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MECHANISM OF THE REACTION OF 2-HALOKETONES WITH 2-AMINOPYRIDINE[1]

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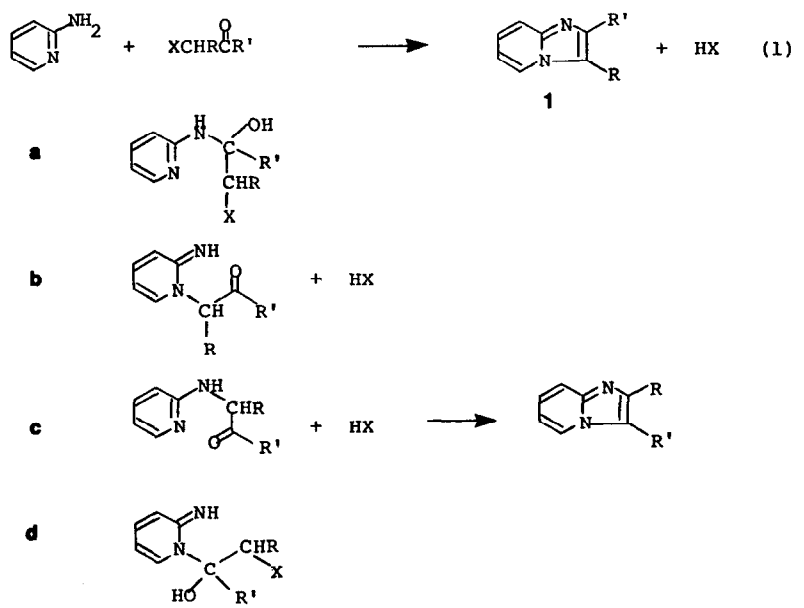
Abstract—Time-dependent ^{1}H NMR spectra of DMSO-d_6 solutions of *p*-substituted phenacyl bromides and 2-aminopyridine indicate that the formation of imidazo[1,2-*a*]pyridines occurs *via* two relatively long-lived intermediates, **C** and **D**, which are in equilibrium with each other. The assigned structures are in accord with chemical shifts, pK_a estimates, and substituent effects (-OMe-CH_3, -H, and -NO_2) on both the equilibrium constant (**C**⇌**D**) and rates of reaction. The slowest step in the reaction with phenacyl bromide is conversion of the intermediate **D** to product **E**. With phenacyl chloride no intermediates are observed and initial formation of **C** determines the overall rate. Even through the intermediate **D** is already protonated, its conversion to **E** is subject to acid catalysis. Compared to the *p*-OMe substituent, the *p*-NO_2 group enhances the rate of formation of **C** and **D** by a factor of only 2.6. The same rate enhancement is observed in the reaction of pyridine with phenacyl bromides. Rates of reaction of a given phenacyl halide with pyridine and 2-aminopyridine are similar. It is concluded that the initial reaction is alkylation of the pyridine nitrogen atom to give **C** and that the other possible initial condensation product, the carbinolamine **F**, cannot be a kinetically significant intermediate. Reasons for preferred N-alkylation are presented. Recommendations for improved syntheses of imidazo[1,2-*a*]pyridines are included.

