

## The Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part 49.<sup>1</sup> Correlation of Standard Rates for Hydrogen Exchange and Nitration of Heteroaromatic Compounds

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Acid-catalysed deuteriodeprotonation rates are recorded for uracil, 1,3-dimethyluracil, 2,6-dimethoxy-pyridine, 4-dimethylaminopyridine, and cinnoline. The rates are extrapolated to give standard rate constants at 100 °C and  $H_2O$  and also at 25 °C and 75%  $H_2SO_4$ . Use of the latter conditions, *i.e.* those previously selected to determine standard nitration rates, give less scatter in a direct comparison with the standard nitration rates. Although the absence of a unique linear relationship is clearly demonstrated, the use of identical standard conditions discloses very good partial linear correlations for substrates of closely related structure.

MUCH data was accumulated over the last decade on the electrophilic reactivity of heteroaromatic compounds. In particular, hydrogen exchange and nitration were widely used as model reactions because of the possibility of studying kinetically substrates of widely differing reactivity, by choice of a medium of appropriate acidity. The comparison of the individual reactivities was carried out by calculating standard ( $k_0$ ) rate constants for acid-catalysed hydrogen exchange at pH 0 and 100 °C,<sup>2</sup> and standard ( $k_2^0$ ) rate constants for nitration at 25 °C and in 75%  $H_2SO_4$ .<sup>3</sup> Such standard rates were listed for a wide variety of benzenoid and heterocyclic compounds.<sup>2,3</sup>

A main aim of this research was to explore the relation between these two independent measures of the susceptibility to electrophilic attack for various rings and ring positions. No simple and general relation was found<sup>4,5</sup> although partial correlations between compounds of closely related structure appeared. In search of further clarification, the acid-catalysed hydrogen exchange of some relevant substrates for which the standard nitration rates were already available have now been measured.

### EXPERIMENTAL

**Materials.**—Uracil,<sup>6</sup> 1,3-dimethyluracil,<sup>6</sup> 2,6-dimethoxy-pyridine,<sup>7</sup> and 4-dimethylaminopyridine<sup>8</sup> were available from previous related studies, whereas cinnoline was a commercial specimen.

**Kinetics.**—The kinetic runs in  $D_2SO_4$  were followed by n.m.r. spectrometry on a JNM-C-60HL instrument, according to a well established procedure.<sup>9</sup> The peak of one or more non-exchanging protons was always used as reference signal.

### RESULTS AND DISCUSSION

The results of the kinetic runs of the five compounds studied are reported in Table 1, and the corresponding rate profiles are illustrated in Figure 1. Table 2 records the calculations to obtain the standard rates.

<sup>1</sup> Part 48, A. R. Katritzky, H. O. Tarhan, and B. Terem, *J.C.S. Perkin II*, 1975, 1632.

<sup>2</sup> A. El-Anani, J. Banger, G. Bianchi, S. Clementi, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1065.

<sup>3</sup> A. R. Katritzky, B. Terem, E. V. Scriven, S. Clementi, and H. O. Tarhan, *J.C.S. Perkin II*, 1975, 1600.

<sup>4</sup> S. Clementi, A. R. Katritzky, and H. O. Tarhan, *Tetrahedron Letters*, 1975, 1395.

**Uracil and 1,3-Dimethyluracil.**—These undergo exchange as free bases, as the reaction rates are little

TABLE 1

Pseudo-first order rate constants for hydrogen exchange

$D_2SO_4$ (%)	$-D_0$ (T)	$10^4 k/s^{-1}$	$-\log k$
(i) Uracil at 60 °C			
65.8	5.00	4.03	3.39
63.5	4.70	5.06	3.30
58.8	4.19	4.33	3.36
54.5	3.73	4.76	3.32
(ii) 1,3-Dimethyluracil at 40 °C			
66.8	5.43	1.56	3.81
61.7	4.74	1.40	3.85
58.2	4.33	2.19	3.67
53.6	3.81	2.30	3.64
(iii) 2,6-Dimethoxy-pyridine at 100 °C			
80.1	6.26	4.95	3.31
76.4	5.81	1.79	3.75
74.7	5.61	1.61	3.79
71.6	5.23	0.887	4.05
68.4	4.85	0.474	4.32
66.0	4.56	0.416	4.38
61.4	4.08	0.499	4.30
57.3	3.71	0.424	4.37
(iv) 4-Dimethylaminopyridine at 80 °C			
77.6	6.26	4.98	3.30
75.5	5.99	4.77	3.32
72.6	5.63	3.63	3.44
70.0	5.29	2.28	3.64
65.2	4.69	0.676	4.17
62.3	4.34	0.380	4.42
56.1	3.74	0.0794	5.10
(v) Cinnoline at 150 °C			
96.2	7.30	0.0347	5.46
93.7	6.99	0.0223	5.65
91.3	6.66	0.0140	5.85
89.8	6.56	0.0156	5.81
86.0	6.18	0.0144	5.84
82.8	5.91	0.0138	5.86

