Polar Effects in the Homolytic Methylation of Pyrimidine: Orientation and Polysubstitution

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The homolytic methylation of pyrimidine in aqueous solution has been investigated with three different radical sources: Bu^{t}OOH–Fe^{2+}, $MeCO_2H$–$S_2O_8^{2-}$–Ag^+, and MeSOMe–H_2O_2–Fe^{2+}. This last reagent, used for the first time in homolytic aromatic substitution, turned out to be the most efficient. The orientation of mono- and poly-methylated derivatives is discussed on the basis of polar effects.

The homolytic substitution of protonated heteroaromatic bases by nucleophilic carbon-centred radicals is one of the most significant reactions in heterocyclic chemistry.[1] Polar effects, related to the nucleophilic character of the radical and the electron deficiency of the aromatic substrate, are considered to be the main cause of selectivity and therefore of any consequent synthetic interest.[1,2]

In this paper we report results obtained in the reaction of protonated pyrimidine with methyl radical. The methyl radical is the least nucleophilic of the simple unsubstituted alkyl radicals;[1,2] however, the polar effect is the result of both the donor character of the radical and the acceptor character of the aromatic ring,[1,2] so that some selectivity might be foreseen for the methyl radical on the grounds of the high electron affinity of the protonated pyrimidine ring. The equivalent pyrimidine positions 4 and 6 are more reactive than position 2 towards ionic nucleophilic species, and it was also of interest to verify if such behaviour is still present with the methyl radical. Furthermore, the observed selectivity was expected to offer indications about the synthetic potential of the reaction.

Results and Discussion

Three simple sources of methyl radical were used for the methylation of pyrimidine:

(i) Bu^{t}OOH and Fe^{2+} [equations (1) and (2)]: [1]

$$Bu^tOOH + Fe^{2+} \longrightarrow Bu^tO^{\cdot} + Fe^{3+} + OH^- \quad (1)$$

$$Bu^tO^{\cdot} \longrightarrow MeCOMe + Me^{\cdot} \quad (2)$$

(ii) MeSOMe, H_2O_2, and Fe^{2+} [equations (3) and (4)]:

$$H_2O_2 + Fe^{2+} \longrightarrow HO^{\cdot} + Fe^{3+} + OH^- \quad (3)$$

$$MeSOMe + {}^{\cdot}OH \longrightarrow Me\overset{O^{\cdot}}{\underset{S}{|}}(OH)Me \longrightarrow Me^{\cdot} + MeSO_2H \quad (4)$$

(iii) $MeCO_2H$, $S_2O_8^{2-}$, and Ag^+ [equations (5)—(7)]:

$$Ag^+ + S_2O_8^{2-} \longrightarrow Ag^{2+} + SO_4^{\cdot -} + SO_4^{2-} \quad (5)$$

$$Ag^+ + SO_4^{\cdot -} \longrightarrow Ag^{2+} + SO_4^{2-} \quad (6)$$

$$MeCO_2H + Ag^{2+} \longrightarrow Ag^+ + H^+ + MeCOO^{\cdot} \longrightarrow Me^{\cdot} + CO_2 \quad (7)$$

All the radical sources were used in aqueous solution, at room temperature with sources (i) and (ii) and at 90 °C with source (iii). The results are summarized in the Table.

Dimethyl sulphoxide in the presence of the redox system H_2O_2–Fe^{2+} was the most efficient among the investigated radical sources; it is the first time, as far as we know, that this source has been used in homolytic aromatic methylation.

The importance of polar effects is clearly shown by the fact that only the positions of high nucleophilic reactivity (2, 4, and 6) are involved. No attack at position 5 was observed, not even at high conversions when significant amounts of 2,4,6-trimethylpyrimidine are present (entries 4 and 5). This orientation can be related to a transition state with considerable charge-transfer character [equation (8)], due to the nucleophilic character of the methyl radical and the electron deficiency of the pyrimidine ring.

The closely similar conversions in the entries 1 and 2, which differ only in the amount of Bu^{t}OOH, indicate that an induced decomposition of Bu^{t}OOH according to equation (9) does not occur significantly.

Rearomatization of the radical adduct, on the other hand, is not likely to occur by electron-transfer oxidation of the protonated form by the metal salt [equation (10)], because of the relatively high redox potential of the protonated pyrimidine ring.

The clean rearomatization of the radical adduct would also exclude in this step a hydrogen abstraction by the intermediate radicals (disproportionation included) [equation (11)].

Thus we suggest that the rearomatization takes place by oxidation of the unprotonated radical adduct. Two routes can be envisaged: (a) an acid–base equilibrium (pyrimidine is a relatively weak base); the equilibrium would be continuously shifted by oxidation of the unprotonated form [equations (12) and (13)]; (b) irreversible loss of a proton with formation of an α-aminoalkyl radical [equation (14)]. It is well known [3] that the amine radical cations easily undergo such a process.

