

HETEROCYCLES, Vol. 65, No. 9, 2005, pp. 2189 - 2194

Received, 16th May, 2005, Accepted, 21st July, 2005, Published online, 26th July, 2005

PREPARATION OF 1-ALKYL-2-ARYL-1*H*-IMIDAZO[4,5-*b*]PYRIDINES FROM 2-ALKYLAMINO-3-AMINOPYRIDINES AND AROMATIC ALDEHYDES USING AIR AS AN OXIDANT

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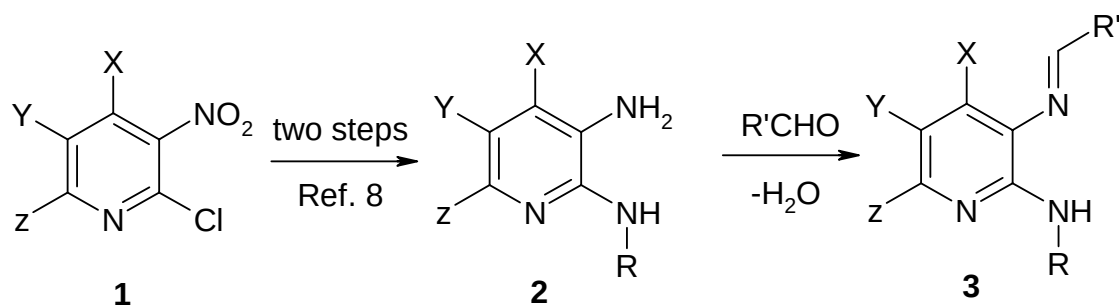
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Abstract - Attempted imine formation between 2-methoxyethylamino-3-aminopyridine (an exemplary 2-alkylamino-3-aminopyridine) and an array of aromatic aldehydes in methanol and ambient atmosphere led to the predominant formation of 1-methoxyethyl-2-aryl-1*H*-imidazo[4,5-*b*]pyridines. The reaction was found to be of immediate preparative importance in the six cases studied.

INTRODUCTION

Our ongoing search for heterocyclic building blocks useful in construction of medicinally important small molecules led us to investigate the synthesis of unsymmetrical 2,3-bis(dialkylamino)pyridines. The latter have been reported as valuable intermediates en route to bioactive compounds among which analgetics,¹ antagonists for platelet activating factor,² thromboxane A₂,³ and angiotensin II⁴ as well as hypoglycemic compounds⁵ are a few notable examples. Preparative methods described in the literature for these diamine compounds include either sequential introduction of two different amino functionalities via Pd-catalyzed amination of a dihalopyridine core,⁶ or LAH reduction of 2,3-bis(acylamino)pyridines.⁷ However, we found no account of a straightforward strategy (Scheme 1) that would include reductive amination on the primary amino group² of 2-alkylamino-3-aminopyridines (**2**) (easily accessible from cheap 2-chloro-3-nitropyridine (**1**) in two high-yielding steps⁸) with intermediacy of respective imines (**3**).

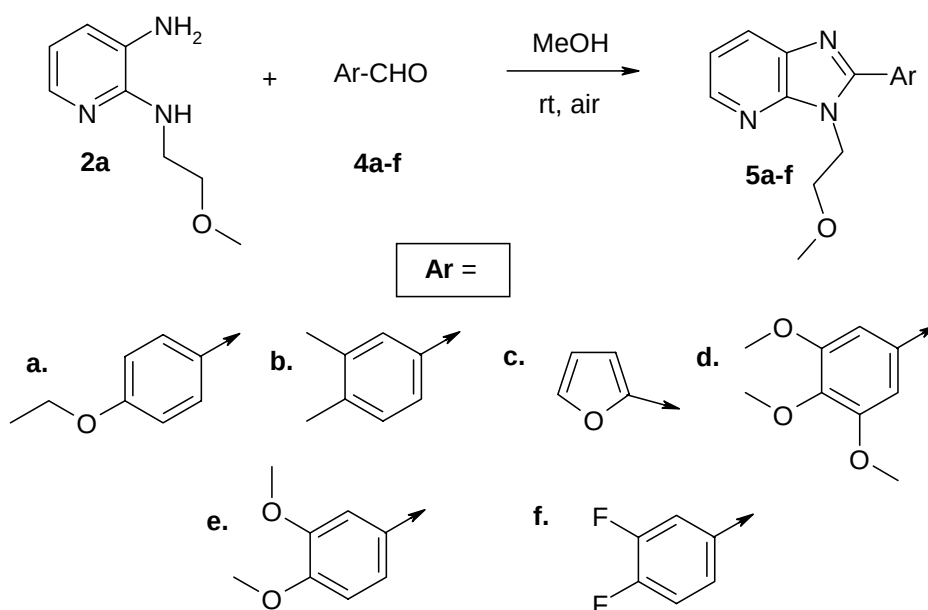
We therefore proceeded by mixing a model starting material (**2a**) with a set of aromatic aldehydes (**4a-f**) in methanolic solution and monitoring the reaction progress while the solutions were being stirred in the air (Scheme 2). As discussed below, the observed reaction followed a different route providing in all cases substantial amounts of 1-methoxyethyl-2-aryl-1*H*-imidazo[4,5-*b*]pyridines (**5a-f**).