affected by variations in acidity. The result is in agreement with the nitration data,<sup>6</sup> as the reacting species are the free bases in both reactions.

<sup>5</sup> A. R. Katritzky, S. Clementi, and H. O. Tarhan, *J.C.S. Perkin II*, 1975, 1624.

<sup>6</sup> C. D. Johnson, A. R. Katritzky, M. Kingsland, and E. F. V. Scriven, *J. Chem. Soc. (B)*, 1971, 1.

<sup>7</sup> A. R. Katritzky, H. O. Tarhan, and S. Tarhan, *J. Chem. Soc. (B)*, 1970, 114.

<sup>8</sup> A. G. Burton, R. D. Frampton, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1972, 1940.

<sup>9</sup> A. El-Anani, P. E. Jones, and A. R. Katritzky, *J. Chem. Soc. (B)*, 1971, 2363.

*2,6-Dimethoxypyridine*.—The rate profile shows a mechanistic changeover at *ca.* 70% D<sub>2</sub>SO<sub>4</sub> (*ca.* D<sub>0</sub> -5 at 100 °C). At lower acidities this compound reacts as free base, but at higher acidities predominantly the protonated species undergoes exchange. Previous work had shown that the conjugate acid was the only species undergoing nitration.<sup>7</sup>

homocyclic protons disappear at rates which are indistinguishable, as the calculated rate constant does not vary with the extent of reaction. At the end of the reaction the remaining homocyclic protons show a singlet, the integration of which indicates the two protons, H-6 and -7, known to have the closest chemical shifts in various solvents.<sup>10</sup> Blank experiments in

TABLE 2  
Standard rates for the compounds studied

Compound	T/°C	Position	Species	Range		-log <i>k</i> (pH 0, T)	-log <i>k</i> (pH 0, 100°)	p <i>K</i> <sub>a</sub>		<i>m</i>	-log <i>k</i> <sub>0</sub>
				D <sub>2</sub> SO <sub>4</sub>	Slope			25°	100°		
Uracil	60	5	FB	55—66	0.00	3.34	1.23	-1.45	-0.97	0.53	1.75
1,3-Dimethyluracil	40	5	FB	54—67	0.00	3.74	0.37	-1.45	-0.97	0.56	0.92
2,6-Dimethoxypyridine	100	3, 5	CA	72—80	0.81	7.77	7.77				7.77
2,6-Dimethoxypyridine	100	3, 5	FB	57—68	0.00	4.34	4.34	2.00	1.73	1.00	2.61
4-Dimethylaminopyridine	80	3, 5	CA	56—73	0.93	8.54	7.54				7.54
Cinnoline	150	5, 8	CA	83—91	0.00	5.84					

TABLE 3

Comparison between standard rates for nitration (log *k*<sub>2</sub><sup>0</sup>)<sup>a</sup> and hydrogen exchange at H<sub>0</sub> 0 and T 100 °C (log *k*<sub>0</sub>)<sup>a</sup> and at H<sub>0</sub> -6.6 and T = 25 °C (log *k*<sub>0</sub>')<sup>b</sup>

