. Values of *ca.* 1.6 for the Me/Bu^t rates are close to the value (1.75) found in 5-deuteriation of 2-alkylpyrroles.[14b] For substrates in which R^3 = Ph a $+M$ activating effect might be expected; the further lowering indicates that the required coplanarity of the phenyl and imidazole rings is sterically unfavourable, and although the 6-*p*-methoxyphenyl compound **3Ad** is more reactive its k_1-value does not exceed that of the 6-Bu^t analogue **3Ab**.

Bromination of the imidazothiazoles occurred preferentially at the imidazothiazole 5-position rather than in any of the 6-substituents. This was expected from earlier work[2] and was predicted by considering the σ^+-values of the systems for which they are available. Only the 6-*p*-nitrophenyl derivative **3Af** presented a practical difficulty; this compound, which is almost insoluble in the usual solvents, was brominated efficiently in hot dimethylformamide (DMF). The stoichiometry of the con-

Scheme 2 Kinetic study of acid-catalysed deuteriation.



If $k_2 = 2k_{-1}$ $\quad 0 = k_1[B_H][D_3O^+] - 3k_{-1}[Int][D_2O]$ $\quad -d[B_H]/dt = \frac{2}{3}k_1[B_H][D_3O^+]$

$-\ln[B_H] = \frac{2}{3}k_1[B_H][D_3O^+]t + \text{const.}$ (1)

If K_a of $B_DD^+ = K_a$ of B_HD^+ $\quad [D_3O^+] = K_a a(b - a)$ (2)

where a and b are the initial concentrations of CF_3CO_2D and B_H, respectively

Hence $-\Delta\ln[B_H]/\Delta t = 2k_1K_a a/3(b - a)$ (3)

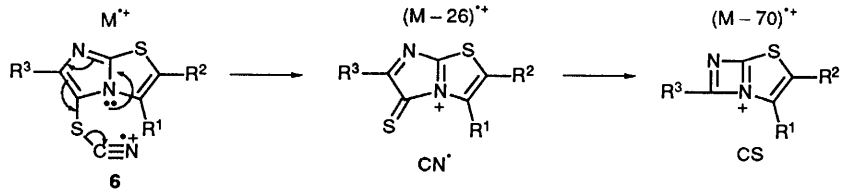
Imidazothiazoles **3**	**Aa**	**Ab**	**Ac**	**Ad**	**Ba**	**Bb**	**Bc**	**Ca**	**Cc**
$10^7k_1K_a(s^{-1})$	3683	2174	6657	39 310	4942	3083	10 140	3004	5155
Estimated pK_a-values	7.5	7.5	6.5	6.2	7.8	7.8	6.8	7.6	6.6
Approx. values of k_1 ($dm^3\ mol^{-1}\ s^{-1}$)	11 500	6900	2100	6200	31 000	19 500	6400	12 000	2050

venient thiocyanation method[8] suggests that the electrophile is $(SCN)_2$ rather than BrSCN. Confirmation that the products **6** are thiocyanates rather than isothiocyanates was provided by the (low) intensity of the IR bands near 2160 cm^{-1} and the characteristic MS fragmentation (Scheme 3). All the 5-nitrosoimidazothiazoles in the literature have an aromatic heterocyclic substituent at position 6. When applied to the 6-alkyl compounds **3Aa**,[8] **3Ab**, **3Ba**,[8] and **3Bb** the standard method[6] (sodium nitrite and acetic acid) gave green solutions but after work-up only dark mixtures were obtained. A milder procedure developed here avoids the presence of acid and the conventional work-up. (This is based on an early, but subsequently largely neglected, report[19] of *N*-nitrosation using an organic nitrite without acid or alkali.) Both methods were effective in nitrosating the 6-(substituted)phenyl and 6-(2-thienyl) compounds **3Ad**,[3] **3Ae**,[13] and **3Ag**.[20] The modified procedure afforded the pure 6-t-butyl-5-nitroso products **7Ab** and **7Bb** as deep-green crystals (which, in solution, decompose at *ca.* 70 °C) but failed with the 6-methylimidazothiazoles **3Aa** and **3Ba**. With regard to the relation between a nitroso compound's stability and the nature of the neighbouring substituent these results closely parallel those found with 4-substituted 2-dimethylamino-5-nitrosothiazoles.[21] The imidazothiazoles **3** were unaffected by heating with acetic anhydride but were readily substituted by trifluoroacetic anhydride (TFAA).

