JOC*Note*

Synthesis of C3-Substituted 4-Azaindoles: An Easy Access to 4-Azamelatonin and Protected 4-Azatryptophan

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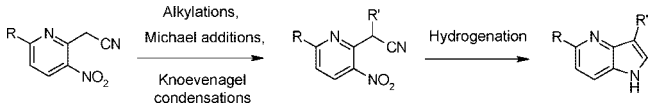
Received May 29, 2008

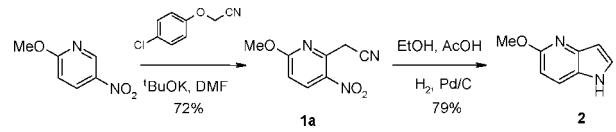


C3-Substituted-4-azaindoles were synthesized from pyridylacetonitriles in a two-step sequence allowing the easy introduction of a range of substituents. This strategy permits the rapid synthesis of 4-azamelatonin and a protected 4-azatryptophan.

In contrast to the plethora of natural products containing an indole moiety, only few incorporate an azaindole ring. This bioisoster of indole possessing remarkable physicochemical and pharmacological properties now attracts increasing interest from the chemistry community.[1]

The fusion of an electron-deficient pyridine ring with a pyrrole ring, forming an azaindole, alters the electronic properties of the π-system, rendering such heteroaromatic rings less reactive than indoles toward electrophilic reagents. As a consequence, direct functionalization at the C3 position with electrophiles is not as straightforward as for indoles. To date, few examples of nitrations,[2] halogenations,[3] formylations,[4] Mannich reactions,[5] Friedel−Crafts acylations,[6] condensations with piperidones,[7] and additions to aryl disulfides[8] have been disclosed in the literature. With the exception of halogenations and acylations, no reliable and general procedure for derivatizing the C3 position of azaindoles has emerged, and conditions are generally optimized for individual substrates.

SCHEME 1. Synthesis of 5-Methoxy-4-azaindole by Makosza and Co-workers



In this paper focusing on the 4-azaindole isomer, we wish to present a versatile approach to unprecedented C-3 substituted 4-azaindoles, with an increased scope and a high synthetic efficiency. To this end, we have been interested in the synthesis of 4-azaindole described by Makosza and co-workers.[9] Cyanomethylation of 5-methoxy-3-nitropyridine via a vicarious nucleophilic substitution of hydrogen gave pyridylacetonitrile **1a**, whose subsequent heterocyclisation under hydrogenation conditions provided the expected 4-azaindole **2** (Scheme 1).

First, we envisaged to take advantage of the acidity of the methylene group in **1a** to introduce various substituents prior to the heterocyclisation under palladium-catalyzed hydrogenation conditions. This methodology, barely applied in indole chemistry,[10] could be of particular interest for a rapid access to C3-substituted 4-azaindoles with a wide range of functionalities. Previous attempts by Macor et al.[11] to prepare azaindoles by this method resulted in the sole isolation of 3-methyl-4-azaindole in only 16% yield. Although they successfully carried out Mitsonobu reactions with **1a**, the subsequent cyclization step failed.

Since alkyl chains could not be directly introduced at the C3 position of the 4-azaindole by Friedel−Craft alkylation, we first investigated the alkylation of pyridylacetonitriles **1a** and **1b** followed by their heterocyclisation under hydrogenation conditions. Results are reported in Table 1.

Deprotonation of **1a** and **1b** with a weak base such as potassium carbonate and subsequent alkylation with benzyl and primary alkyl halides afforded products **3a**−**3f** in moderate to

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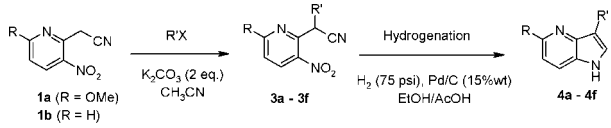
10.1021/jo8011623 CCC: $40.75 © 2008 American Chemical Society
Published on Web 08/26/2008

TABLE 1. Direct Alkylation of Pyridylacetonitriles 1a and 1b Followed by 4-Azaindole Ring Formation



entry	substrate / R'X	product (yield)[a]	product (yield)[a]
1	**1b** / BnBr	**3a** (80%)	**4a** (53%)
2	**1a** / BnBr	**3b** (85%)	**4b** (43%)[d]
3	**1a** / nBuI	**3c** (57%)[c]	**4c** (40%)
4	**1a** / MeI	**3d** (88%)[c]	**4d** (35%)
5	**1a** / $BrCH_2CO_2Et$	**3e** (87%)	**4e** (63%)[e]
6	**1a** / $BrCH_2CN$	**3f** (54%)[b]	**4f** (46%)

[a] After a column flash chromatography. [b] 0.5 equiv of K_2CO_3 was used in DMF as solvent. [c] DMF/CH_3CN mixture was used as solvent. [d] EtOH/MeOH mixture was used as solvent. [e] EtOH was used as solvent.