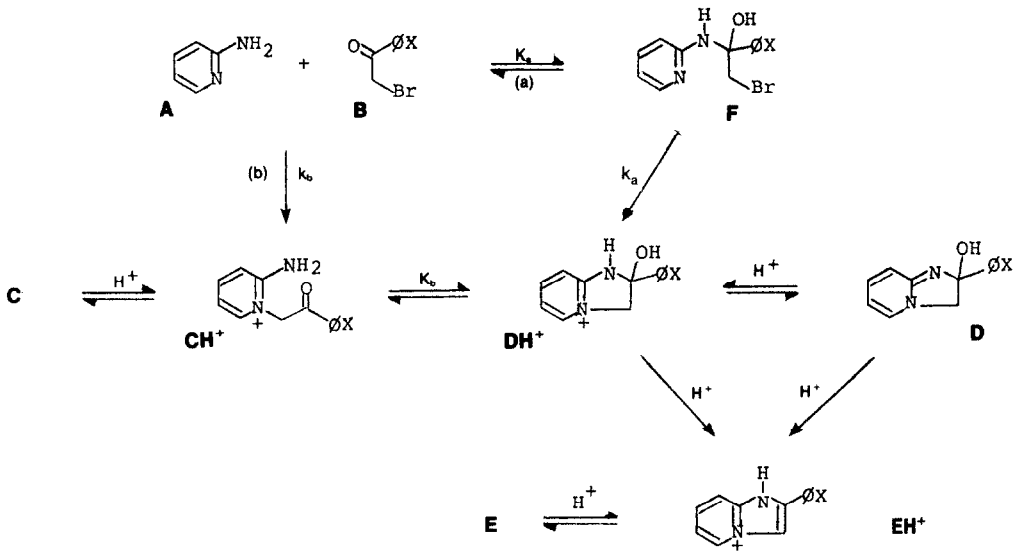
In the condensation of 2-aminopyridines with 2-haloketones or aldehydes, which gives imidazo[1,2-*a*]pyridines (**1**) as the final product (eqn 1), the two reactants may first combine in any one of four ways (*a*–*d*). Products resulting from path *a* or *b* have the substitution pattern shown in eqn (1), whereas R and R′ are interchanged in the products formed *via* path *c* or *d*. From carefully determined structures of the products it is now established that either path *a* or *b* must be the first step when the reaction is carried out in a variety of solvents and in the absence or, more commonly, in the presence of sodium bicarbonate.[2,3] Paths *a* and *b* have both been suggested as the initial step.[8,9] In this report evidence is presented that displacement of halogen by the pyridine nitrogen atom (path *b*) is the first step in the reaction.

RESULTS AND DISCUSSION

The basic steps for the two mechanisms to be considered are shown in Scheme I for the reaction with phenacyl bromides. Note that both paths can give the same intermediates, **DH**$^+$⇌**D** and **CH**$^+$⇌**C**. *Para*-substituted phenacyl bromides were used since different substituents should give variations in reactivity without affecting the steric requirements at the reactive centers. Changes during the reaction were monitored by ^{1}H NMR spectroscopy (DMSO-d_6).

The results are discussed in the following order: A. Spectral changes observed at varying times—formation of two intermediates; B. Structures of intermediates from (1) substituent effects on the equilibrium between them and (2) other data; C. Possible mechanisms for formation of intermediates; D. Improbability of car-





Scheme 1.

binolamine **F** (path *a*) as a kinetically significant intermediate because of (1) the effect of *p*-substituents of phenacyl bromide on its rate of reaction with 2-aminopyridine and (2) comparison of rates of reaction of pyridine and 2-aminopyridine with a given phenacyl bromide; E. Acid catalysis of formation of imidazo[1,2-*a*]pyridines from the intermediate DH^+; F. Reaction of phenacyl chloride; G. Why path *b*? and H. Synthetic considerations.

A. *Spectral changes with time*

The data show that two intermediates, **C** and **D**, are formed, that these are in equilibrium with each other, and that concurrent, but slower, formation of product **E** occurs. Since hydrogen bromide is generated during the reaction, the various bases (**A**, **C**, **D** and **E**) are in equilibrium with the protonated forms.

The changes in the ^1H NMR spectra, illustrated in Fig. 1 for the reaction of *p*-methylphenacyl bromide and *ca.* 20% excess of 2-aminopyridine, are analyzed as follows: (1) The much greater complexity at intermediate times than at the end of the reaction, together with the rapid disappearance of the signals due to phenacyl bromide, indicate that at least one intermediate is formed more rapidly than it is converted to the final product. (2) The gradual down-field shift of the H-3 and H-5 signals of 2-aminopyridine, **A**, (multiplet, 6.9, which separates into a doublet and a triplet) can occur only if **A** is in rapid equilibrium with another species having larger chemical shifts. This condition is satisfied by the formation of acid which is possible only when **C** and/or **D** are formed in significant amounts. Formation of the carbinolamine **F** (and/or its dehydration products) does not generate H^+. (3) The quartet at 5.3, the small singlet at 6.5, and the two doublets near 8 and 8.8 increase and then decrease in intensity and must therefore be due to intermediate(s). (4) The area of the singlet is about 1/5 that of the quartet. Since none of the possible intermediates contains protons in this ratio, these singals are due to two different intermediates. This conclusion is confirmed by the presence of four OMe signals in the spectra of the *p*-methoxyphenacyl bromide reaction (Fig. 2) and their intensity changes with time: **C** and **D** initially increase as **B** decreases, later **E** increases at the expense of the other signals. (5) Since the area ratio of the doublets (8.8 and 8) and the quartet is approximately 1:2:2, these signals can be attributed to one species, the *cyclized* carbinolamine **D** (*vide infra*). (6) The quartet and the doublet at 8.8, both assigned to protons adjacent to nitrogen in structure **D**, fail to move downfield significantly during the course of the reaction. This intermediate therefore exists primarily in the protonated form DH^+, even when the competing base, 2-aminopyridine, is present, and must be a considerably stronger base than 2-aminopyridine. (7) The *relative* areas of the small singlet at 6.5 and the quartet, which cannot be due to the same species (see (4) above), remain approximately constant during the course of the reaction, both when their absolute areas increase and decrease. The species giving rise to these signals are therefore in equilibrium, slow on the NMR time scale, but fast as compared to other steps in the reaction. (8) The most likely species in equilibrium with the cyclic carbinolamine **D** is the aminoketone **C**, and the small singlet is attributable to its $\overset{+}{N}CH_2CO$ protons. This signal does not shift during the course of the reaction, so that this intermediate also is a stronger base than 2-aminopyridine. Other data (*vide infra*) support these conclusions. (9) The 25-min spectrum shows at lowest field the emergence of the H-5 doublet and the H-3 singlet of the final product. These signals become more deshielded as a greater proportion of product becomes protonated by the acid liberated during the consumption of intermediates CH^+ and DH^+. (10) When no further changes occur, all of the signals in the aromatic region can be assigned to product and excess of 2-aminopyridine, both partially protonated. It is estimated that 95% of the phenacyl bromide was converted to the imidazo[1,2-*a*]pyridine.