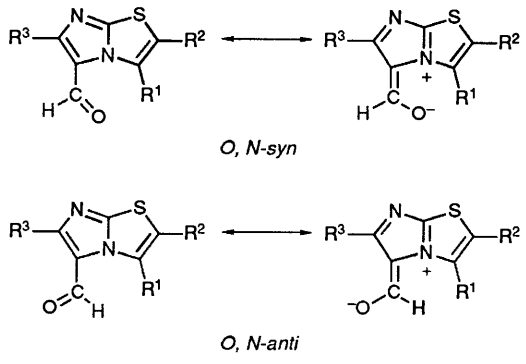
Scheme 3 shows the IR and ^1H NMR characteristics of the 5-formyl compounds **9**, which were prepared in high yield by the Vilsmeyer reaction. The low wavenumbers of the CO bands denote extensive mesomerism, and the products may be regarded as amides rather than aldehydes. For all but one of the substituted imidazothiazoles, compound **9Ba**, the CHO signals appeared as single singlets, the positions of which charged only slightly over the temperature range +30 to −80 °C. This result, and work on the structurally similar pyrrolo[2,1-*b*]thiazole-5-carbaldehydes,[22] establish that the 5-formyl compounds exist predominantly in one of the two possible (*syn* and *anti*) forms. The IR CO doublets observed with compounds **9Aa** and **9Ca** probably arise from Fermi resonance involving the fundamental CO bands at 1641 cm^{-1}. For products of types **9A** and **9C**, with no substituent at position 3, there is a clear steric preference for the *N*(4)-*O*-*syn* form. In compounds **9Bc** and **9Bd** the *syn* form suffers from an unfavourable interaction with the 3-methyl group but this should be less severe than the interaction with the 6-aryl substituent in the *anti* conformer, and the markedly higher wavenumbers indicate that the 3-methyl group reduces the degree of mesomerism in the *syn* form. The conclusion that all these products adopt the *syn* form is supported by the behaviour of the exception, the 3,6-dimethyl compound **9Ba**. In this, destabilisation of the *anti* structure should be less pronounced; a second (minor) isomer is present, and is formulated as the *anti* form (Scheme 3). The relative positions of the absorptions, ^1H NMR and IR, of the rotamers are then in agreement with those of similar compounds.[22]

The imidazothiazoles specified in Scheme 1 reacted with methyl iodide and phenacyl bromide to give salts for which structures **10** and **11** are supported, but not rigorously established, by their ^1H NMR spectra.

Scheme 3 Mass spectra of 5-thiocyanates **6**



Conformations of 5-formyl derivatives **9**.



	O,N-*syn*		O,N-*anti*	
Compd.	C=O	*CHO*	C=O	*CHO*
9Aa	1641 (55)	9.74		
	1651* (45)			
9Ab	1639	9.73		
9Ac	1642	9.87		
9Ad	1641	9.84		
9Ae	1647	9.89		
9Af	1650	9.92		
9Ba	1666 (90)	9.78	1659 (10)	
	at −80 °C	9.77 (93)		10.61 (7)
9Bc	1660	9.89		
9Bd	1660	9.87		
9Ca	1641 (52)	9.76		
	1651* (48)			
9Cc	1641	9.87		

The ^{1}H NMR signals (δ-values) are for solutions in CD_2Cl_2 at 305 K; only in one case did a second CHO signal appear at low temperature. The IR bands (cm^{-1}) are for solutions in $CHCl_3$ at 303 K: those marked * are thought not to be CO absorptions. Where two IR bands or ^{1}H NMR signals are shown the positions are followed in parentheses by the percentage areas of the absorptions. Structures are as in Scheme 1

