HETEROAROMATIC AZO-ACTIVATED NUCLEOPHILIC SUBSTITUTIONS. THE REACTION OF 4-(p-METHOXYPHENYLAZO)PYRIDINIUM METHIODIDE WITH PIPERIDINE IN DIMETHYL SULPHOXIDE

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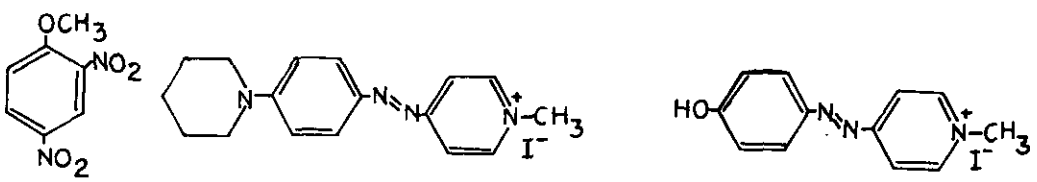
Abstract - The azopyridinium-activated phenyl methyl ether, 1, undergoes nucleophilic attack by piperidine in dimethyl sulphoxide predominantly at the aryl carbon centre in a reaction that is base catalyzed and faster than the corresponding reaction of the dinitro-activated analogue, 2, by more than two decades.

Alkyl aryl ethers are insensitive to hydrolysis and similar nucleophilic substitution reactions. When the aromatic ring is activated through azophenyl substitution these compounds become susceptible to nucleophilic attack in moderately to strong acidic aqueous media[1]. In recent work we have shown that azopyridinyl substitution has a dramatic effect on the reactivity of these compounds particularly when the aza substituent is in a position where it can interact conjugatively with the reaction centre[2]. In these examples, one or more protonation equilibria in the acidic media employed occur prior to nucleophilic attack. In connection with these studies and in furtherance of our recent interest in azo compounds as dyes we have synthesized

1 ⟷ 1a



2 3 4

the azopyridinium-activated phenyl methyl ether, 4-(p-methoxyphenylazo)pyridinium methiodide, 1. We wish to report that 1 undergoes facile nucleophilic attack by piperidine in the dipolar aprotic solvent dimethyl sulphoxide (DMSO) at rates that are significantly faster than the corresponding reactions of 2,4-dinitroanisole, 2, where activation is provided by two nitro groups.

Diazotization of 4-aminopyridine followed by coupling with phenol yielded 4-(p-hydroxyphenylazo)-pyridine. Treatment of this azopyridinyl-substituted phenol with 0.1 M methanolic H_2SO_4 under reflux for 4 h followed by neutralization with ice-cold NaOH solution afforded the azopyridinyl-substituted phenyl methyl ether which, on refluxing with CH_3I in methanol for 8 h at 74°C, gave 1[3].

The kinetics of the reaction of 1 with piperidine in DMSO at 30°C were followed spectrophotometrically with the amine in large enough excess to ensure first order kinetics. The reaction gave experimental absorbance values at infinite time of the product of attack at the aryl carbon, 3, which was less than the calculated infinity values at low piperidine concentrations, e.g. 7.0-10x10^{-3}M piperidine. Good agreement between the two values was obtained at higher piperidine concentrations. This behaviour is due to competing attack by the nucleophile on the aryl carbon to give 3 and on the alkyl carbon to give 4 and N-methylpiperidine at low piperidine concentrations. As compound 4 is known from the work of Buncel and Keum[4] and was identified spectrophotometrically by us, a rate constant for the S_N2 reaction at the alkyl carbon of ca. 1.7x$10^{-3}M^{-1}s^{-1}$ was calculated. The value of this rate constant was independent of piperidine concentration. At higher nucleophile concentrations attack on the aryl carbon centre predominates. The relative values of the rate constants for the attack on the aryl carbon (see Table 1) and the S_N2 reaction explains the increasing preponderance of aromatic nucleophilic substitution (S_NAr) with increasing piperidine concentration.

Table 1. Rate constants ($M^{-1}s^{-1}$) for the reaction of 1 with piperidine in DMSO at 30°C (Initial [1] = 1.50x10^{-4}M).

10^2(piperidine)/M:	0.70	1.00	2.00	4.00	8.00	10.0
10^3k_A :	2.35	3.16	4.79	7.83	11.4	12.8

Concurrent S_NAr and S_N2 reactions have also been observed in the reaction of 2 with piperidine in DMSO, methanol and benzene[5].