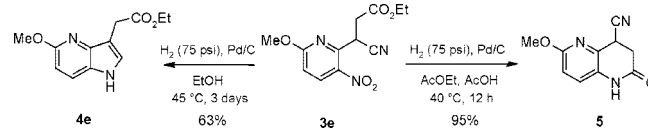
high yields. Several solvents and reaction temperatures were screened to minimize the formation of the bis-alkylated derivatives responsible for the moderate yields (Table 1, entries 3 and 6). Intermediates **3a**−**3f** were then hydrogenated to provide the corresponding C3-alkylated 4-azaindoles in reasonable yields. Adding acetic acid as cosolvent increased the rate of the conversion but did not improve the yields. This strategy proved to be compatible with functional groups present on the side chain (Table 1, entries 5 and 6) and rapidly afforded original 4-azaindoles in moderate to good yields.

It is important to note that the nature of the solvent is crucial. Indeed, as already documented in the literature with phenylacetonitriles,[12] the cyclization of **3e** in ethyl acetate furnished exclusively the tetrahydro-naphtyridine ring (Scheme 2).

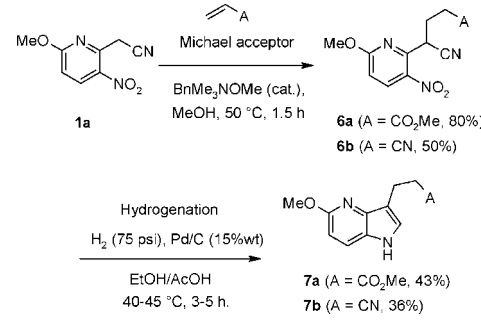
Encouraged by these first successful attempts, we investigated what the outcome of a Michael addition/hydrogenation sequence with **1a** would be (Scheme 3).

Our first attempt toward a 1,4-addition with **1a** using potassium carbonate was unsuccessful. The use of a stronger

SCHEME 2. Solvent Effect on the Cyclisation of 3e



SCHEME 3. Michael Additions on Pyridinylacetonitrile 1a Followed by 4-Azaindoles Ring Formation



base such as LDA did not result in any improvement. Finally, Michael additions with acrylonitrile and ethyl acrylate were accomplished under smooth conditions in moderate to good yields employing benzyltrimethylammonium methoxide.[13] Subsequent heterocyclisation afforded azaindoles **7a** and **7b** in 43% and 36% yield, respectively.

To further extend the scope of this methodology, Knoevenagel condensations on **1a** and **1b** were also carried out. Results of the condensation and the subsequent 4-azaindole ring formation are reported in Table 2. Most of the aromatic aldehydes employed in the Knoevenagel condensation reacted in high yields (up to 97%, Table 2, entry 5). The subsequent 4-azaindole ring formation was carried out in yields ranging between 41% and 55% (Table 2, entries 1−5). However, with indole-3-carboxaldehyde (Table 2, entry 6), we did not manage to isolate any product. Modification of the reaction time or the solvent (ethyl acetate) did not improve the reactivity. The steric hindrance of the indole ring could be ruled out as the reason for the failure of the cyclization (Table 2, entry 6 vs entry 2 with the naphthalene ring) and we incriminated the heteroaroatom present on the aldehyde. This hypothesis was confirmed when pyrrole-2-carboxaldehyde (Table 2, entry 7) and thiophene-2-carboxaldehyde (Table 2, entry 8) were employed, since none of the conditions used allowed formation of the desired products. The lack of reactivity may be due to the electron-rich character of these heterocycles, which prevents addition of the amine onto the nitrile.

To emphasize the great interest of this methodology for the rapid synthesis of biologically active compound analogues, we performed the synthesis of 4-azamelatonin **10** and protected 4-azatryptophan **12**.