Experimental

IR spectra were recorded on a Perkin-Elmer 1750 Fourier Transform spectrometer for solutions in $CHCl_3$. ^{1}H NMR spectra were obtained on a Bruker WH 300 (300 MHz) spectrometer for solutions of the salts (apart from the bromides **11**) in $(CD_3)_2SO$, and of the bromides **11** and the other compounds in $CDCl_3$; *J*-values are given in Hz. Mass spectra were examined by in-beam electron impact. Solvents used in preparations were dried and distilled; light petroleum refers to the fraction boiling in the range 85–95 °C. General procedures are illustrated by examples, and analogues prepared similarly are then listed. An abbreviated form is used in reporting the products' characteristics and, except for the salts **10** and **11**, the ending imidazo[2,1-*b*]thiazole is shortened to im. Thus a standard entry such as 6-*t*-*butylimidazo*[2,1-b)*thiazole* **3Ab** 81%), m.p. 51–52 °C (from light petroleum) (Found: C, 59.8; H, 6.6; N, 15.4. $C_9H_{12}N_2S$ requires C, 60.0; H, 6.7; N, 15.55%) is abbreviated as 6-*t*-*butylim* **3Ab** (81), m.p. 51–52 (light petroleum) (59.8, 6.6, 15.4. $C_9H_{12}N_2S$, 60.0, 6.7, 15.55).

The Imidazothiazoles **3**.—Nine of those required (Scheme 1) were available.[13] The general procedures[13] were used with the appropriate 2-aminothiazoles **1** and α-bromo ketones[2] to give the known imidazo[2,1-*b*]thiazoles **3Ad**,[3] **3Ag**,[20] **3Bd** (m.p. 135–136 °C; lit.,[23] 116–117 °C) and **3bg**,[20] and the following compounds.

2-*Amino*-3-(3,3-*dimethyl*-2-*oxobutyl*)*thiazolium bromide* (87), m.p. 168–169 (EtOH) (39.0, 5.4, 9.9. $C_9H_{15}BrN_2OS$, 38.7, 5.4, 10.0). 2-Amino-3-(3,3-dimethyl-2-oxobutyl)-4-methylthiazolium bromide (92), m.p. 241–243. 2-Amino-3-(*p*-methoxybenzoylmethyl)-4-methylthiazolium bromide (89), m.p. 184–186. 6-*t*-*Butyl*-7H-*imidazo*[2,1-b]*thiazolium bromide* (79), m.p. 196–198 (Pr^iOH) (41.7, 5.0, 10.65. $C_9H_{13}BrN_2S$, 41.4, 5.0, 10.7). 6-*t*-*Butyl*-3-*methyl*-7H-*imidazo*[2,1-b]*thiazolium bromide* (73), m.p. 236–237 (Pr^iOH) (43.4, 5.6, 10.4. $C_{10}H_{15}BrN_2S$, 43.6, 5.5, 10.2). 6-p-*Methoxyphenyl*-3-*methyl*-7H-*imidazo*[2,1-b]*thiazolium bromide* (85), m.p. > 250 (MeOH) (48.1, 4.1, 8.5. $C_{13}H_{13}BrN_2OS$, 48.0, 4.0, 8.6). 6-*t*-*Butylim* **3Ab** (81), b.p. 112–114/3 mmHg; m.p. 51–52 (light petroleum) (59.8, 6.6, 15.4. $C_9H_{12}N_2S$, 60.0, 6.7, 15.55). 6-*t*-*Butyl*-3-*methylim* **3Ba** (78), b.p. 86–88/0.03 mmHg; m.p. 75–76 (61.7, 7.5, 14.5. $C_{10}H_{14}N_2S$, 61.8, 7.3, 14.4).

The 5-*Deuterioimidazothiazoles* **4**.—6-*p*-Methoxyphenylim **3Ad** [165 mg; m.p. 151–152 °C; δ 3.85 (3 H, s, MeO), 6.80 (1 H, d, *J* 5.1, 2-H), 6.95 and 7.75 (both 2 H, d, *J* 10, C_6H_4), 7.41 (1 H, *d*, *J* 5.1, 3-H) and 7.67 (1 H, s, 5-H)] was added to 20% DCl–D_2O (0.5 ml) in D_2O (5 cm^3). The solution was kept in a stoppered flask at 70 °C for 4 h, cooled to 0 °C, basified with 18 mol dm^{-3} NH_4OH and extracted with CH_2Cl_2. The signal (δ_H 7.67) of the residue (144 mg) was reduced to 6% of its original intensity; the other signals were unchanged. Crystallisation from CD_2Cl_2–light petroleum gave 5-*deuterio*-6-p-*methoxyphenylim* **4Ad** (109 mg), m.p. 150–152 °C (Found: C, 62.15. $C_{12}H_9DN_2OS$ requires C, 62.3%); *m/z* 231 (M^+, 100%) and 230 (5).

