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IMPROVED METHOD FOR THE PREPARATION OF 3-ARYL- AND 3-STYRYLIMIDAZO[1,5-*a*]PYRIDINES

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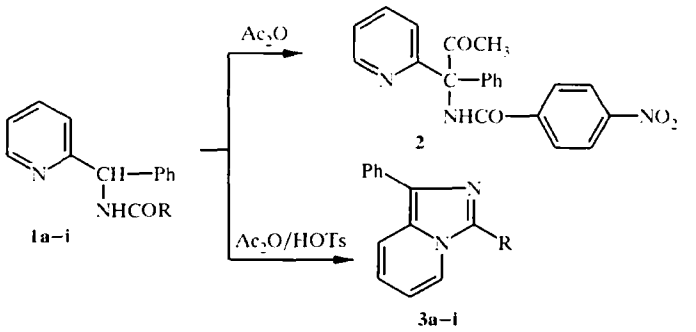
A new convenient method is proposed for the preparation of 3-aryl- and 2-styrylimidazo[1,5-a]pyridines involving the cyclocondensation of 2-(acylaminobenzyl)pyridines in acetic anhydride with adding of p-toluenesulfonic acid.

Keywords: 2-(acylaminobenzyl)pyridines, imidazo[1,5-*a*]pyridines, cyclocondensation.

Imidazo[1,5-*a*]pyridines display physiological activity and are used in antiviral [1] and cardiotonic drugs [2]. These compounds are also employed as inhibitors for certain enzymes [3] and as fluorophors [4, 5].

The most convenient method for the synthesis of imidazo[1,5-*a*]pyridines is the cyclocondensation of 2-(acylaminobenzyl)pyridines in acetic anhydride at reflux [6] but this method is suitable only in the case of aliphatic substituents. On the other hand, the cyclization to give 3-aryl derivatives is carried out using $POCl_3$ [7-9], PCl_3 [10], or polyphosphoric acid [11]. These methods have considerable disadvantages such as cumbersome procedures for isolation and purification of the reaction products, low yields, and insuitability for derivatives sensitive to the action of strong acids.



1, 3a R = 4-$O_2NC_6H_4$, **b** R = 4-$O_2NC_6H_4CH$=CH, **c** R = 2-furyl, **d** R = 4-$CH_3OC_6H_4$, **e** R = 4-ClC_6H_4, **f** R = 3-$O_2NC_6H_4$, **g** R = 4-FC_6H_4, **h** R = 4-(*t*-C_4H_9)C_6H_4, **i** R = 4-ClC_6H_4CH=CH

We have studied the feasibility of preparing **3** by the cyclocondensation of starting 2-(acylaminobenzyl)pyridines **1** with aromatic or styryl substituents using acetic anhydride. In the case of amide **1a**, we found that the reaction does not proceed selectively and the desired product is isolated in low yield. Acetylated derivative **2** obtained as the hydrobromide salt is formed predominantly. The addition of *p*-toluenesulfonic acid prevents C-acetylation and facilitates cyclization. New derivatives **3a-i** were synthesized by this technique.

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TABLE 1. Physical Characteristics of Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (cryst. solvent)	λ_{max}, nm	Yield, %
		C	H	N			
3a	$C_{16}H_{11}N_3O_2$	72.2 / 72.4	4.1 / 4.1	13.4 / 13.4	192-195 (acetic acid)	345	80
3b	$C_{21}H_{15}N_3O_2$	73.9 / 73.9	4.4 / 4.4	12.4 / 12.3	222-225 (acetic acid)	396	91
3c	$C_{17}H_{12}N_2O_2$	78.2 / 78.2	5.0 / 4.9	10.6 / 10.7	127-128 (ethanol)	315	73
3d	$C_{20}H_{16}N_2O$	78.4 / 80.0	5.3 / 5.3	9.5 / 9.3	163-165 (ethanol)	307	76
3e	$C_{16}H_{13}ClN_2$	74.6 / 74.8	4.2 / 4.3	9.2 / 9.2	149-151 (ethanol)	316	68
3f	$C_{21}H_{15}N_3O_2$	74.1 / 73.9	4.4 / 4.4	12.3 / 12.3	168-171 (acetic acid)	396	84
3g	$C_{16}H_{13}FN_2$	79.0 / 79.2	4.4 / 4.5	9.6 / 9.7	142-144 (ethanol)	318	67
3h	$C_{23}H_{22}N_2$	84.6 / 84.7	6.8 / 6.7	8.6 / 8.6	129-131 (ethanol)	311	89
3i	$C_{21}H_{15}ClN_2$	76.3 / 76.2	4.6 / 4.5	8.4 / 8.5	105-108 (ethanol)	401	74
2	$C_{21}H_{18}BrN_3O_4$	54.5 / 55.2	3.9 / 3.9	9.1 / 9.2	227-229 (ethanol)		29

