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One-pot synthesis of 5-nitropyridines by the cyclocondensation of nitroacetone, triethyl orthoformate and enamines

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The convenient one-pot synthesis of 5-nitropyridines based on the tricomponent cyclocondensation of nitroacetone, triethyl orthoformate and various enamines has been developed.

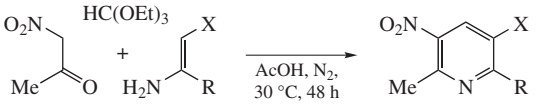
The nitration of highly basic pyridines ($pK_a > 1$) requires severe reaction conditions.[1–4] The scope of the preparative nitrations employing oleum and sodium nitrate is restricted only to lutidine and collidine.[5] An up-to-date method for the nitration of pyridines relies on the reaction with dinitrogen pentoxide in the presence of nucleophilic agents (*e.g.*, SO_3^{2-}, HSO_3^-), proceeding as a [1,5]-nitro group shift in the transient *N*-nitropyridinium.[6–8]

Electron donating groups significantly activate a pyridine ring to increase the substrate reactivity in aromatic electrophilic substitution. Consequently, the majority of known nitropyridines were prepared by nitration of either amino- or hydroxypyridines.[4,9]

An alternative synthesis of nitropyridines is based on aliphatic nitro compounds.[10–20]

New synthetic methods for these compounds are of interest due to a wide range of their biological activities.[4]

Here, we report the one-pot synthesis of 5-nitropyridines (**3a–e**, **4a–c**) by the tricomponent cyclocondensation of nitroacetone, triethyl orthoformate and enamines **1**,**2a–e**† (Scheme 1).‡,§

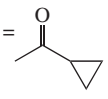


1a–e
2a–c

3a–e
4a–c

1, **3** R = Me
2, **4** R = Ph

a X = CN
b X = COPh
c X = NO_2
d X = COMe
e X =



Scheme 1

† The structures of compounds **1e**, **3a–e**, **4a–c** and **7** were confirmed by ^{1}H NMR and IR spectroscopy, mass spectrometry and elemental analysis. IR spectra were recorded on a Specord IR-75 spectrometer in $CHCl_3$ solutions. ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer at 200.13 MHz in $CDCl_3$ solutions containing TMS as an internal standard. Mass spectra were recorded on an Agilent 5973N mass spectrometer (ionization energy, 70 eV; evaporator temperature, 230–250 °C).

3-Amino-1-cyclopropyl-2-buten-1-one **1e** was prepared in 80% yield as colourless crystals from 1-cyclopropylbutane-1,3-dione[34] in ethanolic ammonia at room temperature, mp 100–101 °C (CCl_4). IR (ν/cm^{-1}): 3297, 3142 (NH_2), 1659 (C=O), 1606 (C=C). ^{1}H NMR, δ: 0.70–0.78 (m, 2H, cyclopropyl), 0.91–0.95 (m, 2H, cyclopropyl), 1.61–1.75 (m, 1H, cyclopropyl), 1.93 (s, 3H, Me), 5.00 (br. s, 1H, NH_2), 5.18 (s, 1H, HC=), 9.65 (br. s, 1H, NH_2). MS, *m*/*z* (%): 125 ($M^{+\cdot}$, 47.63), 110 (14.41), 105 (100), 84 (100), 42 (18.15). Found (%): C, 67.03; H, 8.96; N, 11.05. Calc. for $C_7H_{11}NO$ (%): C, 67.17; H, 8.86; N, 11.19.

The starting enamines were prepared by previously reported methods,[21–26] with the exception of enamine **1e**, which was synthesized for the first time.

Formation of nitropyridines **3**, **4** proceeds through an initial reaction of nitroacetone with triethyl orthoformate resulting in transient 4-(ethoxy)-3-nitro-3-buten-2-one **5** (Scheme 2).[27] The subsequent conjugated addition of enamines **1**, **2** to the activated double bond of compound **5** (Michael reaction) followed by the two-step elimination of ethanol leads to substituted nitroolefin **6**.[28–32] Compound **6** undergoes an intra-

‡ *General procedure for the preparation of nitropyridines* **3a–e** *and* **4a–c**. A solution of nitroacetone (6 mmol), corresponding enamine (6 mmol) and triethyl orthoformate (18 mmol) in glacial acetic acid (5 ml) was stirred for 48 h at 30 °C. The reaction mixture was concentrated in a vacuum, and the residue was refluxed in ethanol (20 ml) with charcoal, filtered, and cooled. The precipitated crystalline solid was filtered off and additionally purified by liquid chromatography (silica Merck 60A, benzene) to give nitropyridines **3**, **4** which were recrystallized from light petroleum (bp 40–70 °C). The indicated yields of **3**, **4** were determined before liquid chromatography.