Analogues: In the other 5-D compounds (Scheme 1) the intensities of the 5-H signals were 4–8% of those of the starting materials' signals.

Rates of Deuteriation.—The masses of the materials in the following example were obtained by weighing volumetric flasks before use and after each addition. CF_3CO_2D (0.1445 g) was added to a 5 cm^3 volumetric flask. D_2O (5.419 g) was added. An aliquot (0.885 g) was added to a 10 cm^3 volumetric flask. $(CD_3)_2CO$ (8.1034 g) was added. This was the stock solution. The imidazothiazole **3Ac** (0.0387 g) was added to a 1 cm^3 volumetric flask. Stock solution (0.8779 g) was added. The solution was kept at 47 °C, and the intensity (denoted *p*) of the 5-H signal (s, δ_H 7.65) relative to those (denoted *q*) of constant signals, *e.g.* the 2-H signal (d, δ_H 6.79), was measured at time intervals. Linear regression analysis of the plot of ln (*p*/*q*) *versus* time gave a correlation coefficient of 0.99. The gradient and the initial concentrations of CF_3CO_2D and of the substrate **3Ac** led to the value of k_1K_a shown in Scheme 2.

The weights of the other imidazothiazoles were such that the mol equiv. proportions of the reactants in Scheme 2 were maintained.

The Bromo Compounds **5**.—A solution of Br_2 (0.59 g) in CH_2Cl_2 (10 cm^3) was added during 10 min to a stirred solution of 6-methylim **3Aa** (0.51 g) in CH_2Cl_2 (6 cm^3) at 0 °C. The solution was stirred with 1 mol dm^{-3} aq. $NaHCO_3$ (30 cm^3) at 20 °C for 15 min. After separation of the layers, the aq. layer was extracted with CH_2Cl_2. The extracts were combined, washed (brine), dried, and evaporated at 20 °C/15 mmHg to give the 5-bromo derivative **5Aa** (0.73 g), m.p. 88–89 °C (lit.,[8] 92–93 °C).

Analogues: 5-*Bromo*-6-*t*-*butylim* **5Ab** (79), m.p. 75–76 (CH_2Cl_2–light petroleum) (41.5, 4.2, 10.9. $C_9H_{11}BrN_2S$, 41.7, 4.3, 10.8). 5-*Bromo*-6-p-*fluorophenylim* **5Ae** (75), m.p. 111–112 (EtOH) (44.6, 2.0, 9.6. $C_{11}H_6BrFN_2S$, 44.5, 2.0, 9.4). 5-Bromo-3,6-dimethylim **5Ba** (78), m.p. 85–86 (sublimation at 0.03 mmHg) (lit.,[8] 96–97). 5-*Bromo*-3-*methyl*-6-p-*nitrophenylim* **5Bf** (61) [prepared from compound **3Bf** (0.52 g) in CH_2Cl_2 (100 cm^3)], m.p. > 250 ($CHCl_3$) (42.4, 2.4, 12.3. $C_{12}H_8BrN_3O_2S$, 42.6, 2.4, 12.4). 5-*Formyl*-6-p-*nitrophenylim* **9Af** (70), m.p. 244–246 (AcOEt) (52.7, 2.4, 15.4. $C_{12}H_7N_3O_3S$, 52.7, 2.6, 15.4). 5-*Bromo*-2-*ethyl*-6-*methylim* **5Ca** (77), m.p. 71–72 (sublimation at 0.03 mmHg) (39.2, 355, 11.7. $C_8H_9BrN_2S$, 39.2, 3.7, 11.45). 5-*Bromo*-2-*ethyl*-6-*phenylim* **5Cc** (83), m.p. 96–97 (AcOEt) (51.0, 3.65, 9.0. $C_{13}H_{11}BrN_2S$, 50.8, 3.6, 9.1).