Moreover, α-aminoalkyl radicals are weaker bases than the parent amines and, at the same time, very easily oxidisable.[4] This behaviour can be related to the canonical structure (A), which increases the nucleophilic character and therefore the oxidisability [equation (15)] of the α-aminoalkyl radicals in comparison with the simple alkyl radicals, and decreases their basic character. This mechanism could be very general for homolytic substitution of protonated heteroaromatic bases and thus explain the ease and the cleanness of the rearomatization of the intermediate radical adducts.

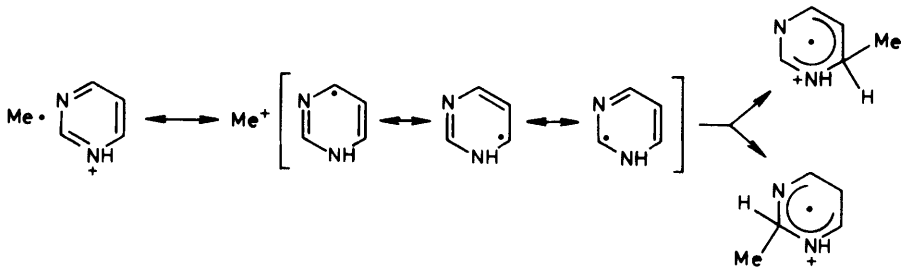
The results in the Table also indicate that the introduction of a methyl group only slightly affects the reactivity of the pyrimidine ring, so that polysubstitution becomes increasingly important with increasing conversion. This suggests that monomethylation of the pyrimidine ring can become synthetically interesting only if two of the positions 2, 4, and 6 are substituted.

It is noteworthy that in all cases the two disubstituted

Table. Homolytic methylation of pyrimidine, 4-methylpyrimidine, and 2-methylpyrimidine

Entry [a]	Radical source (mol per mol of heteroaromatic base)	Conversion (%) [b]	2-Me (%)	4-Me (%)	2,4-Me_2 (%)	4,6-Me_2 (%)	2,4,6-Me_3 (%)
1	Bu^tOOH (0.3), Fe^{2+} (0.3)	7.1	14	84	0.9	0.8	
2	Bu^tOOH (5), Fe^{2+} (0.3)	7.7	14	84	1	1	
3	Bu^tOOH (1), Fe^{2+} (1)	35.8	20	73	4	3	
4	Bu^tOOH (4), Fe^{2+} (4)	55.7	3	38	23	26	10
5	Me_2SO (4), H_2O_2 (4), Fe^{2+} (4)	88.7	4	39	19	16	22
6	$MeCO_2H$ (5), $S_2O_8^{2-}$ (1), Ag^+ (0.2)	28.4	20	73	4	4	
7	Bu^tOOH (0.5), Fe^{2+} (0.5)	15			32	65	3
8	Bu^tOOH (0.5), Fe^{2+} (0.5)	18			96		4

[a] Entries 1—6, pyrimidine; entry 7, 4-methylpyrimidine; entry 8, 2-methylpyrimidine. [b] Overall yields based on converted pyrimidine are >95%.



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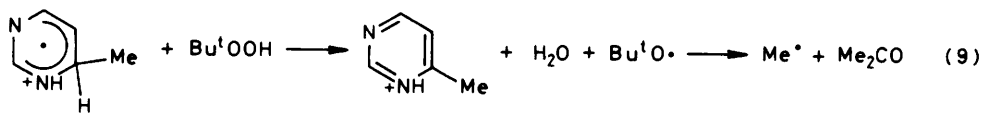

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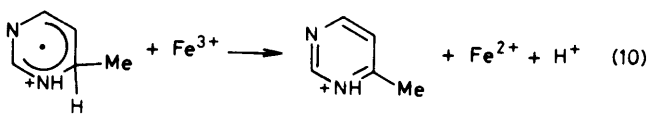

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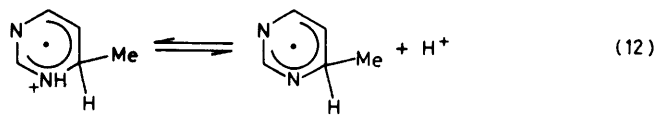

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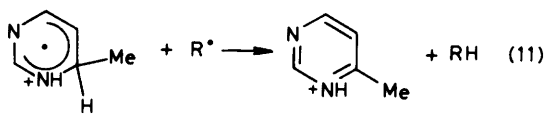

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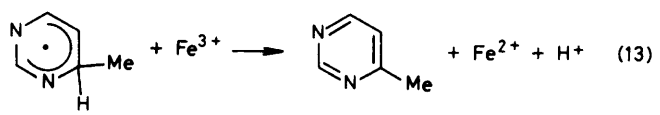