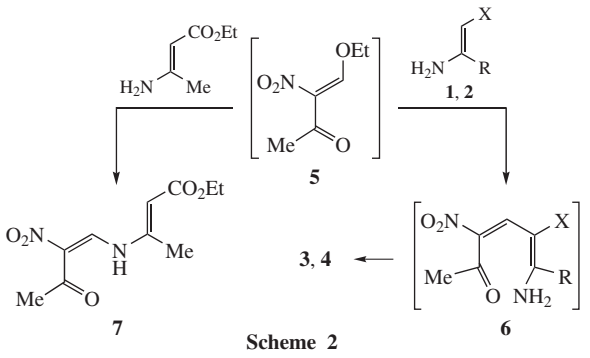
2,6-Dimethyl-5-nitronicotinonitrile **3a**: yield 53%, mp 64–65 °C. IR (ν/cm^{-1}): 2233 (C≡N), 1566, 1340 (NO_2). ^{1}H NMR, δ: 2.85 (s, 3H, 2-Me), 2.92 (s, 3H, 6-Me), 8.52 (s, 1H, 4-H). MS, *m*/*z* (%): 177 ($M^{+\cdot}$, 27.29), 160 (78.81), 132 (19.42), 131 (100), 105 (47.22), 104 (51.82), 78 (18.15), 77 (48.07), 63 (17.28), 62 (10.06), 51 (11.76), 39 (10.87). Found (%): C, 54.25; H, 4.00; N, 23.70. Calc. for $C_8H_7N_3O_2$ (%): C, 54.24; H, 3.98; N, 23.72.

(2,6-Dimethyl-5-nitro-3-pyridyl)(phenyl)methanone **3b**: light yellow crystals, yield 50%, mp 67–68 °C. IR (ν/cm^{-1}): 1645 (C=O), 1579, 1329 (NO_2). ^{1}H NMR, δ: 2.62 (s, 3H, 2-Me), 2.93 (s, 3H, 6-Me), 7.48–7.81 (m, 5H, Ph), 8.28 (s, 1H, 4-H). MS, *m*/*z* (%): 257 (11.20), 256 ($M^{+\cdot}$, 62.78), 255 (68.56), 209 (12.95), 105 (100), 77 (83.00), 51 (17.07). Found (%): C, 65.46; H, 4.78; N, 10.89. Calc. for $C_{14}H_{12}N_2O_3$ (%): C, 65.62; H, 4.72; N, 10.94.

2,6-Dimethyl-3,5-dinitropyridine **3c**: light yellow crystals, yield 52%, mp 69–70 °C (lit.,[35] mp 69–70 °C). ^{1}H NMR, δ: 2.96 (s, 6H, 2,6-Me), 8.96 (s, 1H, 4-H).

1-(2,6-Dimethyl-5-nitro-3-pyridyl)ethanone **3d**: yield 53%, mp 54–55 °C. IR (ν/cm^{-1}): 1684 (C=O), 1539, 1342 (NO_2). ^{1}H NMR, δ: 2.67 (s, 3H, 2-Me), 2.83 (s, 3H, COMe), 2.90 (s, 3H, 6-Me), 8.63 (s, 1H, 4-H). MS, *m*/*z* (%): 194 ($M^{+\cdot}$, 41.36), 179 (100), 133 (10.21), 106 (11.34), 43 (45.37). Found (%): C, 56.10; H, 5.37; N, 14.35. Calc. for $C_9H_{10}N_2O_3$ (%): C, 55.67; H, 5.19; N, 14.43.

(2,6-Dimethyl-5-nitro-3-pyridyl)(cyclopropyl)methanone **3e**: light yellow crystals, yield 40%, mp 56–57 °C. IR (ν/cm^{-1}): 1713 (C=O), 1560, 1351 (NO_2). ^{1}H NMR, δ: 1.13–1.25 (m, 2H, cyclopropyl), 1.32–1.38 (m, 2H, cyclopropyl), 2.39–2.49 (m, 1H, cyclopropyl), 2.90 (s, 3H, 6-Me), 8.63 (s, 1H, 4-H). MS, *m*/*z* (%): 220 ($M^{+\cdot}$, 60.48), 205 (28.82), 203 (16.96), 179 (100), 174 (18.88), 133 (13.46), 105 (13.14), 104 (10.82), 69 (64.49), 64 (10.20), 63 (14.89), 41 (27.77), 39 (13.09). Found (%): C, 60.25; H, 5.47; N, 12.69. Calc. for $C_{11}H_{12}N_2O_3$ (%): C, 59.99; H, 5.49; N, 12.72.



Scheme 2

molecular cyclization by the interaction of amino and acetyl groups to form nitropyridines **3**, **4** (Scheme 2).