A solution of Br_2 (1.03 g) in DMF (5 cm^3) was added during 10 min to a stirred solution of the *p*-nitrophenyl compound **3Af** (1.5 g) in DMF (65 cm^3) at 80 °C. The mixture was cooled, filtered, poured into 1 mol dm^{-3} aq. $NaHCO_3$ (400 cm^3), and extracted with $CHCl_3$ (4 × 60 cm^3). The $CHCl_3$ solution was washed repeatedly with brine, dried, and evaporated at 20 °C/15 mmHg to give 5-bromo-6-*p*-nitrophenylim **5Af** (1.18 g), m.p. 223–224 (brown crystals from DMF) (40.8, 1.7, 13.05. Calc. for $C_{11}H_6BrN_3O_2S$: 40.8, 1.9, 13.0). This product, m.p. 231–234, was prepared previously[24] by the slow reaction of **3Af**·HBr with Me_2SO.

The Thiocyanates **6**.—Br_2 (0.68 g) was added dropwise during 10 min to a stirred solution of the t-butyl compound **3Ab** (0.77 g) and NH_4SCN (0.65 g) in AcOH (10 cm^3) at 15 °C, and the mixture was stirred for 2 h. The solution was poured into water (60 cm^3), and 18 mol dm^{-3} NH_4OH was added (to pH 6). Extraction with $CHCl_3$, and evaporation of the extract at 30 °C/15 mmHg, gave 6-*t*-*butyl*-5-*thiocyanatoim* **6Ab** (0.81 g), m.p. 95–96 ($CHCl_3$–light petroleum) (50.5, 4.5, 5.85. $C_{10}H_{11}N_3S_2$, 50.6, 4.7, 5.9).

Analogues: 6-(2-*Thienyl*)-5-*thiocyanatoim* **6Ag** (81), m.p. 163–164 ($CHCl_3$–light petroleum) (45.9, 2.0, 15.9. $C_{10}H_5N_3S_3$, 45.6, 1.9, 16.0). 3,6-*Dimethyl*-5-*thiocyanatoim* **6Ba** (75), m.p. 119–121 ($CHCl_3$–light petroleum) (45.8, 3.3, 20.0. $C_8H_7N_3S_2$, 45.9, 3.4, 20.1). 3-*Methyl*-6-(2-*thienyl*)-5-*thiocyanatoim* **6Bg** (77), m.p. 184–186 ($CHCl_3$) (47.2, 2.5, 15.4. $C_{11}H_7N_3S_3$, 47.6, 2.6, 15.15). The thiocyanates showed a band at *ca.* 2160 cm^{-1} (ε *ca.* 80).

The Nitroso Compounds **7**.—(a) *Using isoamyl nitrite*. A slow stream of N_2 was passed through a stirred mixture of isoamyl nitrite (4 cm^3; dried over $CaCl_2$ and fractionally distilled, b.p. 96–98 °C) and CH_2Cl_2 (6 cm^3) contained in a 2-neck flask under a reflux condenser fitted with a $CaCl_2$ guard tube. After 10 min the t-butyl compound **3Ab** (0.55 g) was added, and the solution was kept at 45 °C for 30 min. The temperature of the heating bath was lowered to 30 °C, the condenser was removed, and the pressure was gradually reduced to 15 mmHg. The residue was dissolved in a small volume of CH_2Cl_2, and light petroleum was added. Cooling to 0 °C gave 6-*t*-*butyl*-5-*nitrosoim* **7Ab** (0.39 g), deep-green crystals m.p. 129–131 (51.5, 5.4, 20.1. $C_9H_{11}N_3OS$, 51.65, 5.3, 20.1).

Analogues: Apart from the 6-t-butyl compound **7Bb** these were crystallised by the standard technique. 6-p-*Methoxyphenyl*-5-*nitrosoim* **7Ad** (70), m.p. 185–186 (AcOEt) (55.3, 3.4, 16.0. $C_{12}H_9N_3O_2S$, 55.6, 3.5, 16.2). 6-p-*Fluorophenyl*-5-*nitrosoim* **7Ae** (72), m.p. 213–214 (AcOEt) (53.5, 2.45, 16.9. $C_{11}H_6FN_3OS$, 53.4, 2.4, 17.0). 5-*Nitroso*-6-(2-*thienyl*)*im* **7Ag** (74), m.p. 205–207 (AcOEt) (45.8, 2.2, 17.7. $C_9H_5N_3OS_2$, 45.9, 2.1, 17.9). 6-*t*-*Butyl*-3-*methyl*-5-*nitrosoim* **7Bb** (61), m.p. 142–144 (CH_2Cl_2–light petroleum, 0 °C) (53.9, 5.7, 18.55. $C_{10}H_{13}N_3OS$, 53.8, 5.9, 18.8). 3-*Methyl*-5-*nitroso*-6-(2-*thienyl*)*im* **7Bg** (73), m.p. 212–214 (AcOEt) (48.0, 2.8, 16.75. $C_{10}H_7N_3OS_2$, 48.2, 2.8, 16.9).

