α-Hydroxyacylation of Pyridine

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Efficient synthesis of 2-α-hydroxyacylpyridines **10** starting from pyridine *N*-oxide and 2-bromoaldehydes *via* base-induced rearrangement of the resulting *N*-alkoxypyridinium salts **6** is described.

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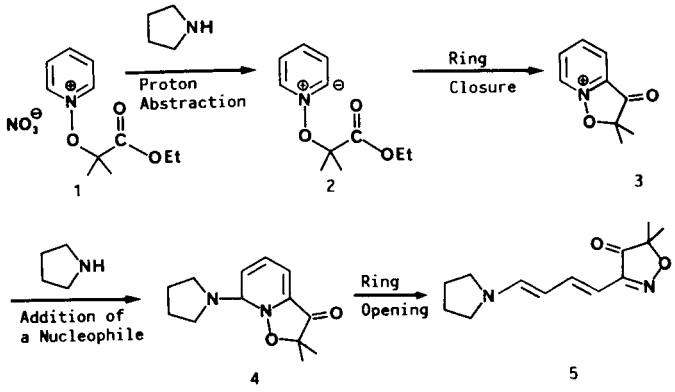
Introduction.

Though the direct introduction of an acyl group into the pyridine nucleus is possible *via* an extension to acid derivatives [1] of the Emmert reaction [2,3] (which involves a nucleophilic attack [4]), the direct electrophilic acylation by the Friedel-Crafts reaction is ineffective as well on the π deficient ring of pyridines as on their electron enriched *N*-oxides [5]. Nevertheless acylation of these latter can be realized *via* their lithio derivatives, but the yields in resulting pyridyl ketones are generally low since the process is not altogether free of side reactions [6,7].

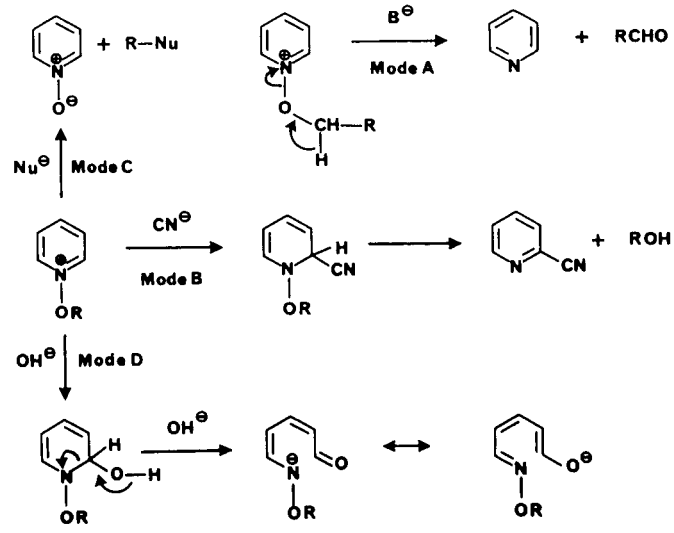
In the course of our study devoted to the multifarious reactivity of functionalized *N*-alkoxypyridinium salts [8] we have anticipated the possibility of an intramolecular acylation involving a nuclear ylid which is readily formed by proton abstraction at -2 position of the ring [9,10]. This indeed occurred upon base treatment of the salt **1** bearing an ester group in its alkoxyl chain as described in Scheme 1. This reaction realizes a heterocyclic ring conversion for which we have proposed a PARC-ANRO mechanism (*P*roton *A*bstraction, *R*ing *C*losure-Addition of *N*ucleophile and *R*ing *O*pening) [11].

Scheme 1



Of course the intermediate **3** could not be isolated owing to its enhanced reactivity towards a nucleophilic attack and suffered the classical ring opening of *N*-alkoxypyridinium salts first described by Katritzky *et al* [12]. These authors have classified the reactions of *N*-alkoxypyridinium salts with nucleophiles according to the four modes depicted in Scheme 2.

