On the Reaction of 2-Aminopyridines With *alpha*-Halocarbonyl Compounds

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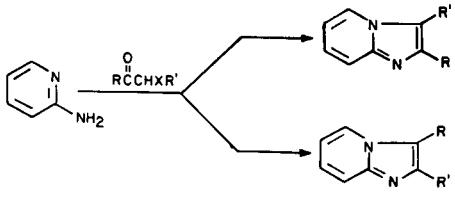
The reactions of 6-substituted-2-aminopyridines with bromoacetone and 3-bromo-2-butanone have been investigated. In contrast to bromoacetone which gives a high yield of the imidazo[1,2-*a*]pyridine, bromobutanone also produces significant amounts of material derived from substitution on the exocyclic nitrogen atom. These adducts, which are not a source of imidazopyridine in the reaction mixture, may be isolated and cyclised under more forcing conditions. The reactions of 2-aminopyridine with 2-chlorocyclohexanone and phenacyl bromide have been re-examined and all the major products identified.

J. Heterocyclic Chem., **19**, 1437 (1982).

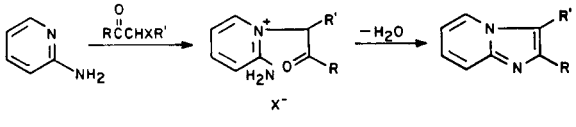
The best general method for preparation of substituted imidazo[1,2-*a*]pyridines is the condensation of substituted 2-aminopyridines with *alpha*-haloaldehydes or *alpha*-haloketones (1). With unsymmetrical carbonyl compounds two isomeric products are possible, the nature of the product being determined by which nitrogen atom initiates the reaction (Scheme 1).

Scheme 1



The reaction is generally believed to proceed via the initial displacement of the halogen atom by the pyridine ring nitrogen followed by the facile closure of the intermediate (Scheme 2).

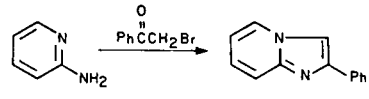
Scheme 2



This mechanism appears reasonable since the intermediate pyridinium salt is resonance stabilised, and recent molecular orbital calculations (2) as well as time-dependent nmr studies (6) support the initial attack by the ring nitrogen atom. The literature, however, contains a number of reports which might indicate that the reaction is not quite this simple. The reaction of 2-aminopyridine with 2-chlorocyclohexanone in refluxing ethanol containing sodium carbonate is reported (3,4) to give a 30% yield of the product **1** derived from attack at the exocyclic nitrogen atom. No mention of the nature of the other products is made. When the weaker base, sodium bicarbonate, is used the imidazopyridine **2** is obtained.

There is another report (5) on the effect of various bases on the condensation of aminopyridine and phenacyl bromide (Scheme 3).

Scheme 3



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In the presence of sodium bicarbonate, sodium carbonate and sodium acetate, the yields of imidazopyridine **3** are reported to be 100%, 88% and 33%, respectively. Again, no mention is made as to the nature of the other products. Lastly, steric effects seem to play a role in the reaction. When 2-aminopyridine is condensed with phenacyl bromide, 3-bromo-2-butanone or desyl chloride (PhCOCHClPh) the imidazopyridine is produced in yields of 88%, 41%, and 38% respectively. (5).

As part of a program aimed at the synthesis of novel agents for the treatment of peptic ulcer disease, we required, for testing, a considerable number of highly substituted imidazo[1,2-*a*]pyridines. In order to establish a sound structure-activity relationship it was important that the structure of the products derived from the condensations of our highly substitued 2-aminopyridines and *alpha*-halocarbonyl compounds be known unequivocally. Most of the compounds we planned to synthesise would not allow easy differentiation between isomeric structures. At the outset, therefore, we felt the following points needed to be clarified concerning the reports in the literature: a. In the event that at least some reaction at the exocyclic nitrogen atom takes place, would the intermediate (*e.g.* **1**) cyclise under the reaction conditions to yield an isomeric imidazo[1,2-*a*]pyridine? b. Why does sodium acetate, intermediate in base strength between sodium bicarbonate and sodium carbonate, give such a low yield of imidazopyridine? c. What are the steric requirements of the reaction?