(b) *Using* $NaNO_2$–AcOH. The general procedure[5,6,21] gave the nitroso compounds **7Ad** (yield 76%), **7Ae** (79) and **7Ag** (75).

The Trifluoroacetyl Compounds **8**.—The general procedure [14] gave the following. 6-*Methyl*-5-*trifluoroacetylim* **8Aa** (85), m.p. 98–99 ($CHCl_3$)–light petroleum) (40.7, 2.2, 11.8. $C_8H_5F_3N_2OS$, 41.0, 2.15, 11.95). 6-*Phenyl*-5-*trifluoroacetylim* **8Ac** (81), m.p. 93–94 ($CHCl_2$–light petroleum) (52.5, 2.7, 9.6. $C_{13}H_7F_3N_2OS$, 52.7, 2.4, 9.45). 3,6-*Dimethyl*-5-*trifluoroacetylim* **8Ba** (83), m.p. 86–87 (AcOEt) (43.2, 2.7, 11.1. $C_9H_7F_3N_2OS$, 43.5, 2.8, 11.3). 3-*Methyl*-6-*phenyl*-5-*trifluoroacetylim* **8Bc** (84), m.p. 106–107 (AcOEt) (54.0, 2.8, 8.9. $C_{14}H_9F_3N_2OS$, 54.2, 2.9, 9.0).

The 5-Formyl Compounds **9**.—A solution of $POCl_3$ (1.13 g; distilled, b.p. 106–107 °C) in DMF (10 cm^3; distilled, b.p. 152–153 °C) was added during 10 min to a stirred solution of the 6-methyl compound **3Aa** (0.51 g) in DMF (10 cm^3) at 20 °C. The solution was heated at 60 °C for 2 h, then poured into water (80 cm^3), and Na_2CO_3 (solid) was added (to pH 7). The material isolated with $CHCl_3$ was evaporated repeatedly with CCl_4 at 60 °C/15 mmHg to give 5-formyl-6-methylim **9Aa** (0.47 g), m.p. 150–151 (MeOH) (lit.,[9] 140–142); δ_H 9.74 (1 H, s, CHO); *m*/*z* 166 (M^+, 100%).

Analogues: 6-*t*-*Butyl*-5-*formylim* **9Ab** (69), m.p. 108–110 (CH_2Cl_2–light petroleum) (57.4, 5.6, 13.5. $C_{10}H_{12}N_2OS$, 57.7, 5.8, 13.5). 5-Formyl-6-phenylim **9Ac** (76), m.p. 130–131 (MeOH) (lit.,[9] 133–135). 5-*Formyl*-6-p-*methoxyphenylim* **9Ad** (71), m.p. 138–139 (CH_2Cl_2–light petroleum) (60.7, 3.7, 10.8. $C_{13}H_{10}N_2O_2S$, 60.5, 3.9, 10.85). 6-p-*Fluorophenyl*-5-*formylim* **9Ae** (74), m.p. 158–159 (EtOH) (58.3, 3.1, 11.5. $C_{12}H_7FN_2OS$, 58.5, 2.9, 11.4). 5-*Formyl*-6-p-*nitrophenylim* **9Af** (70), m.p. 244–246 (AcOEt) (52.7, 2.4, 15.4. $C_{12}H_7N_3O_3S$, 52.7, 2.6, 15.4). 5-*Formyl*-3,6-*dimethylim* **9Ba** (73), m.p. 131–132 (AcOEt) (53.1, 4.2, 15.35. $C_8H_8N_2OS$, 53.3, 4.5, 15.5). 5-Formyl-3-methyl-6-phenylim **9Bc** (70), m.p. 145–146 (AcOEt) (lit.,[25] 167–169) 5-*Formyl*-6-p-*methoxyphenyl*-3-*methylim* **9Bd** (72), m.p. 172–173 (AcOEt) (61.7, 4.2, 10.45. $C_{14}H_{12}N_2O_2S$, 61.8, 4.4, 10.3). 2-*Ethyl*-5-*formyl*-6-*methylim* **9Ca** (75), m.p. 69–70 ($CHCl_3$–light petroleum) (55.5, 5.1, 14.5. $C_{19}H_{10}N_2OS$, 55.65, 5.2, 14.4). 2-*Ethyl*-5-*formyl*-6-*phenylim* **9Cc** (77), 80–81 ($CHCl_3$–light petroleum) (65.75, 4.65, 10.8. $C_{14}H_{12}N_2OS$, 65.6, 4.7, 10.95).