No.	Compound (position)	Species <sup>c</sup>	-log <i>k</i> <sub>2</sub> <sup>0</sup>	-log <i>k</i> <sub>0</sub> '	-log <i>k</i> <sub>0</sub>
1	Benzene	AR	-0.45	6.03	11.00
2	Bromobenzene ( <i>p</i> )	AR	0.15	6.36	11.58
3	Toluene ( <i>m</i> )	AR	-0.26	5.66	11.42
4	Naphthalene ( <i>β</i> )	AR	-0.85	4.74	8.11
5	2,4,6-Trimethylpyridine	CA	10.03	11.75	11.60
6	4-Dimethylaminopyridine	CA	2.98 <sup>d</sup>	5.81	7.54 <sup>f</sup>
7	4-Pyridone	FB <sup>e</sup>	1.69	4.87	4.80
8	2-Pyridone (5)	FB <sup>e</sup>	0.85	5.67	4.80
9	2,6-Dimethoxypyridine	CA	4.73 <sup>d</sup>	7.50	7.77 <sup>b</sup>
10	Uracil	FB	4.38 <sup>d</sup>	2.92	1.23 <sup>b</sup>
11	1,3-Dimethyluracil	FB	3.84 <sup>d</sup>	2.18	0.37 <sup>b</sup>
12	1-Methylpyrazole	CA	7.60	9.09	7.60
13	1,5-Dimethylpyrazole	CA	6.16	7.62	6.60
14	1,3-Dimethylpyrazole	CA	5.94	7.17	6.10
15	1,3,5-Trimethylpyrazole	CA	4.93	5.23	5.40
16	1,2,3,5-Tetramethylpyrazolium	Cation	4.79	5.54	5.00
17	Isothiazole	FB	3.82	6.89	7.50
18	3-Methylisothiazole	FB	2.66	5.56	6.50
19	5-Methylisothiazole	FB	2.94	4.86	6.30
20	3,5-Dimethylisothiazole	CA	9.03	11.09	10.10
21	2,3,5-Trimethylisothiazolium	Cation	9.03	10.28	10.20
22	3,5-Dimethylisoxazole	FB	2.72	2.92	3.40
23	Quinoline (8)	CA	6.36	10.63	11.50
24	Isoquinoline (5)	CA	5.46	9.72	11.70
25	Thieno[2,3- <i>b</i> ]pyridine	CA	3.31	8.45	8.45 <sup>f</sup>

<sup>a</sup> Ref. 5 unless otherwise stated. <sup>b</sup> This work. <sup>c</sup> AR = aromatic non-basic, CA = conjugate acid, FB = free base. <sup>d</sup> Ref. 3. <sup>e</sup> Zwitterion. <sup>f</sup> S. Alunni, S. Clementi, and L. H. Klemm, *J.C.S. Perkin II*, 1976, 1135.

*4-Dimethylaminopyridine*.—The rate profile clearly indicates that the reaction proceeds on the first conjugate acid as majority species in the range 56—70% D<sub>2</sub>SO<sub>4</sub>. At higher acidities the rate tends to level off as we get close to the second p*K*<sub>a</sub> of the substrate, but the reaction still proceeds on the same monoprotonated form as minority species. The extrapolation of the linear arm permits the calculation of the standard rate for this species on which nitration also takes place.<sup>8</sup>

*Cinnoline*.—The n.m.r. spectrum of cinnoline in D<sub>2</sub>SO<sub>4</sub> exhibits the following signals, τ 0.16 (d, *J*<sub>3,4</sub> 6 Hz, H-3), 0.46 (d, *J*<sub>3,4</sub> 6 Hz, H-4), 1.00br (m, homocyclic protons). On prolonged heating at 150 °C (the reaction is complete in about one week) the signals for two of the

H<sub>2</sub>SO<sub>4</sub> showed no appreciable variation of the n.m.r. spectrum. Thus, exchange takes place at C-5 and -8, and this result is in keeping with nitration data, where the 5- and 8-nitro-isomers are formed in similar quantities.<sup>11</sup>

The rate profile indicates that in the range 83—91% D<sub>2</sub>SO<sub>4</sub> exchange takes place on the first conjugate acid of cinnoline as minority species. At higher acidities the reaction seems to proceed on the second conjugate acid. (Work is in progress to determine the second p*K*<sub>a</sub> of cinnoline and therefore to make possible the calculation of the standard rate.) The kinetic data, showing the closeness of the reactivities at C-5 and -8, does not support a fixed form for the monoprotonated cinnoline,

<sup>10</sup> P. J. Black and M. L. Heffernan, *Austral. J. Chem.*, 1965, **18**, 707.

