Facile Dibenzoylation of Picoline

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In the presence of triethylamine, 2- and 4-picolines reacted with an excess of benzoyl chloride in refluxing acetonitrile to give the corresponding 1-benzoyl-phenacylidenedihydropyridines. The difference in reactivity between 2- and 4-picoline toward such a dibenzoylation was studied from the conversion rates under various conditions with hplc. It was also clarified that the dibenzoylation proceeded *via* the intermediate phenacylpyridine and a plausible reaction scheme has been proposed, considering the significant role of triethylamine.

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Several papers have reported on the acylation of 2- or 4-picoline to yield the corresponding (acylmethyl)pyridines. These include the direct acylation of picoline in acyl chloride under reflux [1] and the reaction *via* picolyllithium [2] or picolylmagnesium halide [3].

In the present paper, we wish to report the facile dibenzoylation of 2- and 4-picolines with benzoyl chloride in the presence of an excess of triethylamine under such mild conditions as in refluxing acetonitrile or chloroform. The structures of the products were determined to be 1-benzoyl-2 or 4-phenacylidene-1,2 or 1,4-dihydropyridine (I and II), respectively, on the basis of the analytical and spectral data. The possibility of the isomeric (dibenzoylmethyl)pyridines (III) was excluded since the ^{13}C-nmr spectra showed the doublet signal of olefinic carbon at δ = 116.2 ppm or δ = 114.8 ppm attributed to each phenacylidene group, and no detectable sp^3-carbon signal in the upper field attributable to the dibenzoylmethyl group.

The dibenzoylation of picolines limited to the 2- and 4-isomers, while 3-picoline remained unreacted under similar conditions, as expected because of the known inactivity of the 3-methyl group. The difference in reactivity between 2- and 4-picoline toward dibenzoylation was investigated from the rate of the conversion under various conditions with hplc using an internal standard.

Influence of the Molar Ratio on the Dibenzoylation.

The reaction of picoline (P) with benzoyl chloride (B) in the presence of triethylamine (T) was carried out in acetonitrile at its refluxing temperature, with the initial molar ratio of P:B:T = 1:2:2, 1:4:4 and 1:6:6, respectively. The dibenzoylated product in the reaction mixture was measured by hplc with the lapse of time, the results being shown in Figure I.

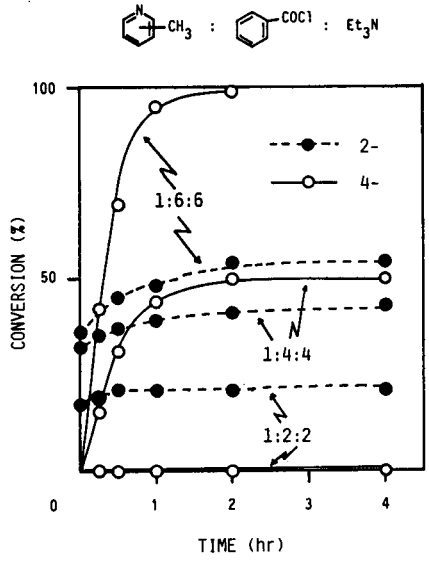


Figure I. Influence of the molar ratio of picoline, benzoyl chloride and triethylamine on the dibenzoylation. Reaction conditions; picoline: 1.0 mmole, solvent: 10 ml of acetonitrile (reflux).

Scheme I

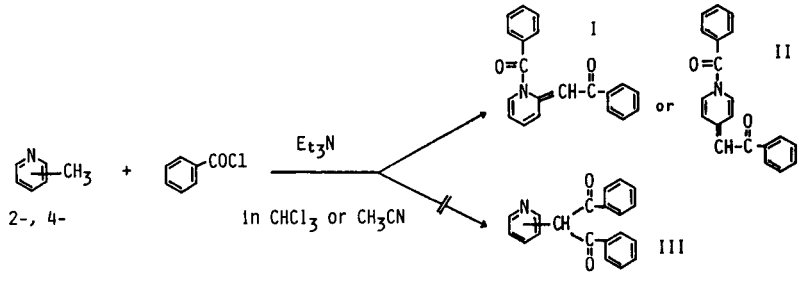


Figure I shows that a larger increase of molar ratio of both benzoyl chloride and triethylamine promotes the dibenzoylation, and such a tendency is much more remarkable for 4-picoline than the 2-isomer. In the case of P:B:T = 1:6:6, 4-picoline could be quantitatively dibenzoylated in 2 hours, while no detectable dibenzoylation occurred in the case of P:B:T = 1:2:2. Here it should be noted that 3-picoline indicated no change in hplc during a similar treatment for 4 hours, without even a detectable amount of either monophenacyl or N-benzoyl derivative.