To this end we have re-examined the reaction of 2-aminopyridine with 2-chlorocyclohexanone and phenacyl bromide under the literature conditions and characterised all the major components of these reactions. Also, we have examined briefly the steric requirements of the reaction at least as they pertained to our own work.

2-Aminopyridine and 2-Chlorocyclohexanone.

The reaction was repeated on twice the literature scale (3), and involved the use of a slight excess of 2-aminopyridine and anhydrous sodium carbonate as the base. After three hours at reflux, the solvent was evaporated *in vacuo* and the reaction mixture chromatographed on silica gel. There was obtained 15% of **1** and 34% of the imidazopyridine **2**, together with unreacted 2-aminopyridine (30%).

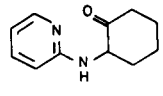
The nmr spectrum of **1** clearly showed that substitution had taken place on the exocyclic nitrogen atom. The methine proton adjacent to the carbonyl appeared as a five line miltiplet which collapsed to a triplet on the addition of deuterium oxide. The NH was observed as a broad doublet. In a separate experiment it was established that **1** was not converted to **2** under the reaction conditions. This conversion is reported (3) to occur in acetic acid-hydrobromic acid at room temperature and in reluxing acetic anhydride. In our hands, only the latter conditions were successful. We further established that **1** was not converted to **2** in refluxing ethanolic hydrobromic acid nor was the cyclisation seen in the mass spectrum of **1** which exhibits a molecular ion (61%) and a base peak of m/e 94 corresponding to 2-aminopyridine. From these results we believe that **2** results solely from the initial attack at the ring nitrogen followed by fast cyclisation of the intermediate as depicted in Scheme 2. The attack at the exocyclic nitrogen atom may only lead to an imidazopyridine under more drastic conditions. This observation was confirmed in our later studies.

2-Aminopyridine and Phenacyl Bromide.

These reactions involved stirring equimolar amounts of the reagents with slight excess of sodium bicarbonate, sodium carbonate or sodium acetate in ethanol at room temperature for 24 hours, followed by heating under reflux for one hour. The imidazopyridine **3** was obtained in 81% and 79% purified yields from the bicarbonate and carbonate reactions respectively. The product mixture from the sodium acetate reaction was chromatographed on silica gel and phenacyl acetate (20%) and **3** (52% after crystallisation) were obtained. Since sodium acetate is soluble in ethanol and is a nucleophilic base, the low yield of **3** reported earlier may easily be explained by competition between 2-aminopyridine and acetate ion for the phenacyl bromide. Allowing for the 20% isolation of phenacyl acetate, the purified yield of **3** is raised to 65% in this reaction. No evidence of any product derived from attack at the exocyclic nitrogen atom was detected.

Steric Requirements.

For our own requirements, we chose to study the condensation of 2-amino-6-(2-phenylethyl)pyridine, **4**, with bromoacetone and 3-bromo-2-butanone. Reaction of equimolar amounts of bromoacetone and **4** in refluxing ethanol overnight gave the imidazopyridine **5** in 75% yield. Under identical conditions, the reaction of **4** with 3-bromo-2-butanone was more complex. After chromatography on silica gel the exocyclic nitrogen adduct **6** (17%), the imidazopyridine **7** (11%) and recovered **4** (57%) were obtained. Once again the methine proton in **6** was observed as a multiplet and the NH as a doublet. Addition of deuterium oxide collapsed the methine resonances to the expected quartet. It was established that **6** was not converted to **7** under the reaction conditions, or in refluxing ethanolic hydrobromic acid. The mass spectrum of **6** showed a molecular ion (4%) but no evidence of cyclisation to **7**. On prolonged heating of **6** in acetic anhydride, the presence of **7** could be detected on tlc but much decomposition had taken place. This was in direct contrast to the smooth cyclisation of **1** under these conditons. A more efficient conversion was effected by the treatment of **6** with refluxing phosphorus oxychloride, when **7** was obtained in 64% yield.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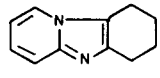
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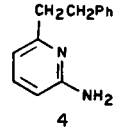
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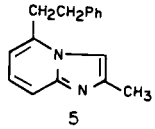
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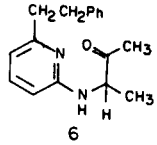
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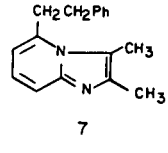
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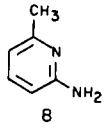
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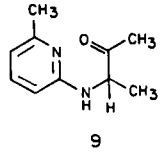
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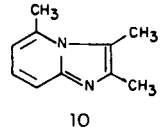
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The dramatic effect of the 6-phenethyl group prompted us to examine the reactions of 2-amino-6-methylpyridine, **8**. Once again the condensation with bromoacetone was routine, but the reaction with 3-bromo-2-butanone gave