Scheme 1. R, R' = alkyl, aryl, heteroaryl; X, Y, Z = any substituent, including a cycle

RESULTS AND DISCUSSION

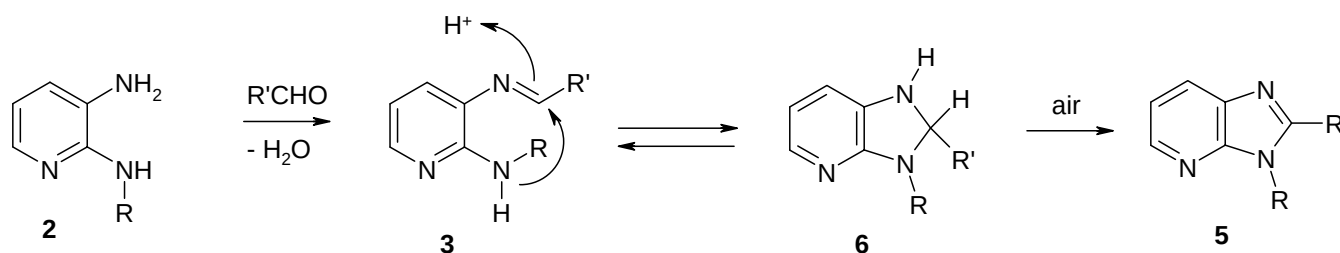
The starting material (**2a**) was prepared from 2-chloro-3-nitropyridine (**1**) according to the well-established two-step protocol.⁸ It was then brought in contact with methanolic solutions of aromatic aldehydes (**4a-f**) in anticipation of the formation of a respective imine (**3**). However, in all cases TLC analysis performed after 3 h indicated predominant formation of a slightly more polar product (presumably different from the desired imine) that did not change when NaBH₄ was subsequently added. The reaction mixtures were worked up and the crude products were analyzed by ¹H NMR spectroscopy indicating the absence of signals of either aldimine proton⁹ or the benzylic methylene group. In all cases, we purified the major reaction product by column chromatography and established its identity by ¹H and ¹³C NMR spectroscopy (as well as MS) as 1-methoxyethyl-2-aryl-1*H*-imidazo[4,5-*b*]pyridines (**5a-f**) (Scheme 2). Notably, the isolated yields of these pharmaceutically important¹⁰ heterocyclic compounds were in the range 40-62% which clearly makes this environmentally benign transformation also synthetically sound.



Scheme 2

Formation of 1*H*-imidazo[4,5-*b*]pyridines upon reacting 2,3-diaminopyridines with aldehydes has been described in the literature.^{3,5,11-13} However, in all cases it required the use of elevated temperatures and introduction of a specific oxidant such as elemental sulfur,¹¹ iodine,^{3,5} copper(II) salts,¹² or nitrobenzene¹³ but we found no report on the use of air as a reactant in this type of cyclization at room temperature.

Mechanistically, the formation of 1*H*-imidazo[4,5-*b*]pyridine nucleus could be justified as presented in Scheme 3. The initially formed aldimine (**3**) exists in equilibrium with imidazoline (**6**). The latter, in presence of an oxidant (such as air) is converted into the isolated 1*H*-imidazo[4,5-*b*]pyridines (**5**).