In the literature, a synthesis of 4-azamelatonin has been reported in six steps with an overall yield of 3.6%.[14] Employing our strategy, key azaindole **4f** was readily obtained. Hydrogenation of **4f** with Raney nickel as catalyst in acetic anhydride gave successfully 4-azamelatonin **10** in only four steps with an overall yield of 17% (Scheme 4).

Despite the potential pharmacological and biological properties of a 4-aza analogue of tryptophan, the synthesis of such a

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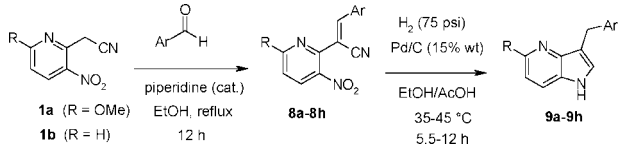
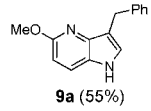
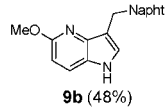
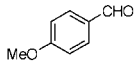
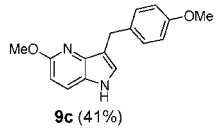
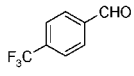
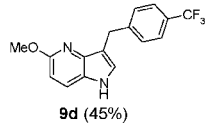
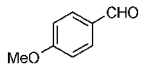
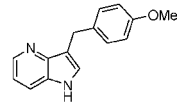
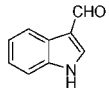
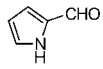
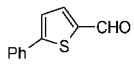
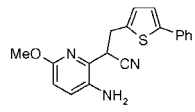
TABLE 2. Knoevenagel Condensations on Pyridyl-acetonitriles Followed by 4-Azaindoles Ring Formation



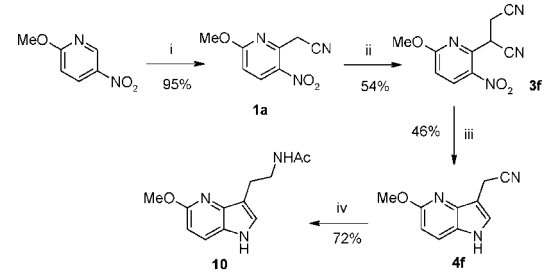
entry	R	ArCHO	product	product after hydrogeation
1	OMe		**8a** (75%)	 **9a** (55%)
2	OMe		**8b** (80%)	 **9b** (48%)
3	OMe		**8c** (85%)	 **9c** (41%)
4	OMe		**8d** (41%)	 **9d** (45%)
5	H		**8e** (97%)	 **9e** (42%)
6	OMe		**8f** (84%)	-[a]
7	OMe		**8g** (95%)	-[a]
8	OMe		**8h** (82%)	 **9h** (72%)

[a] Degradation products were obtained.

compound has never been described, to the best of our knowledge, in the literature. Applying our sequence, pyridine **1b** was alkylated with methyl 2-acetamidoacrylate (Michael acceptor), and the resulting product was subjected to the heterocyclization conditions to furnish protected 4-azatryptophan **12** in two steps (Scheme 5).

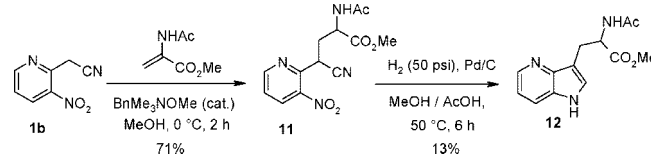
In summary, we have described a straightforward preparation of C3-substituted 4-azaindoles by means of the functionalization of pyridylacetonitriles. This method can be used with a wide range of electrophiles allowing the synthesis of unprecedented

SCHEME 4. New Synthesis of the 4-Azamelatonine 10[a]



[a] Reagents and conditions: (i) 4-chlorophenoxyacetonitrile, *t*BuOK, THF, −10 °C; (ii) $BrCH_2CN$, K_2CO_3, DMF; (iii) H_2, Pd/C, EtOH/AcOH; (iv) H_2, Raney Ni, Ac_2O.

SCHEME 5. Synthesis of Protected 4-Azatryptophan 12



4-azaindoles. Moreover, most of the starting pyridylacetonitriles being commercially available or readily obtained,[15] the method appears to be quite general. This strategy has also proved to be very useful for the synthesis of aza-analogues of biologically active compounds.