B. *Structures of the intermediates C and D*

(1) *Equilibria.* ^1H NMR spectra recorded after short reaction times of other substituted phenacyl bromides and 2-aminopyridine confirm the existence of an equili-

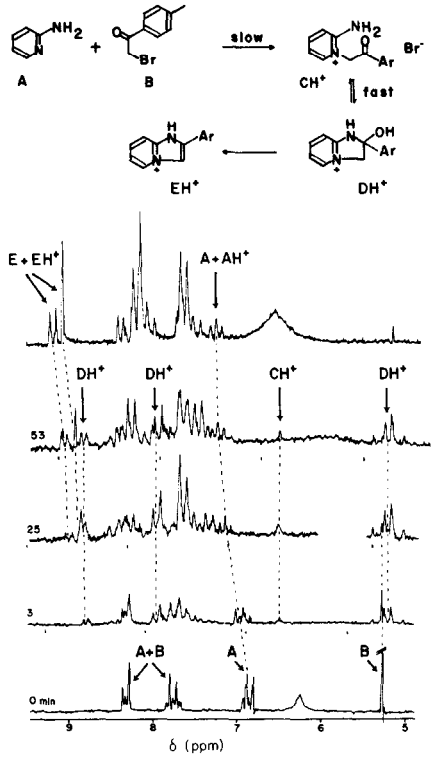


Fig. 1. Partial 100 MHz ^{1}H NMR spectra of a DMSO-d_6 solution recorded 3, 25, and 53 minutes after mixing 2-aminopyridine and *p*-methylphenacyl bromide. The bottom scan is the sum of separately recorded spectra of the two starting materials. The top scan was recorded after no further changes occurred (18 hr). The two lowest spectra are attenuated. Chemical shifts refer to all scans and are relative to external TMS. Relevant assignments are as follows: bottom scan: 5.25 (s): CH_2 protons; 6.9 (m): overlapping H-3 and H-5 signals; 8.3 (m): overlapping signals of *ortho*-protons of **B** and H-6 of **A**; signals connected by dotted lines: A + AH$^+$ (t): H-5 of protonated and non-protonated species; CH$^+$(s): CH_2 protons; DH$^+$: 5.2(q), CH_2 protons; 7.95 (d), phenyl protons *ortho* to carbinolamine substituent; 8.8 (d), proton α to pyridinium introgen; E + EH$^+$: H-3 (s) and H-5 (d) of protonated and nonprotonated species. Top scan: broad peak: NH and H_2O protons; 5.2 (s), side product (see Ref. 10).