Effect of Triethylamine on the Dibenzoylation.

Picoline was treated with benzoyl chloride (P:B = 1:4) in refluxing acetonitrile in the absence of triethylamine for the first 3 hours, and then an excess of triethylamine (T = 4) was added, and the mixture was heated for additional 3 hours. The conversion rates are shown in Figure II.

From Figure II, it is obvious that, in the absence of triethylamine, the picolines remained unreacted in spite of the presence of excess benzoyl chloride, and that triethylamine is essentially required to promote the dibenzoylation.

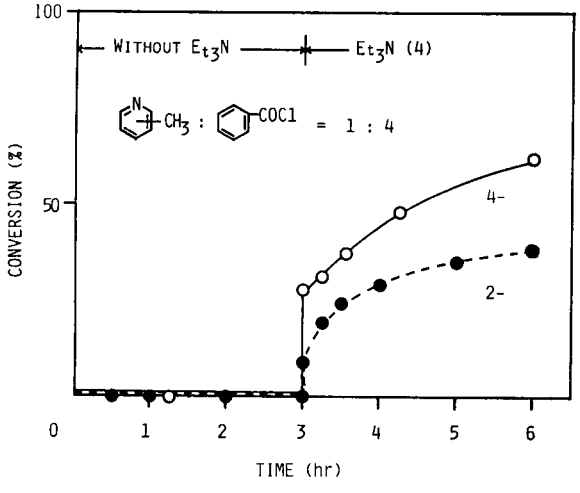


Figure II. Effect of triethylamine on the dibenzoylation. Reaction conditions; picoline: 1.0 mmole, solvent: 10 ml of acetonitrile (reflux).

Benzoylation of Monobenzoylated Picoline.

During the course of pursuing the dibenzoylation with hplc, there was observed a signal attributable to a monobenzoylated intermediate which, however, could not be isolated from the reaction mixture. The final product, 1-benzoyl-4-phenacylidene-1,4-dihydropyridine (II), was partially hydrolyzed with ethanolic sodium carbonate giving 4-phenacylpyridine (IV) quantitatively. The obtained 4-phenacylpyridine (IV) was then treated with benzoyl chloride (B) in the presence of triethylamine (T) with an initial molar ratio of IV:B:T = 1:3:3 in refluxing acetonitrile. The reaction was again monitored by the same procedure. The conversion to 1-benzoyl-4-phenacylidene-1,4-dihydropyridine is shown in Figure III.

The result suggests that phenacylpyridine (IV) must be a possible intermediate in the dibenzoylation of picoline. In contrast to the above mentioned hydrolysis, disproportionation between picoline and the dibenzoylated product (II) did not occur and an attempt to isolate 1-benzoyl-4-methylene-1,4-dihydropyridine (V) failed.