Scheme 3

In summary, we have established a new synthetic protocol to prepare pharmaceutically important 1*H*-imidazo[4,5-*b*]pyridines from 2-alkylamino-3-aminopyridines in presence of air. This transformation does not require the use of strong oxidants and elevated temperatures and clearly offers an attractive, simple, and environmentally friendly alternative to previously reported methods.

EXPERIMENTAL

All reactions were run in oven-dried glassware in atmosphere of nitrogen. Melting points were measured with a Büchi B-520 melting point apparatus and were not corrected. Analytical thin-layer chromatography was carried out on EM Separations Technology F₂₅₄ silica gel plates. Compounds were visualized with short-wavelength UV light. ¹H NMR and ¹³C NMR spectra were recorded on Bruker DPX-300 spectrometers in DMSO-*d*₆ using TMS as an internal standard. MS analyses were obtained on a PE SCIEX API 150EX mass spectrometer. All solvents and reagents were obtained from commercial sources and used without purification.

N₂-(2-Methoxyethyl)pyridine-2,3-diamine (2a).

This material was prepared according to the literature procedure.⁸ To a solution of 2-chloro-3-nitropyridine (25.0 g, 157.68 mmol) in anhydrous dioxane (250 mL) triethylamine (17.55 g, 173.44 mmol) and 2-methoxyethylamine (13.0 g, 173.45 mmol) were added and the mixture was heated at reflux for 2 h. The progress of the reaction was followed by the appearance of yellow coloring and formation of the precipitate, as well as by TLC control (chloroform-MeOH, 79:1). Upon completion, the reaction mixture was cooled to rt, the solid triethylamine hydrochloride was filtered off, washed with dioxane, and discarded. The combined filtrate and washings were concentrated *in vacuo*. The residue was

dispersed in water (150 mL) and acidified with 4N aqueous HCl to pH 4.0. The resulting precipitate was filtered off, washed with water, and air-dried to afford 30.3 g of 2-methoxyethylamino-3-nitropyridine as bright-yellow solid: mp 70-71°C; ^1H NMR (300 MHz, CDCl_3): δ 8.47 (dd, $J = 1.7, 4.5$ Hz, 1H), 8.40 (dd, $J = 1.7, 8.5$ Hz, 1H), 6.76 (dd, $J = 4.5, 8.5$ Hz, 1H), 3.73 (dt, $J_d = 5.7$ Hz, $J_t = 5.6$ Hz, 2H), 3.54 (t, $J = 5.6$ Hz, 2H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.0, 151.9, 135.2, 127.5, 112.0, 70.1, 58.0, 40.1.

The latter (27.0 g) was dissolved in boiling ethanol (1L), the solution was cooled to 45°C and transferred into a pre-heated to 50°C 2-L autoclave chamber. 10% Pd/C (2.7 g) was added and the mixture is hydrogenated at 45°C and 6 bar for 6 h. The mixture was then cooled to rt and the catalyst was filtered off. The filtrate was concentrated *in vacuo* and the residue was dried in high vacuum. The spectroscopically pure product (**2a**) (22.34 g, 97% for two steps) was obtained as dark oil: ^1H NMR (300 MHz, CDCl_3): δ 7.37 (dd, $J = 1.7, 5.1$ Hz, 1H), 6.68 (dd, $J = 1.7, 7.4$ Hz, 1H), 6.34 (dd, $J = 5.1, 7.4$ Hz, 1H), 5.55 (unresolved t, 1H), 4.66 (br s, 2H), 3.49 (m, 4H), 3.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 147.7, 134.9, 130.2, 117.6, 112.3, 71.0, 57.9, 40.4; LCMS m/z 168 ($M + 1$); Anal. Calcd for $\text{C}_8\text{H}_{13}\text{N}_3\text{O}$: C, 57.47; H, 7.84; N, 25.13. Found: C, 57.50; H, 7.88; N, 25.16.

General procedure: preparation of 3H-imidazo[4,5-b]pyridines (5a-f).

The amine (**2a**) (1.0 g, 5.98 mmol) and an aromatic aldehyde (6.00 mmol) in dry methanol (25 mL) were stirred at rt¹³ for 12-24 h (or until full consumption of **3a** was observed by TLC analysis). The solvent was removed *in vacuo* and the residue was partitioned between dichloromethane and water. Organic layer was separated, dried over anhydrous Na_2SO_4 , filtered, and concentrated. Chromatography on silica gel (1→2.5% methanol in chloroform) provided analytically pure 3H-imidazo[4,5-b]pyridines (**5a-f**).