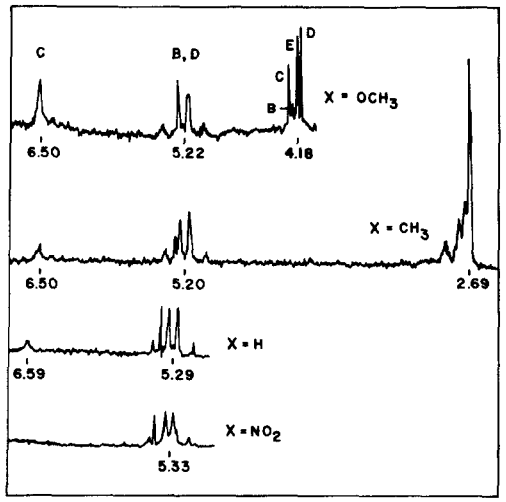


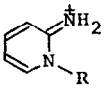
Fig. 2. Partial 100 MHz ^{1}H NMR spectra of DMSO-d_6 solutions of 2-aminopyridine and *p*-X-substituted phenacyl bromides recorded after short reaction times. Chemical shifts are in ppm, relative to external TMS. Assignments are as follows: signals near 6.5: CH_2 protons of intermediates **C**; quartet near 5.2: CH_2 protons of intermediates **D**; singlet overlapping with quartet: CH_2 protons of residual phenacyl bromides **B**; multiplet near 4.18: OCH_3 signals of **B**, **C**, **D** and product **E** (these signals are attenuated); multiplet near 2.69: CH_3 signals of **B**, **C**, **D** and **E** and DMSO-d_5 peak.

brium between two relatively long-lived intermediates (Fig. 2). As in the example of *p*-methylphenacyl bromide, the spectra of the *p*-methoxy- and unsubstituted phenacyl bromide reactions display a singlet (**CH**$^+$) and a quartet (**DH**$^+$). The relative areas of these signals depend on the substituent but remain constant throughout the course of the reaction.

The effect of substituents on the equilibria between the intermediates parallels that observed for carbinolamine formation from *p*-substituted benzaldehydes and amines and supports the assignment of the aminoketone and cyclic carbinolamine structures **C** and **D**. Values of equilibrium constants, [**DH**$^+$]/[**CH**$^+$], obtained from area ratios of the quartet and the singlet, are: $K_{OMe} = 2$; $K_{Me} = 4$–5; and $K_H = 6$–7. From these equilibrium constants and σ values, it is estimated that $K_{NO_2} \sim 200 (\rho \sim 1.9)$. Thus, the concentration of the aminoketone formed from *p*-nitrophenacyl bromide is too low to be detectable, in agreement with the absence of the singlet from the spectrum of this reaction. For comparison, the equilibrium constant of carbinolamine formation from semicarbazide and *p*-nitrobenzaldehyde is more than 100 times larger than that from the *p*–OMe compound ($\rho = 1.81$).[11]

(2) *Other data.* (a) (***CH***$^+$). The chemical shifts (Fig. 2) of the CH_2 protons in the less abundant intermediates **CH**$^+$ are in accord with the assigned structures. The shifts are upfield (*ca.* 0.6 ppm) from the corresponding signals of the phenacylpyridinium bromides, as expected for greater delocalization of the adjacent positive charge in the 2-amino-1-phenacylpyridinium salts **CH**$^+$.

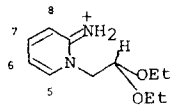
An estimated pK_a value for the assigned structure is in agreement with the conclusion that the intermediate **C** is a stronger base than 2-aminopyridine (A, point 8). The value for **CH**$^+$, $pK_a \sim 10.5$, derived[12] from the pK_a values for 1-methyl-2(H)pyridinimine **4** and the acetal **2**, is considerably larger than that of 2-aminopyridine ($pK_a = 6.86$).[15]



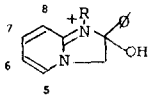
4: R = CH_3
2·H$^+$:R = $CH_2CH(OEt)_2$
CH$^+$:R = $CH_2CO\phi$

(b) (***DH***$^+$). ^{1}H NMR data (Table 1) indicate that the intermediate **DH**$^+$ has the structure shown. Chemical shifts and multiplicities could be obtained from spectra of reaction solutions containing an excess of phenacyl bromide in which overlapping signals due to unreacted 2-aminopyridine and the other intermediate were small. The quartet, assigned to the intrinsically nonequivalent CH_2 protons[16] of the 5-membered ring, shows the typical large coupling (J = 13 Hz) of geminal protons. The chemical shift is the same as that reported[17] for the CH_2 protons in the excellent model compound **3**. The shifts of H-5 in **DH**$^+$ and **3** also coincide. Shifts of the olefinic