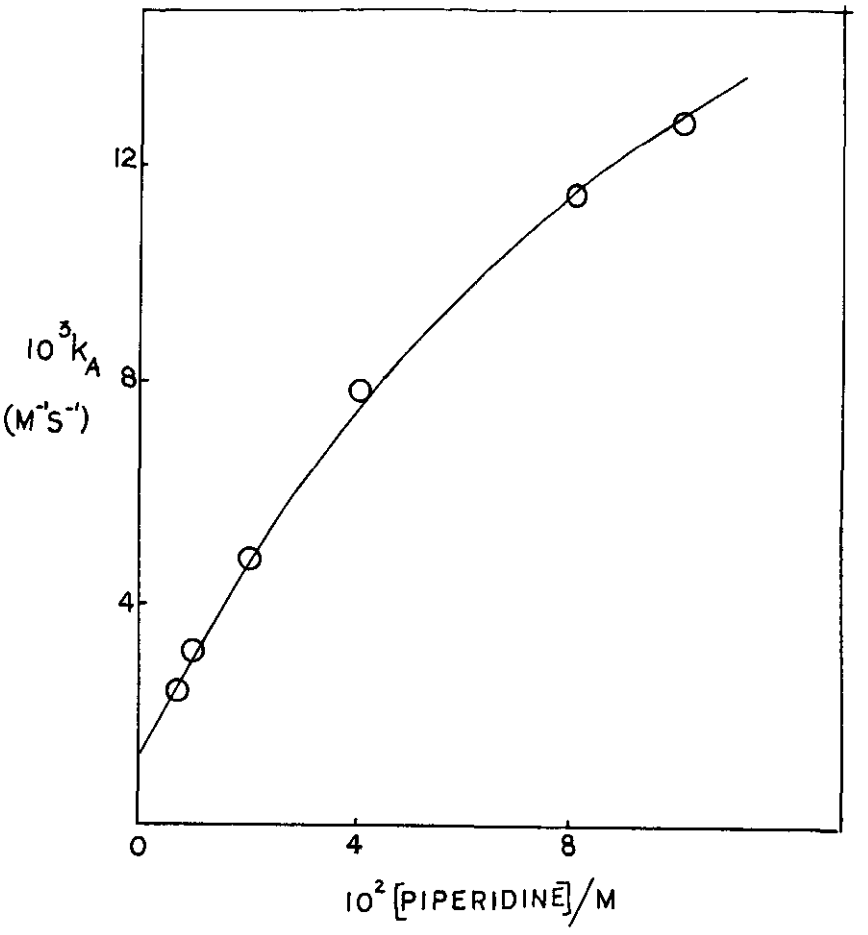


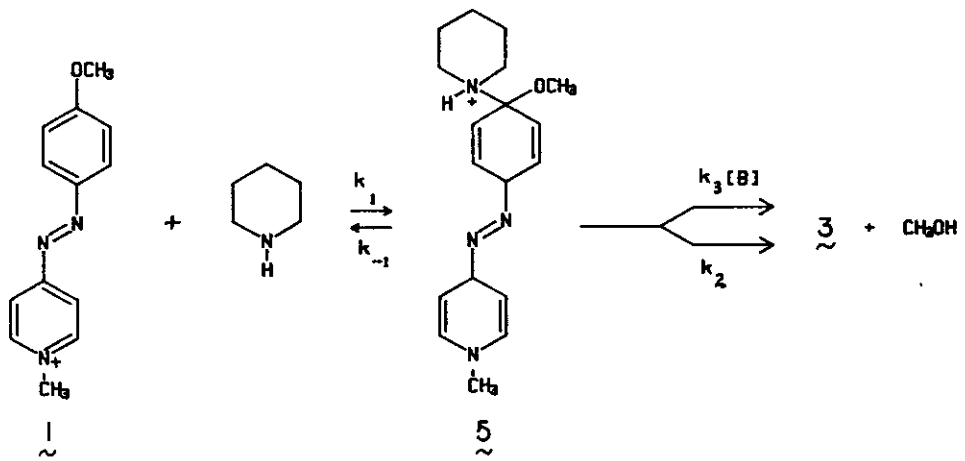
Figure 1. Plot of the second order rate constant, k_A, versus piperidine concentration.

The S_NAr reaction is catalysed by piperidine (see Table 1). A plot of the observed second order rate constant, k_A, against piperidine concentration is curvilinear (Figure 1). This kinetic form is explicable in terms of the accepted mechanism for base catalysed S_NAr reactions given in the scheme. In the steady state rate expression of Eq (i) derived from the mechanism of the scheme, the observed kinetic form corresponds to the condition $k_{-1} \sim k_2 + k_3[B]$,

$$k_A = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]} \qquad (i)$$

in which case the decomposition of the intermediate 5 is rate limiting at least at low base (piperidine) concentrations. There is controversy regarding the detailed mechanism of the base

Scheme



catalysed piperidinodemethoxylation of aromatic substrates[6] and the present results do not allow for a choice between the proffered alternatives.

What these results highlight is the powerful activating influence of the azopyridinium group. A comparison of reactivity of 1 and 2 towards substitution by piperidine[5a] in DMSO reveals that 1 reacts faster than 2 by factors of ca. 2×10^2 and 3×10^2 in the S_NAr and S_N2 reactions respectively. Hence there is a difference in the activation energies of the order of 3-5 k cal mol^{-1} in the reactions of 1 and 2. These impressive differences in rates in both reactions must have their origin in the presence of the azopyridinium function in 1 in which the pyridinium moiety serves as an electron sink by the extensive delocalization of the incoming electrons from the nucleophile. This is evident from the resonance contributing structure 1a. Thus quaternization of the pyridine nitrogen in 1 obviates the need for the protonation(s) in acidic media necessary for the activation of azophenyl and azopyridinyl ethers towards nucleophilic substitution[1,2]. It is also conceivable that transition state effects could as well be important in the determination of the rate ratios noted above. A systematic investigation of the origin of these rate differences as well as the use of 1 as a model compound in seeking further information regarding the details of the mechanisms of base catalysed S_NAr reactions is under active consideration.

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3. Compound 1 was obtained in 21% yield from the starting materials (no attempt was made at optimization of the yield) and has the following characteristics: mp 178-179°C, λ_{max} (ε) in MeOH: 390 nm (31,600 M^{-1} cm^{-1}). Found: C, 44.93; H, 3.93; N, 11.96; I, 36.54%. Calc. for $C_{13}H_{14}N_3OI$: C, 43.96; H, 3.97; N, 11.83; I, 35.73%.

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