2-(4-Ethoxyphenyl)-3-(2-methoxyethyl)-3H-imidazo[4,5-b]pyridine (5a).

Yield 61.5%, mp 72-74°C. ^1H NMR (300 MHz, CDCl_3): δ 8.35 (dd, $J = 1.5, 4.7$ Hz, 1H), 8.05 (dd, $J = 1.5, 8.0$ Hz, 1H), 7.85 (d, $J = 8.9$ Hz, 2H), 7.29 (dd, $J = 4.7, 8.0$ Hz, 1H), 7.10 (d, $J = 8.9$ Hz, 2H), 4.52 (t, $J = 5.5$ Hz, 2H), 4.11 (q, $J = 7.0$ Hz, 2H), 3.76 (t, $J = 5.5$ Hz, 2H), 3.11 (s, 3H), 1.36 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.9, 154.3, 148.6, 143.1, 134.6, 130.8, 126.3, 122.1, 118.3, 114.6, 69.3, 63.2, 58.1, 43.0, 14.5; LCMS m/z 298 ($M + 1$); Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.65; H, 6.40; N, 14.11.

2-(3,4-Dimethylphenyl)-3-(2-methoxyethyl)-3H-imidazo[4,5-b]pyridine (5b).

Yield 62%, mp 56-59°C. ^1H NMR (300 MHz, CDCl_3): δ 8.36 (dd, $J = 1.3, 4.7$ Hz, 1H), 8.06 (dd, $J = 1.3, 8.0$ Hz, 1H), 7.68 (br s, 1H), 7.62 (d, $J = 7.7$ Hz, 1H), 7.33 (d, $J = 7.7$ Hz, 1H), 7.30 (dd, $J = 4.7, 8.0$ Hz, 1H), 4.53 (t, $J = 5.5$ Hz, 2H), 3.73 (t, $J = 5.5$ Hz, 2H), 3.10 (s, 3H), 2.32 (s, 6H); ^{13}C NMR (75 MHz,

DMSO- d_6): δ 154.5, 148.6, 138.5, 136.7, 134.6, 130.3, 129.7, 127.6, 126.6, 126.5, 118.3, 69.3, 58.0, 43.0, 19.3, 19.2; LCMS m/z 282 ($M + 1$); Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.60; H, 6.84; N, 14.97.

2-Furan-2-yl-3-(2-methoxyethyl)-3H-imidazo[4,5-*b*]pyridine (5c).

Yield 53%, mp 39-40°C. 1H NMR (300 MHz, $CDCl_3$): δ 8.36 (dd, $J = 1.3, 4.7$ Hz, 1H), 8.05 (dd, $J = 1.3, 8.1$ Hz, 1H), 8.03 (m, 1H), 7.34 (d, $J = 3.5$ Hz, 1H), 7.30 (dd, $J = 4.7, 8.1$ Hz, 1H), 6.77 (dd, $J = 1.9, 3.5$ Hz, 1H), 4.75 (t, $J = 5.6$ Hz, 2H), 3.74 (t, $J = 5.6$ Hz, 2H), 3.16 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 148.0, 145.5, 144.7, 144.6, 143.7, 134.6, 126.5, 118.7, 113.6, 112.2, 70.0, 58.0, 42.6; LCMS m/z 244 ($M + 1$); Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.15; H, 5.36; N, 17.25.

3-(2-Methoxyethyl)-2-(3,4,5-trimethoxyphenyl)-3H-imidazo[4,5-*b*]pyridine (5d).

Yield 40%, mp 86-88°C. 1H NMR (300 MHz, $CDCl_3$): δ 8.37 (dd, $J = 1.3, 4.7$ Hz, 1H), 8.10 (dd, $J = 1.3, 8.0$ Hz, 1H), 7.32 (dd, $J = 4.7, 8.0$ Hz, 1H), 7.30 (s, 2H), 4.55 (t, $J = 5.1$ Hz, 2H), 3.87 (s, 6H), 3.86 (t, $J = 5.1$ Hz, 2H), 3.77 (s, 3H), 3.18 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 154.3, 152.9, 148.6, 143.4, 139.0, 134.5, 126.6, 125.1, 118.5, 107.1, 69.6, 60.1, 58.3, 56.0, 43.7; LCMS m/z 344 ($M + 1$); Anal. Calcd for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.97; H, 6.16; N, 12.26.

