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Facile synthesis of substituted 1*H*-pyrazolo[3,4-*b*]pyridines

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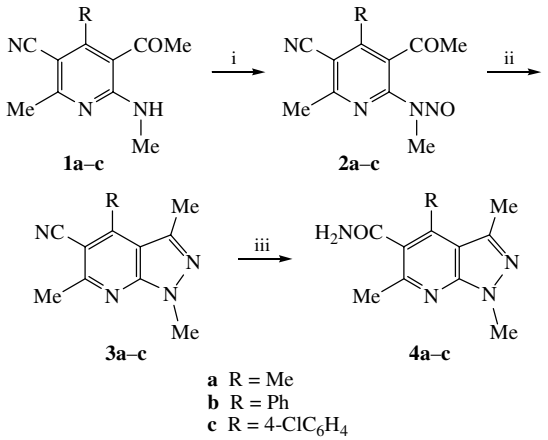
Substituted 1*H*-pyrazolo[3,4-*b*]pyridines were synthesised by construction of pyrazole ring from 4-substituted 5-acetyl-2-methyl-6-(methylamino)nicotinonitriles readily available *via* rearrangement of 3,5-dicyanopyridinium salts.

1*H*-Pyrazolo[3,4-*b*]pyridines and their derivatives possess wide-ranging biological activity (antifungal, antibacterial, citotoxic, analgesic, anxiolytic, hypotensive and other activities).[1–6] The usual synthetic approaches to the pyrazolo[3,4-*b*]pyridine core are the annulation of a pyridine ring onto appropriately substituted pyrazoles or the annulation of a pyrazole ring onto suitably substituted pyridines. The above substances were prepared by the cyclocondensation of 5-aminopyrazole as a starting material with 1,3-dicarbonyl compounds[7–9] or their ethoxymetylene derivatives[5,6,10–14] in the first route. 1*H*-Pyrazolo[3,4-*b*]pyridines were also prepared by the one-pot cyclocondensation of dihydropyrazolone, an aldehyde and ethyl acetoacetate.[15] The promising Diels–Alder cycloaddition of pyrazolyl imines as azadienes with nitroalkenes was reported recently.[16]

In the second approach, 1*H*-pyrazolo[3,4-*b*]pyridines were obtained *via* the reaction of 2-halo-3-substituted pyridines (3-alkanoyl, aroyl, formyl and cyano) with hydrazines.[17,18]



Scheme 1 *Reagents and conditions*: i, $NaNO_2$, AcOH, room temperature, 60 min; ii, Zn, AcOH, room temperature, 60 min; iii, H_2SO_4, 100 °C, 60 min.

Here, we report the synthesis of substituted 1*H*-pyrazolo[3,4-*b*]pyridines from 4-substituted 5-acetyl-2-methyl-6-(methylamino)nicotinonitriles as outlined in Scheme 1. Nicotinonitriles **1a–c** were prepared by a rearrangement of 3,5-dicyanopyridinium salts upon treatment with sodium hydroxide.[19,20] The construction of a pyrazole ring in a fused ring system was done upon N-nitrosation of a secondary amino group in compounds **1a–c** with sodium nitrite in acetic acid followed by the reduction of resulting *N*-nitrosoamines **2a–c**† with zinc powder in acetic acid. During the reduction of the *N*-nitroso group of **2a–c** to a substituted hydrazino group, intramolecular condensation onto acetyl group of pyridine ring simultaneously occurred and resulted in pyrazole ring closure to form **3a–c**.‡ All the reactions were performed under mild conditions and produced **2a–c** and **3a–c** in high yields. 1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxamides **4a–c**§ were prepared by the hydrolysis of the cyano group in **3a–c**.

Compounds **2a–c**, **3a–c** and **4a–c** were purified by recrystallization from ethanol.

The structures of all of the obtained compounds were confirmed by ^{1}H NMR and IR spectroscopy, mass spectrometry and elemental analysis.

† *Synthesis of* N-*nitrosoamines* **2a–c** *(general procedure)*. $NaNO_2$ (3 mmol) was added to a solution or suspension of **1a–c** (2 mmol) in acetic acid (8 ml). The mixture was stirred for 1 h at room temperature, diluted with water and filtered to remove the precipitated crystals of **2a–c**.

2a: yield 98%, mp 183–184 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.35 (s, 3H, Me), 2.55 (s, 3H, Me), 2.80 (s, 3H, COMe), 3.56 (s, 3H, N–Me). IR (KBr, ν/cm^{-1}): 1490 (N=O), 1700 (C=O), 2230 (CN). Found (%): C, 56.92; H, 5.32. Calc. for $C_{11}H_{12}N_4O_2$ (%): C, 56.89; H, 5.21.

2b: yield 92%, mp 134–135 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.90 (s, 3H, Me), 2.87 (s, 3H, COMe), 3.56 (s, 3H, N–Me), 7.35 (m, 2H, Ph), 7.53 (m, 3H, Ph). IR (KBr, ν/cm^{-1}): 1500 (N=O), 1710 (C=O), 2225 (CN). Found (%): C, 65.60; H, 4.73. Calc. for $C_{16}H_{14}N_4O_2$ (%): C, 65.30; H, 4.79.