Experimental Section

General Procedure for Direct Alkylations. 2-Cyanomethyl-6-methoxy-3-nitropyridine **1a** or 2-cyanomethyl-3-nitropyridine **1b** was dissolved in the appropriate solvent (see Table 1). Potassium carbonate was added to this solution, and the corresponding alkyl halide was introduced dropwise. After stirring for a few hours, the solution was slightly acidified to pH 4 with a 1 N HCl solution. The mixture was extracted twice with ethyl acetate, dried over $MgSO_4$, and concentrated. The crude material was purified by flash column chromatography with the appropriate eluent.

2-(3-Nitropyridin-2-yl)-3-phenylpropionitrile (3a). The desired product was obtained according to the general procedure using 200 mg (1.22 mmol) of compound **1b**, 338 mg (2.45 mmol) of potassium carbonate, and 117 μL (1.22 mmol) of benzyl bromide in 5 mL of acetonitrile. The solution was stirred for 3 h at room temperature. The product was isolated with petroleum ether/ethyl acetate (8/2 then 6/4) as eluent as a white solid (80%). Mp = 146 °C. IR (thin film, NaCl): 2220, 1596, 1523, 1350 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 3.36 (d, J = 7.5 Hz, 2H), 5.10 (t, J = 7.5 Hz, 1H), 7.26−7.33 (m, 5H), 7.54 (dd, J = 8.5 Hz, J = 4.6 Hz, 1H), 8.37 (dd, J = 8.5 Hz, J = 1.5 Hz, 1H), 8.94 (dd, J = 4.6 Hz, J = 1.5 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 39.6, 39.8, 118.6, 124.3, 127.8, 129.0, 129.3, 133.6, 135.9, 144.6, 149.7, 153.9. HRMS calcd for $C_{14}H_{11}N_3O_2$ $[M + H]^+$: 254.0930, found 254.0937.

General Procedure for 1,4-Additions. 2-Cyanomethyl-6-methoxy-3-nitropyridine **1a** or 2-cyanomethyl-3-nitropyridine **1b** was dissolved in methanol under argon, and then a catalytic amount of benzyltrimethylammonium methoxide (40 wt % solution in methanol) was added to this solution. The Michael acceptor was added dropwise, and the mixture was stirred at 50 °C during the appropriate time (see Table 2). The crude was diluted with ethyl acetate and washed with a 1 N HCl solution, brine, and finally with water. The organic layer was dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography with the appropriate eluent.

(15) Katz, R. B.; Voyle, M. *Synthesis* **1989**, 314.

Methyl 4-Cyano-4-(6-methoxy-3-nitropyridin-2-yl)butanoate (6a). The desired product was obtained according to the general procedure using 200 mg (1.03 mmol) of compound **1a**, 200 μL (0.5 mmol) of benzyltrimethylammonium methoxide, and 97 μL (1.08 mmol) of methyl acrylate in 10 mL of methanol. The solution was stirred for 1.5 h at 50 °C. The product was isolated with petroleum ether/ethyl acetate (8/2) as eluent as a white solid (80%). Mp = 102 °C. IR (thin film, NaCl): 2944, 2247, 1733, 1596, 1334, 1023 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 2.40 (dd, J = 7.3 Hz, J = 6.9 Hz, 2H), 2.67 (t, J = 7.3 Hz, 2H), 3.68 (s, 3H), 4.11 (s, 3H), 5.09 (t, J = 6.9 Hz, 1H), 6.86 (d, J = 9.1 Hz, 1H), 8.35 (d, J = 9.1 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.2, 31.2, 36.6, 52.0, 55.3, 112.0, 118.3, 136.9, 138.6, 149.4, 165.5, 172.2. HRMS calcd for $C_{12}H_{13}N_3O_5$ $[M + H]^+$: 302.0753, found 302.0759.

General Procedure for Knoevenagel Condensations. 2-Cyanomethyl-6-methoxy-3-nitropyridine **1a** or 2-cyanomethyl-3-nitropyridine **1b** was dissolved in absolute ethanol (generally 5 mL for 200 mg of substrate). To this solution were added the aldehyde and one drop of piperidine. The mixture was stirred overnight then filtered. The solid was washed with a small amount of diethyl ether and dried under vacuum.