Scheme 2



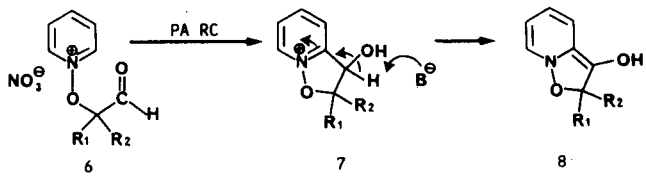
Nevertheless the above PARC-ANRO mechanism has been determined by the study of similar reactions occurring on *N*-alkoxypyridinium salts including a keto group in their alkoxyl chain [13,14]. In that case, the bicyclic isoxazolopyridinium salts carrying an alcohol function (which no more activates the pyridinium ion towards ring opening) could be isolated.

The aim of this paper is to show that extension of our previous studies to the case of *N*-alkoxypyridinium salts **6** bearing a formyl group in their alkoxyl chain can provide a convenient way for α-hydroxyacylation of the pyridine ring [15].

Results and Discussion.

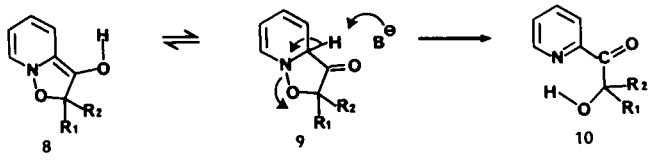
These salts would lead, by an intramolecular cyclization according to the PARC phase of the above process, to the bicyclic pyridinium ion **7**, possessing a secondary alcohol function, for which a deprotonation to an anhydrobase could be expected [17,18] (Scheme 3).

Scheme 3



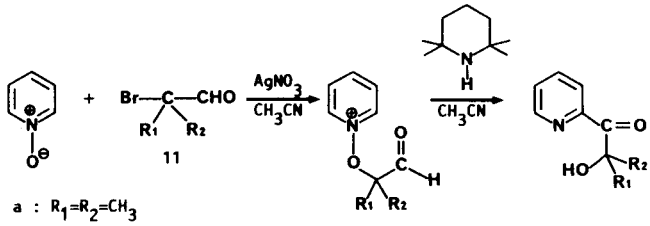
Since the resulting anhydrobase **8** shows an enol structure, its tautomerization to a keto group is expected to yield a dihydropyridine which would afford a 2-α-hydroxyacylpyridine upon aromatization as shown in Scheme 4.

Scheme 4



The overall process would provide a convenient synthesis in two steps of 2-α-hydroxyacylpyridines from pyridine-*N* oxide and α-bromoaldehydes as summarized in Scheme 5.

Scheme 5

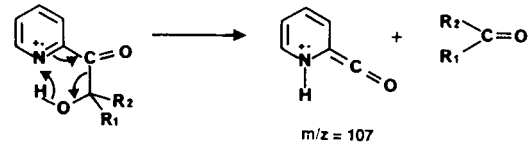


a : $R_1=R_2=CH_3$
b : $R_1=CH_3$, $R_2=C_6H_5$
c : $R_1=R_2=C_6H_5$

In order to prevent any decomposition according to the mode A of the Katritzky classification (see Scheme 2) we have prepared the *N*-alkoxypyridinium salts **6a-c** which are disubstituted at the α-carbon of their alkoxyl chain. The synthesis of these salts has been achieved by reaction of the appropriate bromoaldehyde with pyridine 1-oxide in acetonitrile solution in the presence of silver nitrate following the general procedure that we have used in our previous aforementioned studies. The resulting salts were obtained in 91-93% crude yield as visquous oil by evaporation of their acetonitrile solution, when once the precipitated silver bromide was eliminated by filtration. Although they could be obtained as solids by adding ether at their acetonitrile solution, their purification was not easy owing to their hygroscopicity. As an example, the elemental analysis data of compound **6a** agreed with those of an hemihydrate, while recrystallization from methanol-ether mixture yielded the dimethyl acetal. As a consequence of their hygroscopic behavior these salts showed in ir, in addition to the strong carbonyl absorption in the 1700-1730 cm^{-1} range a wide OH absorption band at 3200-3360 cm^{-1}. Nevertheless the aldehydic proton was recognizable in ^1H nmr by a strongly deshielded singlet which appeared between 9.8 and 10.1 ppm in hexadeuteriodimethyl sulfoxide solution, but which did not integrate for a whole proton. For that reason the salts **6a-c** were used immediately without further purification for the second step of the reaction.