2c: yield 96%, mp 198–199 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.95 (s, 3H, Me), 2.87 (s, 3H, COMe), 3.56 (s, 3H, N–Me), 7.30 (d, 2H, H-2′, H-6′, *J* 8.5 Hz), 7.49 (d, 2H, H-3′, H-5′). IR (KBr, ν/cm^{-1}) δ: 1495 (N=O), 1700 (C=O), 2220 (CN). Found (%): C, 58.60, H, 4.01. Calc. for $C_{16}H_{13}ClN_4O_2$ (%): C, 58.45; H, 3.99.

‡ *Synthesis of 1*H-*pyrazolo[3,4-*b*]pyridines* **3a–c** *(general procedure)*. 10 mmol of zinc powder was added portionwise to a stirred solution of 2 mmol of **2a–c** in 8 ml of acetic acid at a temperature below 10 °C. The mixture was allowed to warm to room temperature, stirred for 1 h and filtered; the filter was washed with acetic acid. The filtrate was diluted with ice water and neutralised with aqueous ammonia; the precipitated crystals of **3a–c** were separated.

3a: yield 91%, mp 146–147 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.67 (s, 3H, Me), 2.80 (s, 3H, Me), 2.84 (s, 3H, Me), 4.02 (s, 3H, Me). IR (KBr, ν/cm^{-1}): 2220 (CN). MS (EI, 70 eV), *m*/*z* (%): 200 ($M^{+\cdot}$, 100%), 199 (95), 185 (25), 172 (9), 157 (5), 156 (6), 132 (29), 131 (6), 104 (5), 103 (5), 77 (8), 76 (7). Found (%): C, 65.91; H, 6.21. Calc. for $C_{11}H_{12}N_4$ (%): C, 65.98; H, 6.04.

3b: yield 75%, mp 165–166 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.00 (s, 3H, Me), 2.84 (s, 3H, Me), 4.02 (s, 3H, Me), 7.42–7.55 (m, 5H, Ph). IR (KBr, ν/cm^{-1}): 2230 (CN). MS (EI, 70 eV), *m*/*z* (%): 262 ($M^{+\cdot}$, 100%), 261 (58), 247 (6), 234 (5), 220 (4), 131 (6), 77 (4). Found (%): C, 73.38; H, 5.50. Calc. for $C_{16}H_{14}N_4$ (%): C, 73.26; H, 5.38.

3c: yield 84%, mp 163–164 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.09 (s, 3H, Me), 2.89 (s, 3H, Me), 4.09 (s, 3H, Me), 7.42 (d, 2H, H-2′, H-6′, *J* 8.5 Hz), 7.55 (d, 2H, H-3′, H-5′). IR (KBr, ν/cm^{-1}): 2225 (CN). MS (EI, 70 eV), *m*/*z* (%): 298 ($M^{+\cdot}$, ^{37}Cl, 34), 296 ($M^{+\cdot}$, ^{35}Cl, 100) 295 (48), 281 (6), 261 (7), 245 (5), 164 (5), 130 (6), 76 (2). Found (%): C, 64.74; H, 4.64. Calc. for $C_{16}H_{13}ClN_4$ (%): C, 64.76; H, 4.42.