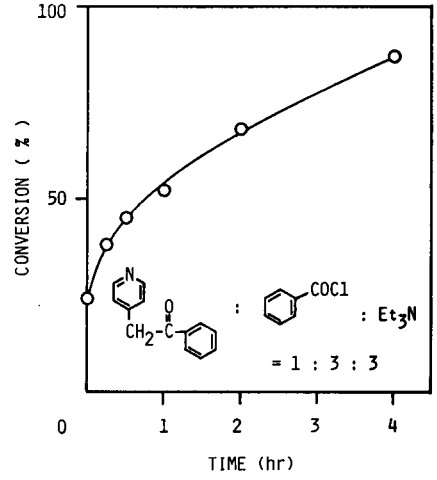
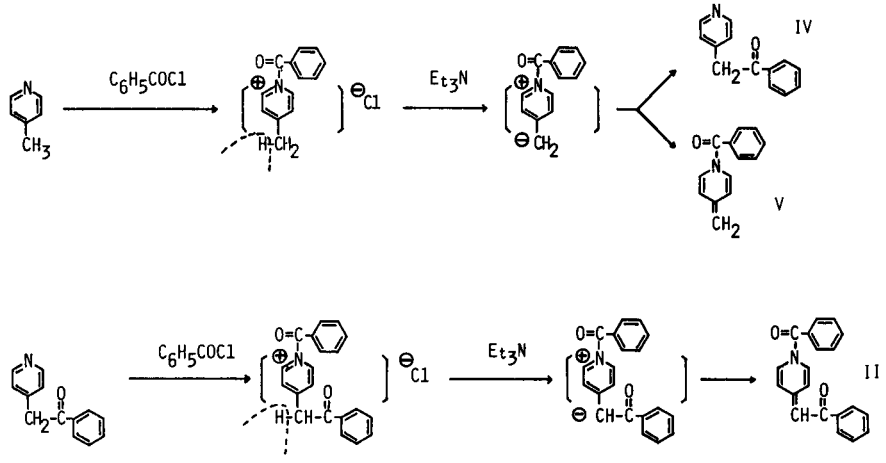


Figure III. Benzoylation of 4-phenacylpyridine. Reaction conditions; 4-phenacylpyridine: 0.5 mmole, solvent: 5 ml of acetonitrile (reflux).

Recently we reported [4-6] that the aromatic primary amines, such as aniline, reacted with an excess of benzoyl chloride by a synergistic catalytic role of pyridine-triethylamine in refluxing chloroform to give the corresponding *N,N*-dibenzoylated derivatives in appreciable yields, and established the mechanism. Based on similar considerations, the dibenzoylation path for picoline is proposed as illustrated in Scheme II.

The activity of the methyl group of picoline is enhanced by the coordination of the benzoyl group in the early stage of the reaction. An acidic proton of the methyl group is then abstracted with triethylamine to form the charged structure, which might be stabilized in two ways: (1) a rearrangement of benzoyl cation to methyl carbanion in order to gain the aromaticity of the pyridine ring, giving IV, or (2) a neutralization of counter charges to form the pyridylidene structure V. The former seems to be more likely, since phenacylpyridine could be further benzoylated as mentioned before, although the possibility of the latter can not be excluded. The second benzoylation may proceed by a similar step to yield the less sterically hindered product II.

Scheme II



EXPERIMENTAL

Melting points were determined in a capillary and are uncorrected. The ir spectra were measured on a JASCO IRA-1 spectrometer in a potassium bromide wafer. The ^{1}H- and ^{13}C-nmr spectra were obtained on JEOL JNM-PMX 60 and JEOL JNM-FX 60 spectrometers, respectively, in deuteriochloroform unless otherwise stated. Chemical shifts are reported in ppm from tetramethylsilane and are given in δ units. Mass spectra were obtained on a Finnigan 3300E GC-MS instrument by means of a chemical ionization method with methane reagent gas. The uv spectra were measured for solutions in ethanol with a Hitachi 340 spectrophotometer.

1-Benzoyl-2 or 4-phenacylidene-1,2 or 1,4-dihydropyridine (I and II).

A solution of benzoyl chloride (16.86 g, 0.12 mole) in chloroform (50 ml) was added to a solution of 2- or 4-picoline (2.79 g, 0.03 mole) and triethylamine (12.12 g, 0.12 mole) in chloroform (150 ml). After heating with stirring under reflux for 6 hours, the mixture was evaporated to dryness under reduced pressure, and extracted with acetone at room temperature. After removal of the solvent, the resulting solid was extracted with benzene. The extract was washed with diluted sodium carbonate aqueous solution and water, dried over anhydrous sodium sulfate, and evaporated to give a solid which was recrystallized repeatedly from hexane, yielding I (3.30 g, 37%) or II (2.57 g, 29%), respectively.

Compound I was obtained as pale yellow needles mp 88-90°; ir: 1730, 1580, 1230, 1080, 1060 cm^{-1}; ^{1}H-nmr: 7.1 (s, phenacylidene =CH, 1H), 7.2-8.3 (m, 3- and 4-pyridyl and phenyl CH, 13H), 8.5 (d, 2-pyridyl CH, 1H); ^{13}C-nmr: 116.2 (d, phenacylidene =CH-); ms: (m/e) 302 MH$^+$; uv: λ max 300 nm (ϵ = 16300), λ max 227 nm (ϵ = 20900).