Table 1. ^{1}H NMR chemical shifts (δ, ppm) in DMSO-d_6 relative to external TMS



$2\cdot H^+$



3, R = CH_3
DH^+, R = H

	2[a]	$2\cdot H^+$	3[c]	DH^+
CH_2	4.34 (d)	4.98 (d)	5.30 (s)	5.29 (q)[d]
H-5	7.64 (d)	8.45[b]	8.88 (d)	8.86 (d)
H-6	6.26 (t)	7.40 (t)		7.52 (t)
H-7	7.38 (q)	8.40[b]	8.62 (m)	8.52 (t)
H-8	6.87 (d)	7.72 (d)		7.71 (d)

[a]The unusual numbering is adopted for facile comparison with with compounds 3 and DH^+. The olefinic protons show further splitting: $J_{5,6}$~$J_{6,7}$ = 7; $J_{5,7}$ = 2; $J_{6,8} \leq 1$; $J_{7,8}$ = 9Hz. [b]These signals overlap. [c]The shifts were calculated from those reported (Ref. 17) relative to internal TMS by the addition of 0.4 ppm. The 8.62 signal, reported for H-8, is here attributed to H-7. The remaining signals (δ = 7.45 - 9.40 ppm) where not assigned. [d]Center of the quartet. The phenyl protons show a multiplet centered at 7.97 ppm.

protons in $\mathbf{DH}^+$ were assigned by analogy[18] to those of the protonated species $\mathbf{2\cdot H}^+$. The observed upfield shift of the *ortho* phenyl protons ($\delta \sim 8.0$) relative to those in phenacyl bromide ($\delta \sim 8.3$) conforms to substitution of an sp^3 center for the carbonyl sp^2 center.

C. *Possible mechanisms for formation of C and D*

From the above data it is established that intermediates **C** and **D** are present and that **F** is not detectable. This eliminates a mechanism of path *a* in which *rapid* formation of **F** is followed by its slow conversion to $\mathbf{DH}^+$, but does not exclude the two other mechanisms which could proceed *via* path *a*: (1) *slower* formation of **F** (i.e. the concentration of **F** does not build up) than its conversion to $\mathbf{DH}^+$ and (2) unfavorable *equilibrium* formation of **F** with subsequent slow formation of $\mathbf{DH}^+$. Mechanism (1) is incompatible with the observations that the reaction with phenacyl chloride is much slower than that of the bromide and that no intermediates are observable. Displacement of halogen (which is always faster for bromine than chlorine[19]), is therefore the slow step in the reaction. Mechanism (2) of path *a* and reaction *via* path *b* are both compatible with the data. The former is *a priori* less likely than the latter since equilibrium constants for carbinolamine formation, especially from *p*-nitrophenyl carbonyl compounds, tend to be large.[11,20]

D. *Improbability of carbinolamine F as a kinetically significant intermediate*

The results of comparative rate studies render the preequilibrium mechanism (2) of path *a* highly improbable. In such a mechanism, the rate of formation of intermediate $\mathbf{DH}^+$ is proportional to k_aK_a (see Scheme I), where K_a is the equilibrium constant for formation of **F** and k_a is the rate constant for the subsequent intramolecular displacement of bromide in **F**. Electron-withdrawing substituents *enhance* both k_a and K_a. The effect on k_a is expected to be small[21] since only inductive effects can be operative and the reactive site is far removed from the substituents. The effect on K_a, however, should be large (*vide supra*). The *rate* of $\mathbf{DH}^+$ formation *via* **F** is expected to be perhaps 100 times faster when the substituent is *p*-NO_2 as compared to *p*-OMe.

1. *Effect of substituents.* That *p*-substituents have little effect on the reactivity of phenacyl bromide was inferred from the similarity in peak height of the residual CH_2 signals, after a given time interval, in the total spectra of the reactions with *ca.* 20% excess of 2-aminopyridine. More accurate kinetic measurements confirm this conclusion.

An excellent, simple method of determining *relative* rates constants is by competition experiments.[22a] For two competing, second-order reactions in which S is the common reagent,

$$S + T \xrightarrow{k_1} x \quad \text{and} \quad S + U \xrightarrow{k_2} y$$

$$\frac{dx}{k_1[T]} = \frac{dy}{k_2[U]} \quad \text{and} \quad [T] = T_o] - x; [U] = [U_o] - y$$

from which (when [T] and [U] $\neq 0$)

$$\frac{\log [T]/[T_o]}{\log [U]/[U_o]} = \frac{k_1}{k_2}. \qquad (2)$$

Equation (2) applies when either incomplete reaction has occurred, or when an insufficient amount of S is used, so that both T and U are present at the end of the reaction. Many of the difficulties of determining individual rate

constants are avoided in such experiments. In particular, concentration changes in S due to protonation (when S = 2-aminopyridine) and changes in ionic strength and temperature do not affect the rate constant ratio. This technique could be used for assessing the relative rates of reaction of 2-aminopyridine with *p*-nitro- and *p*-methoxyphenacyl bromide since the chemical shifts of the CH_2 signals of these materials are sufficiently different to permit integration.