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References

1 F. E. Goda, A. M. Abdel-Aziz Alaa and O. A. Attef, *Bioorg. Med. Chem.*, 2004, **12**, 1845.
2 Y. S. Sanghvi, S. B. Larson, R. S. Willis, R. K. Robins and G. R. Revankar, *J. Med. Chem.*, 1989, **32**, 945.
3 M. A. Gaston, L. R. S. Dias, A. C. C. Freitas, A. L. P. Miranda and T. J. Barreiro, *Pharm. Acta Helv.*, 1996, **71**, 213.
4 E. A. Barnard and P. Srolnick, *Pharmacol. Rev.*, 1988, **50**, 291.
5 H. Hohn, Th. Denzel and W. Janssen, *J. Heterocycl. Chem.*, 1972, **9**, 235.
6 H. Hoehn and T. Denzel, *US Patent*, 3925388, 1975 (*Chem. Abstr.*, 1976, **85**, 21450s).
7 V. L. Rusinov, A. Yu. Petrov and O. N. Chupakhin, *Khim. Geterotsikl. Soedin*., 1985, 147 [*Chem. Heterocycl. Compd*. (*Engl. Transl*.), 1985, **21**, 113].
8 B. M. Lynch, M. A. Khan, Y. C. Teo and F. Perdotti, *Can. J. Chem*., 1988, **66**, 420.
9 V. K. Ahluwalia and G. Bindu, *Synth. Commun.*, 1996, **26**, 1341.
10 H. Mello, E. F. Silva, A. Echevarria and V. G. Carvalho, *QUÍMIKA NOVA*, 1999, **22**, 26.
11 S. Schenone, O. Bruno, P. Fossa, A. Ranise, G. Menozzi, L. Mosti, F. Bondavalli, C. Martini and L. Trincavelli, *Bioorg. Med. Chem. Lett*., 2001, **11**, 2529.
12 R. N. Misra, Hai-yun Xiao, D. B. Rawlins, W. Shan, K. A. Kellar, J. G. Mulheron, J. S. Sack, J. S. Tokarski, S. D. Kimball and K. R. Webster, *Bioorg. Med. Chem. Lett*., 2003, **13**, 2405.
13 T. M. Bare, C. D. McLaren, J. B. Campbell, J. W. Firor, J. F. Resch, C. P. Walters, A. I. Salama, B. A. Meiners and J. B. Patel, *J. Med. Chem*., 1989, **32**, 2561.
14 G. Yu, H. J. Mason, X. Wu, J. Wang, S. Chong, G. Dorough, A. Henwood, R. Pongrac, L. Seliger, B. He, D. Normandin, L. Adam, J. Krupinski and J. Macor, *J. Med. Chem.*, 2001, **44**, 1025.
15 S. A. El-Assiery, G. H. Sayed and A. Fouda, *Acta Pharm.*, 2004, **54**, 143.
16 A. Diaz-Ortiz, A. Hoz and F. Langa, *Green Chemistry*, 2000, **2**, 165.
17 K. Peseke, M. Michalik and U. Schonhusen, *J. Prakt. Chem.*, 1987, **329**, 877.
18 Z. A. Kalme, B. Roloff, Yu. E. Pelcher, Yu. Yu. Popelis, F. Khagen and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, 1992, **12**, 1646 [*Chem. Heterocycl. Compd*. (*Engl. Transl*.), 1992, **28**, 1411].
19 G. P. Shkil, V. Lusis, D. Muceniece and R. S. Sagitullin, *Tetrahedron*, 1995, **51**, 8599.
20 G. P. Sagitullina, L. V. Glizdinskaya, S. I. Oleinikova, E. G. Atavin and R. S. Sagitullin, *Zh. Org. Khim.*, 2005, **41**, 1395 (*Russ. J. Org. Chem.*, 2005, **41**, 1367).

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§ *Synthethis of 1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamides* **4a–c** *(general procedure)*. A solution of 1 mmol of **3a–c** in 2 ml of sulfuric acid was heated in an oil bath (100 °C) for 1 h. After cooling, the mixture was diluted with water, neutralised with aqeuous ammonia and filtered to remove the precipitated solid of **4a–c**.

4a: yield 76%, mp 242–244 °C. ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 2.53 (s, 3H, Me), 2.57 (s, 3H, Me), 2.58 (s, 3H, Me), 3.89 (s, 3H, Me), 7.6 (s, 1H, *anti*-$CONH_2$), 7.8 (s, 1H, *sin*-$CONH_2$). IR (KBr, ν/cm^{-1}): 1670, 3400, 3525 ($CONH_2$). MS (EI, 70 eV), *m*/*z* (%): 218 ($M^{+\cdot}$, 100), 217 (6), 203 (13), 202 (82), 201 (38), 174 (18), 158 (11), 100 (6), 92 (7), 77 (8). Found (%): C, 60.54; H, 6.30. Calc. for $C_{11}H_{14}N_4O$ (%): C, 60.53; H, 6.47.

4b: yield 94%, mp 217–219 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.90 (s, 3H, Me), 2.67 (s, 3H, Me), 4.00 (s, 3H, Me), 5.32 (s, 1H, *anti*-$CONH_2$), 5.67 (s, 1H, *sin*-$CONH_2$), 7.34–7.37 (m, 5H, Ph). IR (KBr, ν/cm^{-1}): 1690, 3400, 3525 ($CONH_2$). MS (EI, 70 eV), *m*/*z* (%): 280 ($M^{+\cdot}$, 100), 279 (42), 265 (16), 264 (72), 263 (22), 236 (6), 140 (14). Found (%): C, 68.39; H, 5.90. Calc. for $C_{16}H_{16}N_4O$ (%): C, 68.55; H, 5.75.

4c: yield 92%, mp 273–275 °C. ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 1.94 (s, 3H, Me), 2.71 (s, 3H, Me), 4.03 (s, 3H, Me), 7.42 (d, 2H, H-2′, H-6′, *J* 8.6 Hz), 7.44 (d, 2H, H-3′, H-5′), 7.1 (s, 1H, *anti*-$CONH_2$), 7.5 (s, 1H, *sin*-$CONH_2$). MS (EI, 70 eV), *m*/*z* (%): 316 ($M^{+\cdot}$, ^{37}Cl, 36), 314 ($M^{+\cdot}$, ^{35}Cl, 100), 313 (39), 300 (27), 299 (22), 295 (81), 297 (20), 262 (14), 235 (11), 234 (11), 190 (7), 140 (11), 139 (15), 138 (8), 89 (2), 76 (3). Found (%): C, 60.82; H, 4.98. Calc. for $C_{16}H_{15}ClN_4O$ (%): C, 61.05; H, 4.80.

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