equal amounts of **9** and the imidazopyridine **10** (26%) together with unchanged **8** (31%). The necessary control experiments again showed that **10** did not result from **9** under reaction conditions.

Complete conversion of **9** and **10** could not be effected in refluxing acetic anhydride but was accomplished in refluxing phosphorus oxychloride.

From these results we believe that certain conclusions may be drawn concerning the reaction of 2-aminopyridines with *alpha*-halocarbonyl compounds. Firstly, if an imidazopyridine derivative is isolated directly from the reaction mixture under conditions which are usually employed for this reaction, then the product has resulted from a reaction mechanism depicted in Scheme 2. Secondly, a low yield of imidazopyridine may be the result of attack at the exocyclic nitrogen atom to give an intermediate which will not cyclise under normal reaction conditions. This mode of reaction may be the result of the base used or steric hindrance around the ring nitrogen atom. The steric hinderance may be a combination of 6-substitution in the pyridine ring and the use of a secondary or tertiary halide. The intermediate resulting from exocyclic nitrogen substitution may be isolated and cyclised under forcing conditions to give the isomeric imidazopyridine. Lastly, the use of a nucleophilic base which will compete for the *alpha*-halocarbonyl substrate must be avoided.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The nmr spectra were recorded on a Varian CFT-20 spectrometer, ir spectra were recorded on a Perkin-Elmer 221 spectrophotometer, and mass spectra were determined with a Varian MAT CH5. Microanalyses were perfomed by the Physical Analytical Services Department of the Schering-Plough Corp.

Reactions of 2-Aminopyridine.

(a) With 2-Chlorocyclohexanone (3).

2-Aminopyridine (9.0 g, 0.096 mole), 2-chlorocyclohexanone (10.0 g, 0.076 mole), sodium carbonate (6 g) and ethanol (200 ml) were stirred together and heated under reflux for 3 hours, then allowed to cool. The inorganics were removed by filtration and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel (350 g, E. Merck 7736) and the products were eluted with chloroform. The initial product obtained was **1** (2.2 g, 15%) which crystallised from ethanol as colorless needles, mp 144° (lit (3) 147-149°) nmr (deuteriochloroform) 1.2-3.0 (m, 8H), 4.60 (m, 1H, sharpens to t with deuterium oxide), 5.41 (br d, NH), 6.3-7.5 (aromatics, 3H); ms: m/e (% relative intensity) 190 (61); ir: 3300, 1710 cm^{-1}.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.19; H, 7.26; N, 14.65.

The imidazopyridine **2** (4.7 g, 34%) was eluted next and crystallised from hexane as colorless needles, mp 85-86° (lit (3) 95-96°); nmr (deuteriochloroform) 1.6-2.2 (m, 4H), 2.5-3.0 (m, 4H), 6.3-7.6 (m, 4H); ms: m/e (% relative intensity) 172 (58).

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.66; H, 7.26; N, 16.23.

2-Aminopyridine (2.3 g, 30%) was also obtained.

(b) With Phenacyl Bromide (5).