This method permits us to obtain a broad range of 3-aryl- and 3-styrylimidazo[1,5-*a*]pyridines in high yield over a short period and simplifies the isolation and purification of these products. The structures of products **3** were confirmed by the electronic absorption and ^{1}H NMR spectroscopic data, which correlate with the literature values.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Varian VXR-300 spectrometer for solutions in DMSO-d_6 with TMS as the internal standard. The electronic absorption spectra were taken on a Shimadzu UV-3100 spectrometer for $2 \cdot 10^{-5}$ mol/l solutions in acetonitrile. The reaction course and purity of the products were monitored by thin layer chromatography on Silufol UV-254 plates with 3:1 ethyl acetate–petroleum ether as the eluent.

The electronic spectral and elemental analysis data are given in Table 1.

2-[1-Acetyl-1-(4-nitrobenzoylamino)benzyl]pyridinium Hydrobromide (2). A solution of amide **1a** (3 g, 8 mmol) in acetic anhydride (15 ml) was heated at reflux for 30 min, cooled, and poured into 10% aq. ammonia (100 ml). The oil was extracted with dichloromethane, dried over sodium sulfate, and evaporated. The residue was dissolved in 2-propanol and filtered to give solid product (0.5 g) identified as **3a** by its ^{1}H NMR spectrum and elemental analysis. Then, 48% hydrobromic acid (2 ml) was added to the filtrate. The precipitate formed was filtered off to give compound **2** (1.2 g). ^{1}H NMR spectrum: 3.07 (3H, s, CH_3); 6.92 (1H, s, NH); 7.24 (2H, *m*-, *o*-H_{Ph}); 7.61 (3H, m, *m*- and *p*-H_{Ph}); 7.94 (2H, d, J = 9 Hz, *o*-$H_{nitrophenyl}$); 8.06 (1H, d, J = 7 Hz, 2-H_{Py}); 8.26 (1H, m, 4-H_{Py}); 8.43 (2H, d, J = 9 Hz, *m*-$H_{nitrophenyl}$); 6.65 (1H, t, J = 8 Hz, 3-H_{Py}); 8.90 ppm (1H, d, J = 6 Hz, 5-H_{Py}).

3-Aryl- and 3-Styrylimidazo[1,5-*a*]pyridines (3a-i). A sample of *p*-toluenesulfonic acid (5 mmol) was added to the corresponding amide **1a-d** (5 mmol) in acetic anhydride (10-15 ml) and heated at reflux for 30 min. The solution was cooled and poured into 10% aq. ammonia (100 ml). The precipitate formed was filtered off and crystallized.

^{1}H NMR spectrum of compound **3a**: 6.92 (1H, dd, J = Hz, 5-H); 7.08 (1H, t, J = 10 Hz, p-H_{Ph}); 7.33 (1H, dd, J = 7 Hz, 6-H); 7.50 (2H, t, J = 8 Hz, m-H_{Ph}); 7.96 (2H, d, J = 8 Hz, o-H_{Ph}); 8.06 (1H, d, J = 10 Hz, 7-H); 8.21 (2H, d, J = 9 Hz, o-$H_{nitrophenyl}$); 8.36 (2H, d, J = 9 Hz, m-$H_{nitrophenyl}$); 8.68 ppm (1H, d, J = 6 Hz, 4-H).