(*Z*)-2-(6-Methoxy-3-nitropyridin-2-yl)-3-phenylacrylonitrile (8a). The desired product was obtained according to the general procedure using 200 mg (1.03 mmol) of 2-cyanomethyl-6-methoxy-3-nitropyridine **1a** and 105 μL (1.03 mmol) of benzaldehyde. The product was obtained as a yellow solid (75%). Mp = 166 °C. IR (thin film, NaCl): 3082, 2240, 1573, 1504, 1467, 1321 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 4.09 (s, 3H), 6.87 (d, J = 9.0 Hz, 1H), 7.49−7.52 (m, 3H), 7.73 (s, 1H), 7.94−7.98 (m, 2H), 8.28 (d, J = 9.0 Hz, 1H).^{13}C NMR (62.5 MHz, $CDCl_3$): δ 55.1, 108.8, 112.0, 115.9, 129.2, 130.1, 131.9, 132.9, 136.5, 147.0, 149.4, 165.0. HRMS calcd for $C_{15}H_{11}N_3O_3$ $[M + H]^+$: 282.0879, found 282.0870. The stereochemistry of the double bond was determined by calculation from *Table of Spectral Data for Structure Determination of Organic Compounds* (Pretsh, E.; Clerc, T.; Seibl, J.; Simmon, W. Springer-Verlag: New York, 1998): δ (H-Z isomer) = 7.54 ppm vs δ (H-E isomer) = 7.31 ppm.

General Procedure for Hydrogenations. In a hydrogenation reactor, the pyridylacetonitrile was dissolved in an ethanol/acetic acid (25/1, v/v) mixture. Palladium on carbon (15 wt %) was added, and the mixture was hydrogenated under 75 psi of hydrogen. The crude material was then filtered through a plug of celite and concentrated. This crude material was purified by flash column chromatography with the appropriate eluent.

3-Benzyl-1*H*-pyrrolo[3,2-*b*]pyridine (4a). The desired product was obtained according to the general procedure using 800 mg (3.16 mmol) of compound **3a**, in 40 mL of the ethanol/acetic acid mixture. The solution was hydrogenated for 5.5 h at 35 °C. The product was isolated with petroleum ether/ethyl acetate (1/1) as eluent as a white solid (53%). Mp = 155 °C. IR (thin film, NaCl): 1493, 1455, 1413, 1288 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.22 (s, 2H), 7.01−7.28 (m, 7H), 7.58 (d, J = 6.8 Hz, 1H), 8.46 (bs, 1H), 9.31 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.3, 116.5, 116.9, 118.5, 126.0, 126.5, 128.4, 128.9, 129.4, 141.3, 142.7, 145.1. HRMS calcd for $C_{14}H_{12}N_2$ $[M + H]^+$: 209.1079, found 209.1080.

4-Azamelatonin (10). In a hydrogenation reactor, 823 mg (4.42 mmol) of compound **4f** was dissolved in 30 mL of acetic anhydride. To this solution were added 544 mg (6.63 mmol) of sodium acetate and a catalytic amount of Raney nickel. The mixture was hydrogenated for 24 h under 60 psi of hydrogen at room temperature. The crude was then filtered through a short plug of celite. After the addition of 60 mL of ethyl acetate to the filtrate, acetic anhydride was quenched by the addition of a saturated solution of Na_2CO_3. The organic layer was separated, and the aqueous layer was extracted with a further 40 mL of ethyl acetate. The organic layers were combined, washed with water, dried over $MgSO_4$, and then concentrated. The residue was purified by flash column chromatography with ethyl acetate as eluent, and the desired product was obtained as a slightly brown solid (72%). Mp = 144 °C (recrystallized from ethyl acetate) (lit.[14] mp =155−156 °C (pentane)). IR (thin film, NaCl): 2945, 1731, 1520, 1320, 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.94 (s, 3H), 2.98 (t, J = 6.0 Hz, 2H), 3.55−3.59 (m, 2H), 4.02 (s, 3H), 6.62 (d, J = 8.6 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.36 (bs, 1H), 7.58 (d, J = 8.6 Hz, 1H), 8.53 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 24.1, 41.9, 53.4, 105.7, 114.1, 122.4, 125.0, 125.1, 141.7, 160.0, 170.4. HRMS calcd for $C_{12}H_{15}N_3O_2$ $[M + H]^+$: 234.1243, found = 234.1250.

Acknowledgment. The authors acknowledge Les Laboratoires Servier for financial support (M.J.).

Supporting Information Available: General and chemical information plus experimental procedures and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8011623