2-Aminopyridine (9.4 g, 0.1 mole), phenacyl bromide (19.9 g, 0.1 mole) and sodium bicarbonate (10.8 g, 0.12 mole), sodium carbonate (12.8 g, 0.12 mole) or sodium acetate (11.4 g, 0.12 mole) were stirred together in ethanol (300 ml) overnight. The mixtures were then boiled under reflux for one hour and allowed to cool. The inorganics were removed by filtration, the residue dissolved in chloroform (300 ml), the solution filtered and the chloroform evaporated *in vacuo*. In the case of the sodium bicarbonate and sodium carbonate reaction mixtures the imidazopyridine **3** was crystallised from 1-chlorobutane-hexane as colorless needles, mp 134-135° (lit (5) 135-136°) in the amounts of 15.7 g (81%) and 15.3 g (79%), respectively. The reaction mixture derived from sodium acetate was chromatographed on silica gel (400 g, E. Merck 7736) using chloroform. Phenacyl acetate 3.5 g, (20%), identified by nmr, ms and tlc, was eluted first, followed by **3** which crystallised from 1-chlorobutane-hexane as colorless needles, mp 135-136° (lit (5) 135-136°), yield 10.1 g (52%).

Reactions of 2-Amino-6-(2-phenylethyl)pyridine (**4**).

(a) With Bromoacetone.

Compound **4** (2.2 g, 0.011 mole), bromoacetone (1.8 g, 0.011 mole) and ethanol (100 ml) were stirred together and boiled under reflux for 18 hours. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate (200 ml) and saturated sodium carbonate (200 ml). The organic layer was separated, dried (sodium sulfate) and evaporated *in vacuo*. The residue crystallised from isopropyl ether to give **5** as colorless needles, mp 86-88°, 1.95 g (75%); nmr (deuteriochloroform) 2.48 (s, 3H), 3.10 (s, 4H), 6.4-7.5 (aromatics, 8H); ms: m/e (% relative intensity) 236 (46).

Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.34; H, 6.84; N, 11.85. Found: C, 81.29; H, 6.74; N, 11.88.

(b) With 3-Bromo-2-butanone.

Compound **4** (5.6 g, 0.0283 mole), 3-bromo-2-butanone (4.26 g, 0.0283 mole) and ethanol (300 ml) were stirred together and boiled under reflux for 18 hours. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate (300 ml) and saturated sodium carbonate (300 ml). The organic layer was separated, dried (sodium sulfate) and evaporated *in vacuo*. The residue was chromatographed on silica gel (300 g, E. Merck 7736) using chloroform as eluant. Compound **6** (1.3 g, 17%) was obtained as a yellow oil; nmr (deuteriochloroform): 1.37 (d, 3H, J = 6 Hz), 2.20 (s, 3H), 2.98 (s, 4H), 4.46 (m, 1H, sharpens to q with deuterium oxide), 5.22 (br d, NH), 6.3-7.2 (aromatics, 8H); ms: Calcd. for $C_{17}H_{20}N_2O$ 268.1575; Measured 268.1580; ir: 3380, 1718 cm^{-1}.

Unchanged **4** (3.2 g, 57%) was eluted next, followed by the imidazopyridine **5** (0.8 g, 11%) which was crystallised from ethyl acetate as colorless needles, mp 101-103°; nmr (deuteriochloroform); 2.40 (s, 3H), 2.71 (s, 3H), 2.8-3.6 (m, 4H), 6.3-7.4 (aromatics, 8H); ms: m/e (% relative intensity) 250 (46).

Anal. Calcd. for $C_{18}H_{17}N_2$: C, 81.55; H, 7.26; N, 11.18. Found: C, 81.60; H, 7.29; N, 11.17.

Reactions of 2-Amino-6-methylpyridine (**8**).

(a) With Bromoacetone.

Compound **8** (7.0 g, 0.064 mole), bromoacetone (8.8 g, 0.064 mole) and ethanol (250 ml) were stirred together and boiled under reflux for 18 hours. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate (300 ml) and saturated sodium carbonate solution (300 ml). The organic layer was separated, dried (sodium sulfate) and evaporated *in vacuo*. The residual oil was treated with ethereal hydrogen chloride and the white salt (9.6 g, 82%) was recrystallised from ethanol to give 2,5-dimethylimidazo[1,2-*a*]pyridine as colorless needles, mp 288-290°; nmr (deuteriodimethylsulfoxide): 2.62 (s, 3H), 2.74 (s, 3H), 7.2-8.3 (aromatics 4H); ms: m/e (% relative intensity) 146 (100).