This conversion to acyloins was performed upon treatment by 2,2,6,6-tetramethylpiperidine in acetonitrile solution. This sterically crowded base was chosen in order to avoid nucleophilic attack at the reactive carbonyl group as well as a possible ring opening according to the Mode D. The reaction was carried in acetonitrile solution, at room temperature and appeared to be rather fast in the case of the salt **6a** for which a voluminous precipitate of tetramethylpiperidinium nitrate occurred within a few minutes. Filtration followed by solvent evaporation and subsequent distillation for **10a** or recrystallization for **10b** and **10c** afforded the 2-α-hydroxyacylpyridines in yields ranging from 85 to 94%. Their structure was ascertained by ir, ^1H and ^{13}C nmr and mass spectrometry studies. For all these compounds one noticed a strong conjugated carbonyl absorption at 1695 cm^{-1} and a wide bonded OH absorption in the range 3240-3350 cm^{-1} in addition to the ring stretching bands at 1580 and 1565-1540 cm^{-1}. In the ^1H nmr the pronounced deshielding of the OH signal at 6.4-8.2 ppm (which disappeared upon exchange with deuterium oxide) was also indicative of chelation. The observed chemical shifts and coupling constants clearly established that the substitution pattern of the ring was that of a 2-substituted pyridine [19]. Furthermore this conclusion is corroborated by mass spectroscopy analysis showing a peak at m/z = 107, which appears to be the base peak for the compound **10a**. The corresponding fragment results from a Mac Lafferty type rearrangement (see Scheme 6) which is characteristic of 2-substituted azines [20].

Scheme 6



m/z = 107

In conclusion these results show that one can take advantage of the versatile reactivity of *N*-alkoxypyridinium salts to realize a regioselective acylation of the pyridine ring. Since the solvent is the same in the two steps of the transformation described in Scheme 5, and the intermediate *N*-alkoxypyridinium salts do not need to be purified, the overall process can be considered as a nearly one-pot reaction leading from pyridine *N*-oxide to 2-α-hydroxyacylpyridines.

EXPERIMENTAL

Melting points were determined in capillary tubes on a Büchi SMP 20 apparatus and are uncorrected. Infrared spectra were obtained in potassium bromide pellets for solids and in thin film between potassium bromide disks for liquids on a Perkin-Elmer Model 1420 spectrophotometer. Proton and carbon nmr spectra were recorded in deuteriochloroform or hexadeuteriodimethyl

sulfoxide solution on a Bruker WP 80 or AM 400 WB spectrometer. Chemical shifts are reported in parts per million (δ) downfield from TMS as an internal reference for deuteriochloroform solution and as an external reference for dimethyl sulfoxide-d_6 solution. Mass spectra were taken on a R10-10 Riber spectrometer under 70 ev. Microanalyses were performed by the "Centre National de la Recherche Scientifique".

General Method for the Preparation of α-Bromoaldehydes **11**.

The α-bromoaldehydes **11a-c** were prepared according to the procedure described by Duhamel *et al* [21] with two modifications: (i) the reactions were carried out under a nitrogen atmosphere; (ii) the reaction mixture was neutralized with solid sodium carbonate instead of a saturated solution. The following α-bromoaldehydes were prepared.

2-Bromo-2-methylpropanal (**11a**).

This compound was obtained in 59% yield (lit [21] 55%) as a colorless liquid, bp 113-114° (lit [22] 111-112°); n_D^{24} 1.4510 (lit [22] n_D^{25} 1.4500).

2-Bromo-2-phenylpropanal (**11b**).

This compound was obtained in 76% yield as a colorless liquid $bp_{0.4}$ 73-74 (lit [23] bp_1 86-87°); n_D^{26} 1.5610 (lit [23] n_D^{25} 1.5620).

2-Bromo-2,2-diphenylethanal (**11c**).

This compound was obtained in 95% yield as a solid which was recrystallized from chloroform, mp 46° (lit [24] bp_1 152°); ir (potassium bromide): 2835, 2720 (carbonyl CH), 1730 cm^{-1} (CO); pmr (deuteriochloroform): δ 7.4 (m, 10H, phenyl groups), 9.8 ppm (s, 1H, CHO).

General Method for the Preparation of *N*-Alkoxypyridinium Salts **6**.