2-(3,4-Dimethoxyphenyl)-3-(2-methoxyethyl)-3H-imidazo[4,5-*b*]pyridine (5e).

Yield 41%, mp 70-72°C. 1H NMR (300 MHz, $CDCl_3$): δ 8.35 (dd, $J = 1.1, 4.8$ Hz, 1H), 8.07 (dd, $J = 1.1, 7.9$ Hz, 1H), 7.56 (s, 1H), 7.49 (dd, $J = 1.7, 8.5$ Hz, 1H), 7.30 (dd, $J = 4.8, 8.1$ Hz, 1H), 7.11 (d, $J = 8.5$ Hz, 1H), 4.54 (t, $J = 5.3$ Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.81 (t, $J = 5.3$ Hz, 2H), 3.15 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 154.4, 150.3, 148.7, 148.6, 143.1, 134.6, 126.4, 122.2, 118.3, 112.8, 111.7, 69.5, 58.2, 55.6 (two peaks), 43.3; LCMS m/z 314 ($M + 1$); Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.12; H, 6.08; N, 13.39.

2-(3,4-Difluorophenyl)-3-(2-methoxyethyl)-3H-imidazo[4,5-*b*]pyridine (5f).

Yield 49%, mp 77-79°C. 1H NMR (300 MHz, $CDCl_3$): δ 8.41 (dd, $J = 1.3, 4.7$ Hz, 1H), 8.11 (dd, $J = 1.3, 7.9$ Hz, 1H), 8.02 (ddd, $J = 2.1, 7.7, 11.5$ Hz, 1H), 7.77 – 7.82 (m, 1H), 7.66 (dt, $J_d = 10.6, J_t = 8.3$ Hz, 1H), 7.34 (dd, $J = 3.2, 10.6$ Hz, 1H), 4.53 (t, $J = 5.5$ Hz, 2H), 3.75 (t, $J = 5.5$ Hz, 2H), 3.11 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 152.3, 151.6 (dd, $^2J_{C-F} = 100.0$ Hz, $^3J_{C-F} = 9.7$ Hz), 148.3, 148.2 (dd, $^2J_{C-F} = 97.1$ Hz, $^3J_{C-F} = 12.0$ Hz), 143.9, 134.4, 127.5 (dd, $^3J_{C-F} = 7.4$ Hz, $^4J_{C-F} = 4.0$ Hz), 127.0, 126.8 (dd, $^3J_{C-F} = 6.3$ Hz, $^4J_{C-F} = 2.9$ Hz), 118.7, 118.4 (dd, $^1J_{C-F} = 293.1$ Hz, $^2J_{C-F} = 48.0$ Hz), 111.1 (dd, $^1J_{C-F} = 297.6$ Hz, $^2J_{C-F} = 52.1$ Hz), LCMS m/z 290 ($M + 1$); Anal. Calcd for $C_{15}H_{13}N_3OF_2$: C, 62.28; H, 4.53; N, 14.53. Found: C, 62.30; H, 4.55; N, 14.56.

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9. We subsequently established the intermediacy of the aldimines (**3**) in the described process by detecting the presence of respective characteristic signals in the ^1H NMR spectrum of the reaction mixture aliquot measured after 1 h of 2-alkylamino-3-aminopyridine (**2a**) reacting with aldehyde (**4a**): δ 8.60 (s, $\text{CH}=\text{N}$, rel. int. 1H), 6.21 (t, $J = 5.1$ Hz, $\text{NH}-\text{CH}_2$, rel. int. 1H), 4.10 (d, $J = 7.0$ Hz, OCH_2CH_3 , rel. int. 2H), 3.27 (s, OCH_3 , rel. int. 3H), 1.35 (t, $J = 7.0$ Hz, OCH_2CH_3 , rel. int. 3H). It was present in rather small concentration (~ 10 mol. %) and could not be detected by TLC analysis due to decomposition on silica gel.
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14. We found that carrying out the reaction at a slightly elevated temperature (50°C) does accelerate the consumption of the starting material, however, it results in larger amounts of unidentified by-products compared to the reactions performed at room temperature.