Experiments with widely differing concentrations and quenching at different times (Table 2) gave the same small rate constant ratio,[23] $k(NO_2)/k(OCH_3) = 2.6 \pm 0.1$. This small substituent effect does not fit the behavior predicted for mechanism (2), path *a*, but is as expected for path *b*: if displacement of bromide is the slow step in the formation of $\mathbf{DH}^+$ via $\mathbf{CH}^+$, the equilibrium constant K_b does not enter into the rate law, i.e. the rate is proportional only to k_b, which, again, is expected to be relatively insensitive to the *p*-substituents.

2. *Reaction rates of 2-aminopyridine* vs *pyridine.* The rate constant ratio $k(NO_2)/k(OCH_3)$ is the same for the reactions of the phenacyl bromides with both 2-aminopyridine and pyridine (Table 2). Since N-alkylation is the only reaction possible with pyridine, the identical substituent effects are independent evidence for path *b* in the 2-aminopyridine reactions. (The identity of the substituent effects is also evidence against possible alternate reaction of 2-aminopyridine *via* its thermodynamically disfavored form, the iminopyridone.)

Second-order rate constants (Table 2) show that the reaction of a given phenacyl halide is somewhat faster with pyridine than with 2-aminopyridine,[25] in accord with the known sensitivity of pyridine alkylation to steric effects in both reagents.[22b,26] 2-Dimethylaminopyridine failed to react with phenacyl bromide in DMSO.

E. *Acid catalysis of product formation from* $\mathbf{DH}^+$

This is indicated by the following observations: under the reaction conditions the intermediate exists primarily in its protonated form. When only the acid generated in the reaction was present, conversion of $\mathbf{DH}^+$ to product required several hours. Total conversion occurred in less than one minute when *ca.* 1 mmole of concentrated hydrochloric acid was added to the ^1H NMR samples

Table 2. Rate constants[a] and relative rate constants of the reactions of *p*-substituted phenacyl halides[b] with pyridine and 2-aminopyridine in DMSO-d_6 at 32°.

Competition of Phenacyl Bromides (Br) for 2-Aminopyridine (Ampy)

p-Subst.	[Br][a]	[Ampy][a]	% Reaction	$\frac{k(NO_2)}{k(OCH_3)}$
NO_2	0.24	0.38	100	2.5
OCH_3	0.33			
NO_2	0.12	0.19	100	2.7
OCH_3	0.30			
NO_2	0.09	0.28	27	2.7
OCH_3	0.35			
NO_2	0.14	0.19	30	2.6
OCH_3	0.19			

Pyridine (Py) + Phenacyl Bromide (Br)

p-Subst.	[Br]	[Py]	$k(M^{-1}\text{-}min^{-1})$	$\frac{k(NO_2)}{k(OCH_3)}$
NO_2	0.42	0.42	3.5	2.6
H	0.43	0.62	1.45	
	0.44	0.62	1.5	
OCH_3	0.43	0.62	1.4	
	0.42	0.42	1.3	

2-Aminopyridine (Ampy) + Phenacyl Bromide (Br)

p-Subst.	[Br]	[Ampy]	$k(M^{-1}\text{-}min^{-1})$	$\frac{k(NO_2)}{k(OCH_3)}$
NO_2	0.42	0.38	1.5	2.5
	0.42	0.48	1.5	
H	0.43	0.57	0.70	
OCH_3	0.42	0.38	0.69	
	0.42	0.48	0.45	
	0.43	0.57	0.70	
			av. 0.61	

[a] Concentrations are in moles/liter of solvent.
[b] For pyridine + phenacyl chloride, $k = 1.2 \times 10^{-2} M^{-1}\text{-}min^{-1}$; for 2-aminopyridine + phenacyl chloride, $k \sim 0.8 \times 10^{-2} M^{-1}\text{-}min^{-1}$ (see Experimental Section).

containing 0.05–0.15 mmole of intermediates. The addition of water had little effect on the rate of conversion of intermediates to product.