The 7-Methyl Salts **10**.—The ending imidazo[2,1-*b*]-thiazolium iodide is abbreviated to 'im iod'.

A solution of the 6-methyl compound **3Aa** (0.51 g) in MeI (2.5 cm^3) was stirred at 20 °C for 24 h. The crystalline product was collected, and washed with dry Me_2CO to give 6,7-*dimethylim iod* **10Aa** (0.86 g), m.p. 210–212 (EtOH) (30.1, 3.5, 9.9 $C_7H_9IN_2S$, 30.0, 3.2, 10.0); δ_H [$(CD_3)_2SO$] 2.42 (3 H, s, 6-Me), 3.85 (3 H, s, 7-Me) 7.70 (1 H d, *J* 5.3, 2-H), 8.01 (1 H, s, 5-H) and 8.22 (1 H, d, *J* 5.3, 3-H).

Analogues: 7-*Methyl*-6-*phenylim iod* **10Ac** (82), m.p. 170–172 (EtOH) (42.2, 3.1, 8.2. $C_{12}H_{11}IN_2S$, 42.1, 3.2, 8.2). 6-p-*Fluorophenyl*-7-*methylim iod* **10Ae** (79), m.p. 229–230 (MeOH) (40.2, 2.65, 7.7. $C_{12}H_{10}FIN_2S$, 40.0, 2.8, 7.8). 3,6,7-*Trimethylim iod* **10Ba** (80), m.p. 211–212 (EtOH) (32.9, 3.6, 9.3. $C_8H_{11}IN_2S$,

32.7, 3.8, 9.5). 3,7-*Dimethyl*-6-*phenylim iod* **10Bc** (77), m.p. 228–229 (MeOH) (43.5, 3.7, 7.7. $C_{13}H_{13}IN_2S$, 43.8, 3.7, 7.9). 2-*Ethyl*-6,7-*dimethylim iod* **10Ca** (74), m.p. 133–134 (MeOH) (34.95, 4.2, 9.1. $C_9H_{13}IN_2S$, 35.05, 4.25, 9.1). 2-*Ethyl*-7-*methyl*-6-*phenylim iod* **10Cc** (85), m.p. 159–160 (MeOH) (45.5, 4.2, 7.4. $C_{14}H_{15}IN_2S$, 45.4, 4.1, 7.6).

The Phenyl Salts **11**.—$PhCOCH_2Br$ (0.69 g) was added to a stirred solution of the 3,6-dimethyl compound **3Ba** (0.52 g) in Me_2CO (20 cm^3) at 20 °C. After 24 h the insoluble material was collected, and washed with CCl_4 to give 3,6-*dimethyl*-7-*phenacylimidazo*[2,1-b]thiazolium bromide **11Ba** (0.91 g), m.p. 118–120 (EtOH) (51.1, 4.1, 8.1. $C_{15}H_{15}BrN_2OS$, 51.3, 4.3, 8.0); δ_H 2.44 (3 H, d, *J* 1.0, 6-Me), 2.56 (3 H, d, *J* 1.2, 3-Me), 6.48 (2 H, s, CH_2CO), 7.289 and 7.293 (2 signals) (1 H, 2-H), 7.780 and 7.783 (2 signals) (1 H, 5-H) and 7.52 (2 H, t), 7.65 (1 H, s) and 8.23 (2 H, d) (Ph). Similarly, the 3-methyl-6-phenyl compound **3Bc** gave 3-*methyl*-7-*phenacyl*-6-*phenylimidazo*[2,1-b]*thiazolium bromide* **11Bc** (72), m.p. 140–142 (EtOH) (58.3, 4.3, 6.9. $C_{20}H_{17}BrN_2OS$, 58.1, 4.1, 6.8).

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