<sup>11</sup> R. B. Moodie, E. A. Qureshi, K. Schofield, and J. T. Glegghorn, *J. Chem. Soc. (B)*, 1968, 312.

otherwise one of the two positions should have been deactivated. Although previous work favours predominant N-2 protonation,<sup>12,13</sup> our results suggest an equilibrium between protonation at N-1 and -2, thus

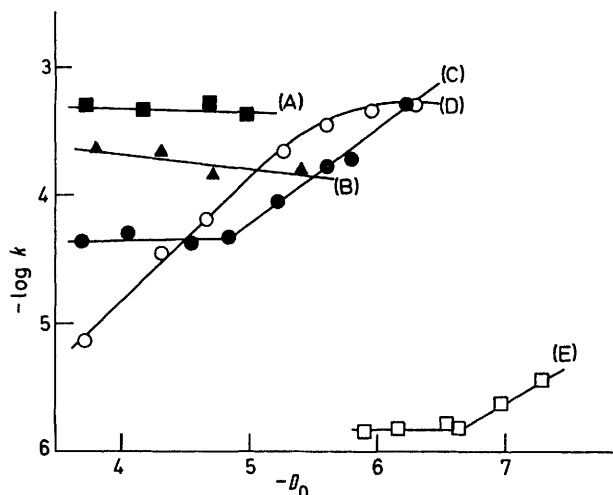


FIGURE 1 Rate profiles for hydrogen exchange of 5-H of 1,3-dimethyluracil at 40 °C (A), of 5-H of uracil at 80 °C (B), of 3- and 5-H of 2,6-dimethoxypyridine at 100 °C (C), of 3- and 5-H of 4-dimethylaminopyridine at 80 °C (D), and of 5- and 8-H of cinnoline at 150 °C (E)

supporting the view that the difference between the two  $pK_a$  values for the first proton uptake is small.<sup>13</sup>

*Correlation between Standard Hydrogen Exchange and Nitration Rates.*—In our initial comparison of the standard rates of individual substrates towards hydrogen exchange (at  $H_0$  0 and  $T$  100 °C) and nitration (at  $H_0$  -6.6 and  $T$  25 °C) we used 30 points. This plot clearly demonstrated the absence of a unique linear relationship.<sup>5</sup>

To avoid a possible failure of the correlation because of the variation of the acidities used in the two standardisation procedures we have now extrapolated the hydrogen exchange rates to the same standard conditions selected for nitration ( $k_0'$ ). The results for all the compounds used are collected in Table 3. The variations in the nitration-hydrogen exchange correlation due to the change in the standard conditions for the latter are shown in Figure 2. The change in temperature has necessarily no effect as an average value of 30 kcal mol<sup>-1</sup> was used as activation enthalpy for all substrates.<sup>2</sup> The big variations in the standard rate changes for hydrogen exchange are due to large differences in the slopes of rate profiles for individual substrates (from 1.6 for non-basid benzenoid aromatics to 0.5 for pyrazole derivatives).

Use of the same standard conditions for the two reactions should help avoid different activity coefficients for the substrates in the partial rate factors.<sup>14</sup> Never-

<sup>12</sup> D. E. Ames, G. V. Boyd, R. F. Chapman, A. W. Ellis, A. C. Lovesey, and D. Waite, *J. Chem. Soc. (B)*, 1967, 748.

<sup>13</sup> J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, 'The Tautomerism of Heterocycles,' Supplement 1 of the series 'Advances in Heterocyclic Chemistry,' Academic Press, New York, 1976, p. 82 and references quoted therein.

theless Figure 2 clearly shows that, although the correlation is improved (the correlation coefficient increases from 0.429 to 0.787), it is still far from an acceptable linear relation. The trend of the arrows could be taken to indicate a still better linearity at higher acidities. However at higher acidities the standard nitration rates should also be changed to maintain identical conditions, and the slopes of the nitration profiles are much steeper than those for hydrogen exchange.