F. *Reaction of phenacyl chloride*

Although no intermediates are observed in the ^1H NMR spectra of mixtures of phenacyl chloride and 2-aminopyridine, several observations indicate that this reaction follows the same sequence as now established for the phenacyl bromides. First, the same cationic species is the ultimate product, as shown by spectral comparison. Second, the rates of reaction of phenacyl chloride with 2-aminopyridine and with pyridine are similar. Third, product formation from phenacyl chloride and 2-aminopyridine is *slower* than product formation from the observable intermediates in the phenacyl bromide reaction: spectra of reaction mixtures containing comparable concentrations of reagents show that approximately 50% of the intermediates are converted to product in 30 minutes, whereas only about 15% of phenacyl chloride has reacted during the same time.[27] Conversion of intermediate to product is fast compared to displacement of chloride, but slow compared to displacement of bromide.

G. *Why path b?*

The fact that path *b* is favored over other paths demonstrates that the transition state (*b*) for displacement of halogen activated by an adjacent CO group[6b,21b] is of lower energy than the transition state for the rate determining step in an equilibrium addition followed by intramolecular displacement of an unactivated halogen (*d*). Reaction of the pyridine nitrogen (paths *b* or *d*) rather than reaction of the NH_2 nitrogen (paths *a* or *c*) is the lower energy path since the positive charge that develops in the transition state on the attacking nitrogen atom is stabilized by resonance interaction with the adjacent amino group.

H. *Synthetic considerations*

Several comments can be made in regard to the general synthesis of imidazo[1,2-*a*] pyridines. Bromoketones (aldehydes) are preferred over the chloro analogs. Absence of sodium bicarbonate may be beneficial. Failure to detect starting material does not necessarily indicate that product formation is complete. The factors affecting quaternization of pyridines—about which a great deal is known[22b]—should also be important in this reaction. In particular, the application of pressure[28] should permit the preparation of imidazo[1,2-*a*]pyridines bearing bulky substituents in the 3 and 5 positions.

EXPERIMENTAL

Materials. *p*-Methylphenacyl bromide was prepared by a reported procedure.[29] The compounds, recrystallized one to three times from the solvents indicated and dried *in vacuo* for several hr, had the following (uncorrected) m.p: phenacyl bromides: *p*-NO_2 (ØH, then EtOH) m.p. 98.5–98.7°; *p*-OMe (EtOH) m.p. 69–70.2°; *p*-Me (aqueous 80% EtOH) m.p. 50–51.5° (Lit.[29] m.p. 48–50°); *p*–H (EtOH) m.p. 48.5–49.5°; phenacyl chloride (EtOH/H_2O) m.p. 53–54°; 2-aminopyridine (Charcoal, ØH) m.p. 56.8–57.8°. Pyridine, distilled from CaH_2, was stored over 4A molecular sieves. Dimethylsulfoxide-d_6 (Stohler Isotope Chemicals) was stored over 4A sieves.

Methods. A Varian HA-100 spectrometer was used to record the spectral changes. The instrument was adjusted with the sample tubes containing DMSO-d_6 (0.4 mL) solns of known amounts of phenacyl halides (30–50 mg) and a coaxial tube with TMS. Solid 2-aminopyridine (*ca.* 20 mg) was scooped into the top of the sample tube for weighing and the reagents were mixed just prior to starting the scans. Small and variable amounts of H_2O were absorbed in this process. Consecutive scans were taken for several hr; the final spectrum was recorded after 16–20 hr. A check on some of the samples showed that no further changes occurred during several days.

For the rate constant determinations, a 60 MHz Hitachi/Perkin-Elmer R-20B spectrometer was used and no reference compound was necessary. In a typical run, a soln of *p*-NO_2 phenacyl bromide (41.4 mg, 0.17 mmole) in 0.30 mL of dry DMSO-d_6 was equilibrated for 10 min in the spectrometer probe (32°); an aliquot (100 μL, 0.19 mmole) of a stock soln of 2-aminopyridine in DMSO-d_6 (kept over 4A sieves) at 32° was added with a syringe; the mixture was vigorously shaken for 10–15 sec; and the CH_2 spectral region was then recorded at 15-sec intervals. The first recording was obtained 35 sec after the addition of 2-aminopyridine; one half of the phenacyl bromide was consumed after 2 min. The data were analyzed by estimating the extent of overlap with the CH_2 signal of $\mathbf{DH}^+$ and counting squares of the area attributable to the phenacyl CH_2 peak. Initial areas were taken as the average of the sum of all of the CH_2 peak areas recorded in the first few scans. Instrumental drift was assumed to be negligible. The initial concentration of 2-aminopyridine was determined by titration of an aliquot of the stock solution with aqueous HCl. Rate constants (Table 2) were obtained from data for the first 1.5 to 2 half-times when pH changes should have been small.