To a stirred and cooled (0°) solution of pyridine *N*-oxide (4.75 g, 50 mmoles) and silver nitrate (8.49 g, 50 mmoles) in dry acetonitrile (20 ml) a solution of α-bromoaldehyde (50 mmoles) in acetonitrile (10 ml) was added drop by drop for ten minutes. The mixture was then allowed to warm gradually at ambient temperature and was stirred for an additional 24 hours. The precipitated silver bromide was eliminated by filtration and the resulting filtrate was evaporated under reduced pressure to give an oily residue which yielded a hygroscopic solid by trituration with ether. Owing to their hygroscopicity the products were generally used as a crude oil without further purification for the next step.

1-(1'-Formyl-1'-methyl)ethoxypyridinium Nitrate (**6a**).

This compound was obtained in 93% yield as a hemihydrate, mp 121°; ir (film): 3360 (OH), 1700 (CO), 1580, 1570 (ring) 1360 cm^{-1} (NO_3^-); pmr (hexadeuteriodimethyl sulfoxide): 1.6 (s, 6, $(CH_3)_2$), 8.3 (dd, 2, 3-H, 5-H), 8.7 (dd, 1, 4-H), 9.4 (dd, 2, -2H, -6H), 9.8 ppm (s, 0.5H, CHO).

Anal. Calcd. for $C_9H_{12}N_2O_5 \cdot 0.5H_2O$: C, 45.57; H, 5.53; N, 11.81. Found: C, 45.25; H, 5.56; N, 11.58.

Recrystallization of this compound in a mixture of methanol-ether yielded the dimethyl acetal, mp 90°.

Anal. Calcd. for $C_{11}H_{18}N_2O_6$: C, 47.70; H, 6.62; N, 10.21. Found: C, 47.69; H, 6.63; N, 10.28.

1-(1'-Formyl-1'-phenyl)ethoxypyridinium Nitrate (**6b**).

This salt was obtained as a crude oil in 92% yield [25]; ir: 1730, (CHO), 1630, 1615, 1470 (rings), 1370 cm^{-1} (NO_3^-); pmr (hexadeuteriodimethyl sulfoxide): 2.1 (s, 3, CH_3), 7.55 (m, 5, C_6H_5), 8.2 (t, 2, -3H, 5-H), 8.6 (dd, 1, 4-H), 9.3 (dd, 2, 2-H, 6-H), 10.1 ppm (s, CHO).

1-(1'-Formyl-1'-phenyl)benzyloxypyridinium Nitrate (**6c**).

This salt was obtained as a crude oil in 91% yield [25]; ir: 2810 (aldehydic CH), 1730 (CHO) 1645, 1470 (rings) 1360 cm^{-1} (NO_3^-); pmr (hexadeuteriodimethyl sulfoxide): δ 7.5 (m, 10H $(C_6H_5)_2$), 7.9 (m, 2H, -3H, 5-H), 8.7 (m, 3H, -4H, -2H, -6H), 10.1 (s, CHO).

General Method for the Preparation of 1-α-Hydroxyacylpyridines **10**.

To a stirred and cooled (0°) saturated solution of the preceding *N*-alkoxypyridinium salts **6** (20 moles) in acetonitrile, 2,2,6,6-tetramethylpiperidine (22 mmoles) was added drop by drop for ten minutes. The reaction mixture was then allowed to warm gradually at ambient temperature and was stirred overnight. The resulting precipitate of tetramethyl piperidinium nitrate was eliminated by filtration and the filtrate was evaporated under reduced pressure to give an oil (in the case **a**) which was distilled *in vacuo* or a solid (in the cases **b** and **c**) which was recrystallized.

2-(2'-Hydroxy-2'-methyl)propanoylpyridine (**10a**).

This compound was obtained by distillation *in vacuo* in 85% yield, $bp_{0.45}$ 69°; ir (film): 3350 (bonded OH), 1695 (CO, 1580, 1565 cm^{-1} (ring); pmr (deuteriochloroform): δ 1.60 (s, 6H, $(CH_3)_2$), 6.40 (br s, 1H, OH), 7.52 (ddd, 1H, 5-H, J_{4-5} = 7.4 Hz, J_{5-6} = 4.6 Hz, J_{3-5} = 1.6 Hz), 7.93 (dt, 1H, 4-H, $J_{3-4} = J_{4-5}$ = 7.4 Hz, J_{4-6} = 1.75 Hz), 8.10 (ddd, 1H, 3-H, J_{3-6} = 0.9 Hz), 8.62 ppm (ddd, 1H, 6-H); cmr (deuteriochloroform): δ 27.5 ($(CH_3)_2$), 77.2 (-C-OH), 123.8 (C-3), 127.5 (C-5), 138.2 (C-4), 148.1 (C-6), 152.5 (C-2), 201.9 ppm (C=O); ms: m/z (relative abundance) 166 (10), M^++1, 126 (37.5), 107 (100), 95 (99.8), 80 (99.9), 79 (97.7), 78 (99.6), 59 (84.6), 52 (99.4), 51 (99.2), 50 (36.5), 43 (70.4), 41 (63.7), 39 (99.6).