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.72; H, 5.01; N, 4.61.

Compound II was obtained as white needles, mp 116-119°; ir: 1730, 1590, 1230, 1080, 1060 cm^{-1}; ^{1}H-nmr: 6.7 (s, phenacylidene =CH, 1H), 7.2-8.3 (m, 3-pyridyl and phenyl CH, 12H), 8.5 (d, 2-pyridyl CH, 2H); ^{13}C-nmr: 114.8 (d, phenacylidene =CH-); ms: (m/e) 302 MH$^+$; uv: λ max 294 nm (ϵ = 22400), λ max 232 nm (ϵ = 21400).

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.57; H, 4.90; N, 4.50.

4-Phenacylpyridine (IV).

A mixture of II (0.19 g, 0.63 mmole) and sodium carbonate (2.00 g, 18.87 mmoles) in ethanol-water (30 ml-20 ml) was heated under reflux for 2 hours. The mixture was evaporated to dryness under reduced pressure and the residue was extracted with acetone and evaporated again. The resulting solid was recrystallized from hexane to yield IV (0.12 g, 97%) as pale yellow leaflets, mp 114-116° (lit [2], mp 114-115°); ir: 1680, 1600, 1330, 1220, 1200 cm^{-1}; ^{1}H-nmr (carbon tetrachloride): 4.2 (s, methylene CH_2, 2H), 7.1 (d, J = 6 Hz, 3-pyridyl CH, 2H), 7.3-8.1 (m, phenyl CH, 5H), 8.5 (d, J = 6 Hz, 2-pyridyl CH, 2H); ^{13}C-nmr: 44.4 (t, methylene -CH_2-); ms: (m/e) 198 MH$^+$; uv: λ max 244 nm (ϵ = 14900).

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 79.06; H, 5.61; N, 7.03.

Measurement of the Conversion Rate by HPLC.

The conversion rate in the case of the initial molar ratio P:B:T = 1:4:4 was measured by hplc as follows (other measurements were carried out in a similar way).

Picoline (0.096 g, 1.03 mmoles), triethylamine (0.406 g, 4.01 mmoles) and *m*-dinitriobenzene (0.169 g, 1.01 mmoles) as an internal standard were weighed accurately and dissolved in acetonitrile (10 ml) in a 30 ml flask. Immediately after benzoyl chloride (0.567 g, 4.03 mmoles) was added to the solution, the flask was immersed into an oil bath heated at 90°. At certain interval after the immersion, each 0.1 ml portion of the reaction mixture was sampled, poured into 0.3 ml of 94% moist acetonitrile, and then subjected to hplc to determine the amount of dibenzoylated products.

The conditions (hplc) were: column, 3 mm ϕ × 300 mm; stationary phase, LS-120B [7] (Toyo Soda Co.); mobile phase, methanol; flow rate, 0.7 ml/minute; detector, uv (254 nm).

Product	Retention Time (Minutes)	Molar Sensitivity Ratio (Standard) (Product/Internal Standard)
I	9.5	2.834 (acenaphthylene)
II	8.6	0.7265 (*m*-dinitrobenzene)

REFERENCES AND NOTES

[1] Yu. V. Kurbatov, A. S. Kurbatova, M. A. Solekhova, O. S. Otroshchenko and A. S. Sadykov, *Tr. Samarkand. Gos. Univ.*, **167**, 192 (1969); *Chem. Abstr.*, **73**, 109642u (1970).

[2] T. Kato, H. Yamanaka and T. Adachi, *Yakugaku Zasshi*, **85**, 611 (1965).

[3] J. W. Hey and J. P. Wibaut, *Rec. Trav. Chim.*, **72**, 522 (1953).

[4] T. Suzuki and K. Mitsuhashi, *Nippon Kagaku Kaishi*, 631 (1979).

[5] T. Suzuki and K. Mitsuhashi, *Nippon Kagaku Kaishi*, 667 (1980).

[6] T. Suzuki and K. Mitsuhashi, *Nippon Kagaku Kaishi*, 1926 (1980).

[7] Styrene-divinylbenzene porous copolymer gel, particle diameter, 10 μm.