Compound 3b: 7.36 (1H, dd, J = 7 Hz, 5-H); 7.42 (1H, t, J = 8 Hz, p-H_{Ph}); 7.5-7.8 (7H, m); 7.90 (2H, d, J = 8 Hz, o-$H_{nitrophenyl}$); 8.03 (1H, d, J = 9 Hz, 7-H); 8.40 (2H, d, J = 8 Hz, m-$H_{nitrophenyl}$); 8.56 ppm (1H, d, J = 6 Hz, 6-H).

Compound 3c: 6.77 (1H, m, 4-H_{furyl}); 6.92 (1H, m, 3-H_{furyl}); 7.01 (1H, t, J = 8 Hz, p-H_{Ph}); 7.14 (1H, m, 2-H_{furyl}); 7.32 (1H, dd, J = 7 Hz, 6-H); 7.49 (2H, t, J = 8 Hz, m-H_{Ph}); 7.9-8.1 (4H, m); 8.70 ppm (1H, d, J = 7 Hz, 4-H).

Compound 3d: 3.85 (3H, s, OCH_3); 6.74 (1H, t, J = 7 Hz, 5-H); 6.93 (1H, dd, J = 10 Hz, 6-H); 7.13 (2H, d, J = 10 Hz, o-H_{Ph}); 7.28 (1H, t, J = 8 Hz, p-H_{Ph}); 7.47 (2H, t, J = 8 Hz, m-H_{Ph}); 7.79 (2H, d, J = 9 Hz, m-$H_{methoxyphenyl}$); 7.94 (2H, d, J = 9 Hz, o-$H_{methoxyphenyl}$); 7.98 (1H, d, J = 9 Hz, 7-H); 8.36 ppm (1H, d, J = 8 Hz, 4-H).

Compound 3e: 6.79 (1H, t, J = 7 Hz, 5-H); 6.98 (1H, dd, J = 10 Hz, 6-H); 7.30 (1H, t, J = 10 Hz, p-H_{Ph}); 7.47 (2H, t, J = 8 Hz, m-H_{Ph}); 7.62 (2H, d, J = 9 Hz, o-H_{Ph}); 7.9-8.0 (5H, m); 8.45 ppm (1H, d, J = 7 Hz, 4-H).

Compound 3f: 6.87 (1H, t, J = 7 Hz, 5-H); 6.99 (1H, dd, J = 10 Hz, 6-H); 7.31 (1H, t, J = 8 Hz, p-H_{Ph}); 7.48 (2H, t, J = 8 Hz, m-H_{Ph}); 7.6-7.7 (2H, m); 7.9-8.0 (4H, m); 8.07 (1H, d, J = 9 Hz, 7-H); 8.17 (1H, d, J = 8 Hz, 4-$H_{nitrophenyl}$); 8.65 (1H, s, 2-$H_{nitrophenyl}$); 8.86 ppm (1H, d, J = 7 Hz, 4-H).

Compound 3g: 6.76 (1H, t, J = 7 Hz, 5-H); 6.95 (1H, dd, J = 10 Hz, 6-H); 7.29 (1H, t, J = 8 Hz, p-H_{Ph}); 7.37 (4H, m); 7.9 (5H, m); 8.38 ppm (4H, d, J = 7 Hz).

Compound 3h: 1.42 (9H, s, CH_3); 6.75 (1H, t, J = 6 Hz, 5-H); 6.95 (1H, dd, J = 9 Hz, 6-H); 7.28 (1H, t, J = 8 Hz, p-H_{Ph}); 7.47 (2H, t, J = 8 Hz, m-H_{Ph}); 7.58 (2H, d, J = 10 Hz, m-$H_{tert\text{-}butylphenyl}$); 7.80 (2H, d, J = 10 Hz, o-$H_{tert\text{-}butylphenyl}$); 7.9-8.0 (3H, m); 8.44 ppm (1H, d, J = 7 Hz, 4-H).

Compound 3i: 6.68 (1H, t, J = 6 Hz, 5-H); 6.97 (1H, dd, J = 8 Hz, 6-H); 7.31 (1H, t, J = 8 Hz, p-H_{Ph}); 7.4-7.6 (5H, m); 7.8-8.0 (6H, m); 8.81 ppm (1H, d, J = 7 Hz, 4-H).

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