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.45; H, 6.66; N, 8.48. Found: C, 65.47; H, 6.79; N, 8.49.

2-(2'-Hydroxy-2'-phenyl)propanoylpyridine (**10b**).

This compound was obtained by recrystallization from ethanol in 94% yield, mp 78°; ir (potassium bromide): 3240 (bonded OH), 1695 (conjugated C=O), 1580 cm^{-1} (ring); pmr (hexadeuteriodimethyl sulfoxide): δ 1.69 (s, 3H, CH_3), 7.08 (s, 1H, OH), 7.18 (tt, 1H, *para* H of C_6H_5), 7.29 (dt, 2H, *meta* H of C_6H_5), 7.46 (m, 2H, *ortho* H of C_6H_5), 7.53 (ddd, 1H, 5-H), 7.94 (m, 1H, 4-H), 7.97 (m, 1H, 3-H), 8.53 ppm (m, 1H, 6-H); cmr (deuteriochloroform): δ 27.6 (CH_3), 81.2 (C-OH), 124.0 (C-3), 124.5 (*ortho* C of phenyl), 127.0 (*para* C of phenyl), 127.4 (C-5), 128.2 (*meta* C of phenyl), 138.1 (C-4), 144.1 (*ipso* C of phenyl), 147.9 (C-6), 151.9 (C-2), 198.0 ppm (C=O); ms: m/z (relative abundance) 227 (1.56) M^+, 199 (4.2), 107 (26.4), 105 (11.6), 80 (13.2), 79 (100), 78 (13.4), 77 (13.3), 52 (12.4), 51 (11.5).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.95; H, 5.77; N, 6.15. Found: C, 73.56; H, 5.75; N, 6.17.

2-(2'-Hydroxy-2',2'-diphenyl)ethanoylpyridine (**10c**).

This compound was obtained by recristallization from chloroform in 92% yield, mp 134°; ir (potassium bromide): 3240 (bonded OH), 1695 (conjugated C=O), 1580 cm^{-1} (ring); pmr (deuteriochloroform): δ 7.25-7.37 (m, 6H) *meta* and *para* H of phenyl), 7.39 (ddd, 1H, 5-H, J_{4-5} = 7.7 Hz, J_{5-6} = 4.85 Hz, J_{3-5} =

1.3 Hz), 7.45-7.50 (m, 4H, *ortho* H of phenyl), 7.87 (dt, 1H, 4-H), J_{3-4} = 7.9 Hz, J_{3-5} = 1.3 Hz), 8.18 (s, 1H, OH), 8.20 (ddd, 1H, 3-H, J_{3-6} = 0.9 Hz), 8.43 ppm (ddd, 1H, 6-H); cmr (deuteriochloroform): δ 85.4 (C-OH), 124.5 (C-3), 126.7 (*ortho* C of phenyl), 127.3 (*para* C of phenyl), 127.7 (C-5), 127.9 (*meta* C of phenyl), 138.7 (C-4), 142.8 (*ipso* C of phenyl), 147.8 (C-6), 152.3 (C-2), 196.4 ppm (C=O); ms: m/z (relative abundance) 289 (2.81) M^+, 261 (19.2) 183 (10.5), 107 (19.2), 106 (10.2), 105 (100), 80 (10.5), 79 (90), 78 (24.4), 77 (80.7), 52 (16.4), 51 (27.6).

Anal. Calcd. for $C_{19}H_{15}NO_2$: C, 78.97; H, 5.22; N, 4.83. Found: C, 79.05; H, 5.10; N, 4.65.

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[25] Owing to its hygroscopicity this compound was not submitted to elemental analysis and was used without further purification for the ensuing step.