In the experiments with pyridine integration of the phenacyl CH_2 peak area was performed at 15-sec intervals; one half of *p*-NO_2 phenacyl bromide was consumed in 55 sec, 90% in 5 min. Initial areas were obtained from spectra prior to the addition of neat pyridine (10–20 μL to 0.40 mL of DMSO-d_6) and by extrapolation to t_0 of a plot of area vs time. Data from runs in which these initial areas differed by no more than 10% were used. In the runs with excess pyridine, areas of the product CH_2 peaks at the completion of the reaction were within 10% of the initial phenacyl bromide CH_2 peak areas. Consistent second-order rate constants (Table 2) were obtained.

For the competition experiments, an insufficient quantity of 2-aminopyridine dissolved in DMSO-d_6 was added to DMSO-d_6 solutions of known amounts of *p*-NO_2 and *p*-OMe phenacyl bromides equilibrated for *ca.* 10 min in the probe. Conc HCl was added after varying periods of time had elapsed in order to quench the reaction and to hasten conversion of intermediates to products. The CH_2 region of the spectra was then free of overlapping signals due to intermediates. Concentrations of unreacted phenacyl halides were determined from the (integrated) areas of their CH_2 signals, the known initial concentration of *p*-OMe compound and the area ($\times 2/3$) of the OMe signals. Relative rate constants were calculated by use of eqn (2).

The rate constant for the reaction of phenacyl chloride and 2-aminopyridine was obtained from data of the first 20% of reaction, which was assumed to be second-order. Since in this reaction no intermediates build up, the generated HCl protonates primarily 2-aminopyridine, so that in effect 2 moles of this are removed for each mole that reacts. Log $([a-x]/[b-2x])$ was plotted vs time, and k was obtained from the slope $\times 2.3/[2a-b]$, where a and b are the initial concentrations of phenacyl chloride and 2-aminopyridine, respectively. (For a derivation of the equation for the more general case of second-order reactions in which concentration changes in the reactants are not equal to those of product formed, see Ref. 30.) Concentration changes were monitored by integration of the CH_2 peak area; periodic tuning of the instrument to maximize the sharp CH_2 signal gave reproducible areas for the DMSO-d_5 peak. For this reaction, as well as that of phenacyl chloride with pyridine, only one rate constant determination was carried out. ^1H NMR spectra, taken after all of the phenacyl chloride had reacted, were the same as those obtained in reactions with phenacyl bromide.

Isolation of products

2-(4-Tolyl)-imidazo[1,2-a]pyridine. After a soln of *p*-Me phenacyl bromide (38.8 mg, 0.19 mmole) and 2-aminopyridine (22 mg, 0.23 mmole) in DMSO-d_6 (0.4 mL) had stood for 18 hr, it

was poured into 4 mL of H_2O and NaOH was added to pH ~10. The solid (35 mg, 89%) was filtered, rinsed with H_2O, air dried, and recrystallized from hexane to give colorless needles, m.p. 145–146°, which were sublimed (105°/0.2 torr) for analysis. (Found: C, 80.84, H, 5.41; N, 13.31. Calc. for $C_{14}H_{12}N_2$: C, 80.74, H, 5.81; N, 13.45%.)

2-(4-Nitrophenyl)-imidazo[1,2-a]pyridine. A solid separated about 15 min after mixing *p*-NO_2 phenacyl bromide (44.6 mg, 0.18 mmole), 2-aminopyridine (21.5 mg, 0.23 mmole), and DMSO-d_6 (0.4 mL). Addition of conc HCl (2 drops, *ca.* 0.7 mmole) solubilized the material. Another solid precipitated when the solution was left to stand overnight. After filtration, the solid was treated with 5 mL of 80% EtOH and NaOH. The mixture was stirred for 30 min. The insoluble material (30 mg, 70%) was filtered, rinsed with H_2O, recrystallized from EtOH, and then had m.p. 261–262° (Lit[31] m.p. 263–264°).

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