Anal. Calcd. for $C_9H_{10}N_2 \cdot HCl$: C, 59.17; H, 6.08; N, 15.33. Found: C, 58.95; H, 5.85; H, 15.32.

(b) With 3-Bromo-2-butanone.

Compound **8** (10.8 g, 0.1 mole), 3-bromo-2-butanone (15.1 g, 0.1 mole) and ethanol (500 ml) were stirred together and boiled under reflux for 18 hours. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate (300 ml) and saturated carbonate solution (200 ml). The organic layer was separated, dried (sodium sulfate) and evaporated *in vacuo*. The residue was chromatographed on silica gel (300 g, E. Merck 7736) using chloroform as eluant. Compound **9** (3.2 g, 26%) was obtained just as yellow oil; nmr (deuteriochloroform): 1.37 (d, 3H, J = 6 Hz), 2.20 (s, 3H), 2.31 (s, 3H), 2.31 (s, 3H), 4.42 (m, sharpens to q with deuterium oxide, 1H), 5.19 (br d, NH), 6.1-7.4 (aromatics 3H); ms: Calcd. for $C_{10}H_{14}N_2$ 178.1105; Measured 178.1095; ir: 3390, 1715 cm^{-1}.

The imidazopyridine **10** was eluted next (2.9 g, 26%) and was crystallised from 1-chlorobutane-hexane as colorless needles, mp 111°; nmr (deuteriodimethylsulfoxide): 2.21 (s, 3H), 2.62 (s, 3H), 2.77 (s, 3H), 6.4-7.3 (aromatics, 3H); ms: m/e (% relative intensity) 160 (99).

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.87; H, 7.64; N, 17.81.

The starting pyridine **8** was eluted last and yielded 3.4 g (31%).

Cyclisation Reactions.

Cyclisation of adducts **1**, **6** and **9** was attempted without success under the following conditions: (a) ethanol, reflux 4 hours; (b) ethanol saturated with hydrobromic acid, reflux 4 hours; (c) ethanol containing an equivalent of 2-aminopyridine, reflux 4 hour; (d) acetic acid saturated with hydrobromic acid, 25° 1 hour.

Complete cyclisation of **1** did occur in refluxing acetic anhydride according to the reported procedure (3). Under same conditions **6** and **9** were only partially cyclised (tlc).

Phosphorus Oxychloride Reactions.

The adduct **6** (5.3 g, 0.02 mole) and phosphorus oxychloride (30 ml) were stirred together and boiled under reflux for six hours. The excess phosphorus oxychloride was removed *in vacuo* and the residue was partitioned between 3*M* sodium hydroxide solution (100 ml) and ethyl acetate (300 ml). The organic layer was separated, dried (magnesium sulfate), and evaporated *in vacuo*. The residue (3.2 g, 64%) was found (ir, pmr, tlc) to be identical with compound **7**.

Under similar conditions **9** was completely converted to **10** (tlc).

REFERENCES AND NOTES

(1) H. L. Blewitt in "Special Topics in Heterocyclic Chemistry," A. Weissberger and E. C. Taylor, eds., John Wiley and Sons, New York, 1977, p 117.

(2) J. Fossey, A. Loupy and H. Strzelecka, *Tetrahedron*, **37**, 1935 (1981).

(3) N. Campbell and E. B. McCall, *J. Chem. Soc.*, 2411 (1951).

(4) J. Reitmann, British Patent 360,027; *Chem. Abstr.*, **26** 3514 (1932).

(5) I. A. Kaye, C. L. Parris and W. J. Burlant, *J. Am. Chem. Soc.*, **75**, 746 (1953).

(6) E. S. Hand and W. W. Paudler, *Tetrahedron*, **38**, 49 (1982).