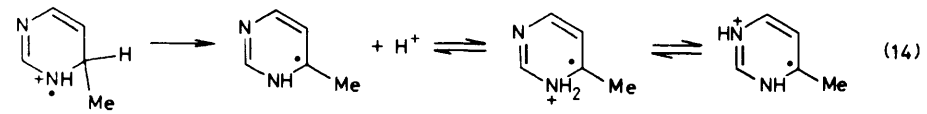
(13)

isomers (2,4 and 4,6) are formed in similar amounts. This can be considered the result of two factors: the different reactivity of the 2- and 4-methylpyrimidines, and the fact that further methylation of the 2-methyl isomer gives rise only to the 2,4-dimethyl isomer (entry 8), whereas methylation of the 4-methyl isomer gives a mixture of 2,4- and 4,6-dimethyl derivatives (entry 7).

Despite the apparent wealth of synthetic information on nucleophilic displacement of halogeno, alkylsulphonyl, and other leaving groups from the pyrimidine ring, only a few quantitative reactivity data are available.[5,6] A 4-chloropyrimidine is usually a little more reactive than its 2-chloro isomer towards aminolysis, although inversion of this relative reactivity takes place at the isokinetic temperature.[7] Also aminolysis of 2,4-dichloropyrimidine generally leads to a slight prevalence of the substitution of the chlorine in position 4; this selectivity is increased by using a protic solvent.[8]

Homolytic methylation shows an analogous trend. Position 4 is considerably more reactive than position 2; however, the 2 : 4 isomer ratio gives a measure of the relative rates only at low conversion. At higher conversions increasing amounts of polymethylated pyrimidines affect the isomer ratio. It appears that protonation of the pyrimidine ring, besides causing the obvious increase in overall nucleophilic reactivity, also determines a higher selectivity between positions 4 and 2. The protonation effect in homolytic methylation is similar to that of protic solvents in ionic nucleophilic substitutions; the formation of hydrogen bonds between the solvent and the heterocyclic nitrogen might increase the selectivity for position 4 in ionic substitution.

The similarity of behaviour between nucleophilic free radicals and ionic nucleophilic species may find a common mechanistic point in the model developed by Shaik and Pross [9] for nucleophilic substitutions. In this model an electron-transfer configuration [equation (16)] can contribute to the transition state to a greater or lesser extent depending on the donor properties of the nucleophile and the acceptor properties of the substrate. Complete electron transfers are limit cases of this transition state; they actually occur between heteroaromatic compounds and both nucleophilic radicals [10] and ionic nucleophiles [11] when the redox potentials of the partners make the electron-transfer equilibria favourable.



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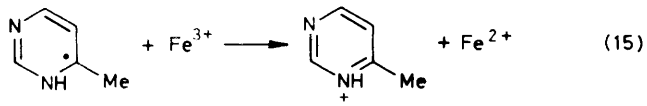

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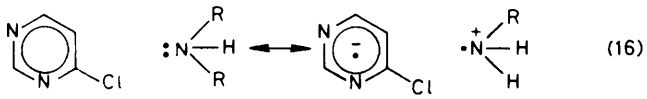

(16)

Experimental

Radical Source (i).—Saturated aqueous solutions of Bu^{t}OOH and $FeSO_4$ (in the ratios reported in the Table) were added simultaneously to a solution of pyrimidine (40 mmol) in water (40 ml) and 50% H_2SO_4 (6 ml; 40 mmol) with stirring at 20—25 °C within 30 min. The solution was made alkaline with 10% NaOH and exhaustively extracted continuously with CH_2Cl_2. The organic layer was analysed by g.l.c. (C.E.4200 instrument, SP 4100 integrator, column D-OV 101 on Chromosorb W HP 10%; 4-methylpyridine as internal standard).

Radical Source (ii).—Aqueous 30% H_2O_2 and saturated aqueous $FeSO_4$ solution (in the ratios reported in the Table) were added simultaneously to a solution of dimethyl sulphoxide (amounts reported in the Table) and pyrimidine (40 mmol) in water (40 ml) and 50% H_2SO_4 (6 ml). The solution was made alkaline with 10% NaOH and exhaustively extracted continuously with CH_2Cl_2. The organic layer was analysed by g.l.c.

Radical Source (iii).—A solution of pyrimidine (40 mmol), acetic acid (200 mmol), $(NH_4)_2S_2O_8$ (40 mmol), and $AgNO_3$ (8 mmol) was heated with stirring at 90 °C for 2 h. After cooling, the solution was made alkaline with 10% NaOH and exhaustively extracted continuously with CH_2Cl_2; the organic layer was analysed by g.l.c.

All the methylpyrimidines were known compounds; they were identified by g.l.c. and spectroscopic (i.r., n.m.r.) comparison with authentic samples (2-methyl,[12] 4-methyl,[13] 2,4-dimethyl,[14] 4,6-dimethyl,[15] 2,4,6-trimethyl [16]).

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