The calculation of the  $\log k_0'$  values reported in Table 3 is straightforward for the substrates reacting as conjugate acids; as the linear arm of the rate profile is extrapolated to  $H_0$  -6.6, and the quantity 4.42 (from  $\Delta\bar{H} \neq 30$  kcal mol<sup>-1</sup>) subtracted to account for the temperature variation from 100 to 25 °C. The calculation for free base reactivities requires  $pK_a$  values at 25 °C, whereas  $\log k_0$  was deduced from  $pK_a$  values at 100 °C. The procedure utilised commences with  $\log k$  (stoich) at  $H_0$  0 and  $T$  100 °C (an intermediate step in the calculation of  $\log k_0$ ) and further steps summarised as follows: (a) acidity extrapolation (all cases),  $\log k$  (stoich) + 6.6 d( $\log k$ )/d(- $H_0$ ) = A; (b) temperature extrapolation (all cases),  $A - 4.42 = B$ ; (c) minority species correction (free base reactions only), for  $pK_2 < 0$ ,  $\log k_0' = B + m(6.6 + pK_a)$ , for  $pK_a > 0$ ,  $\log k_0' = B + pK_a + 6.6m$ , where  $m$  represents  $1/n$ , i.e. the slope of the plot  $\log I$  versus (- $H_0$ ). Figure 3 illustrates the minority species correction for the case  $pK_a < 0$ .

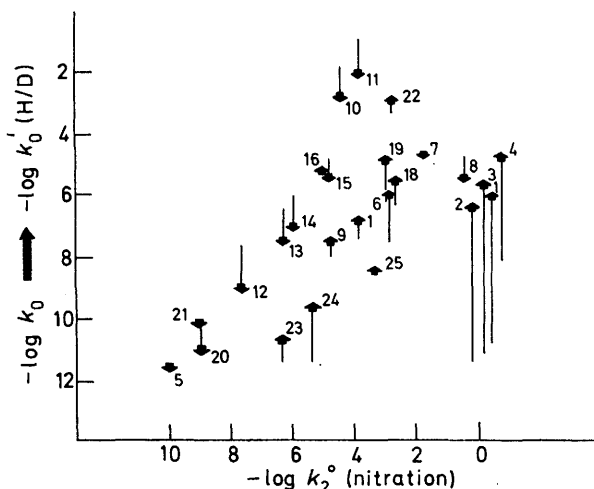


FIGURE 2 Correlation between standard exchange and nitration rates. Variations induced by the modification of the standard exchange rates from  $H_0$  0 and  $T$  100 °C to  $H_0$  -6.6 and  $T$  25 °C

The final plot of the standard rates for the two reactions at  $H_0 = -6.6$  and 25 °C is shown in Figure 4. The data for the compounds previously used,<sup>5</sup> for which the nitration rate was limited by the encounter rate, are excluded as well as those for the less reactive positions of quinoline, isoquinoline, and 2-pyridone, since they could be misleading. Six new points were added. A striking conclusion from the graph is that the reactivities of some pairs of compounds is reversed towards the two

<sup>14</sup> R. A. McClelland, T. A. Modro, M. F. Goldman, and K. Yates, *J. Amer. Chem. Soc.*, 1975, **97**, 5223.

electrophiles. For instance 4-pyridone is more reactive than benzene towards deuteration, but less reactive towards nitration. This fact is not compatible with any postulate that the susceptibility to electrophilic attack derives uniquely from the electron density (or any other theoretical index) of the substrates. Nevertheless, we believe the evidence for the existence of reactivity inversions to be compelling.\* Consequently, there is no unique order of the susceptibility of individual ring positions towards electrophilic attack, and therefore no quantum chemical calculation can provide a general measure of reactivity, unless it considers explicitly the role of reagent and/or solvent.

The second important conclusion from Figure 4 is that the five-membered rings, the six-membered rings, and the bicyclic compounds individually give three good linear correlations. (i) Points 12—15 and 20 (pyrazoles as CA) give  $r$  0.992. Inclusion of 22 (isoxazole, FB) also gives 0.993. Further inclusion of 16 and 21 (cation perchlorates) still gives 0.986, although inclusion of 17—19 (isothiazoles, FB) lowers  $r$  to 0.922. (ii) Points 5—7 and 9 give an excellent straight line ( $r$  0.999 6) for the only four 4-substituted pyridines. The inclusion of 8 (2-pyridone) still gives an acceptable  $r$  value (0.964),

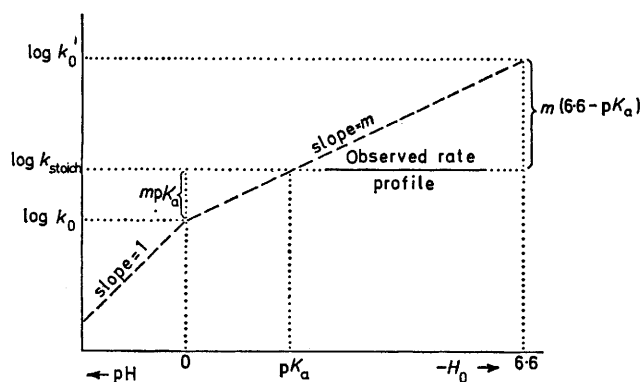


FIGURE 3 Minority species correction required for extrapolation to  $H_0 = 6.6$  (case of  $pK_a < 0$ )

although the two uracils are further from linearity. (iii) The four bicyclic compounds also fall on a good straight line ( $r$  0.997).

The compounds reacting as free bases (except the

\* Unfortunately, direct competitive experiments to demonstrate reactivity inversions are not easy to carry out. Thus all the compounds on the right hand side of Figure 4 react as free bases; and concentration effects overwhelm the expected reactivity differences. Substrates reacting as majority species (those on the left hand side of Figure 4) possess reactivities too low to be measured at or near the standard conditions, and the variation of acidity or temperature would not provide compelling evidence of the validity of the standardisation procedure, because of the large differences in the rate profile slopes of individual compounds.

pyridones which can be considered as zwitterions and therefore compared with protonated pyridines) follow less clear relationships.

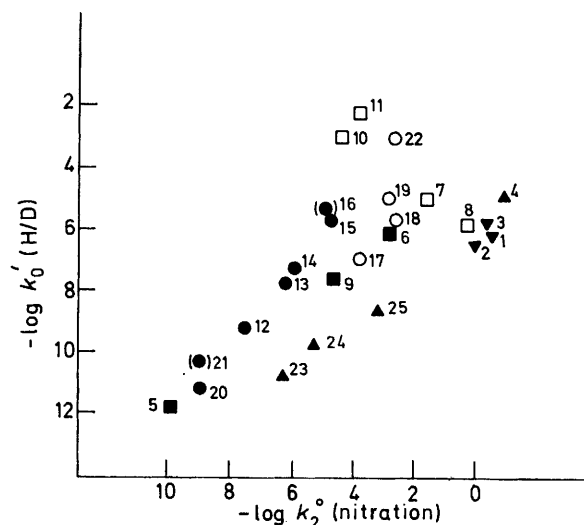


FIGURE 4 Plot of rates for hydrogen exchange against rates for nitration at the same standard conditions ( $H_0 = 6.6$ ,  $T$  25 °C). The numbers identify the compounds as in Table 3

**Conclusions.**—This work establishes the absence of a unique scale of reactivity valid for electrophilic substitution reactions, even when the same acidity is used as standard. For conjugate acid reactivities each class of closely related compounds shows individual linearity. The existence of such partial correlations suggests that it is the differing significance of interactions between substituents in the different transition states for nitration and hydrogen-exchange which preclude the definition of a unique sequence for electrophilic reactivity.

*Note added in proof:* Part of the reason for non-linearity in Figure 2 may be due to *ortho*-substitution affecting nitration and hydrogen exchange unequally.† Since this paper was written, we have been increasingly concerned that the nitration rates may often not reflect positional reactivities:‡ we have shown ‡ that the complications found by Ridd *et al.*‡ for the nitration of *NN*-dimethyl-*p*-toluidine probably apply to the nitration of methylpyridones.

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‡ Unpublished work by S. Clementi and G. V. Sebastiani.

‡ R. B. Moodie and K. Schofield, *Accounts Chem. Research*, 1976, 9, 287; T. Banwell, C. S. Morse, P. C. Myhre, and A. Vollmar, *J. Amer. Chem. Soc.*, 1977, 99, 3042; R. B. Moodie, P. N. Thomas, and K. Schofield, *J.C.S. Perkin II*, 1977, 1693.

‡ K. Fujiwara, J. C. Giffney, and J. H. Ridd, *J.C.S. Chem. Comm.*, 1977, 301.