However, the use of ethyl 3-aminocrotonate under the same reaction conditions does not provide expected 2,6-dimethyl-5-ethoxycarbonyl-3-nitropyridine but compound **7** in 52% yield.¶

In this case, at the stage of nucleophilic addition, an ambident enamine attacks by nitrogen on the generated *in situ* intermediate **5** (Scheme 2).[33]

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§ *6-Methyl-5-nitro-2-phenylnicotinonitrile* **4a**: yield 83%, mp 111–112 °C. IR (ν/cm^{-1}): 2229 (C≡N), 1552, 1340 (NO_2). ^{1}H NMR, δ: 3.02 (s, 3H, Me), 7.54–7.60 (m, 3H, Ph), 7.99–8.04 (m, 2H, Ph), 8.70 (s, 1H, 4-H). MS, *m*/*z* (%): 240 (14.10), 239 ($M^{+\cdot}$, 100), 208 (10.31), 194 (10.77), 193 (27.40), 192 (55.77), 181 (14.07), 167 (10.75), 166 (38.18), 140 (28.20), 139 (14.29), 77 (18.49). Found (%): C, 65.45; H, 3.75; N, 17.46. Calc. for $C_{13}H_9N_3O_2$ (%): C, 65.27; H, 3.79; N, 17.56.

(6-Methyl-5-nitro-2-phenyl-3-pyridyl)(phenyl)methanone **4b**: light yellow crystals, yield 25%, mp 118–119 °C. IR (ν/cm^{-1}): 1660 (C=O), 1551, 1331 (NO_2). ^{1}H NMR, δ: 3.03 (s, 3H, Me), 7.28–7.70 (m, 10H, Ph, COPh), 8.48 (s, 1H, 4-H). MS, *m*/*z* (%): 319 (19.47), 318 ($M^{+\cdot}$, 100), 317 (58.74), 290 (14.96), 289 (69.64), 272 (36.04), 271 (13.91), 243 (23.85), 241 (16.36), 105 (95.77), 77 (72.22). Found (%): C, 71.87; H, 4.49; N, 8.68. Calc. for $C_{19}H_{14}N_2O_3$ (%): C, 71.69; H, 4.43; N, 8.80.

3,5-Dinitro-2-methyl-6-phenylpyridine **4c**: light yellow crystals, yield 25%, mp 87–88 °C. IR (ν/cm^{-1}): 1537, 1340 (NO_2). ^{1}H NMR, δ: 3.02 (s, 3H, Me), 7.47–7.64 (m, 5H, Ph), 8.81 (s, 1H, 4-H). MS, *m*/*z* (%): 260 (10.35), 259 ($M^{+\cdot}$, 72.67), 232 (13.10), 231 (86.00), 229 (16.21), 216 (11.28), 214 (19.79), 213 (15.52), 185 (16.43), 184 (31.74), 183 (51.49), 182 (36.95), 169 (18.86), 168 (22.20), 167 (49.60), 166 (100), 157 (27.15), 156 (18.56), 155 (23.62), 154 (28.28), 143 (17.18), 142 (16.17), 141 (16.77), 140 (75.10), 139 (53.34), 130 (10.48), 129 (12.14), 128 (21.66), 127 (26.07), 126 (47.90), 116 (11.32), 115 (27.85), 114 (38.57), 113 (24.03), 109 (18.10), 105 (18.85), 104 (30.62), 103 (19.54), 102 (17.99), 89 (11.12), 88 (14.83), 87 (13.81), 81 (97.57), 78 (29.88), 77 (49.53), 76 (30.14), 75 (17.60), 74 (15.42), 64 (18.54), 63 (41.50), 62 (14.57), 53 (20.81), 52 (25.89), 51 (29.86), 50 (13.15), 44 (12.73), 43 (18.43), 40 (12.22), 39 (12.96). Found (%): C, 55.63; H, 3.51; N, 16.58. Calc. for $C_{12}H_9N_3O_4$ (%): C, 55.60; H, 3.50; N, 16.21.

¶ *Ethyl 3-[(2-nitro-3-oxo-1-buten-1-yl)amino]-2-butenoate* (*Z*/*E*, 1:1) **7**: yield 52%. IR (ν/cm^{-1}): 1687 (COOEt), 1661 (C=O), 1509, 1354 (NO_2). ^{1}H NMR, δ: (*Z*) 1.28 (t, 3H, CH_2*Me*, ^3J 7.1 Hz), 2.20 (s, 3H, Me), 2.61 (s, 3H, COMe), 4.25 (q, 2H, C*H*$_2$Me, ^3J 7.1 Hz), 5.39 (s, 1H, 2-H), 8.20 (d, 1H, 1-H, ^3J 14.6 Hz), 13.85 (d, 1H, NH, ^3J 14.6 Hz); (*E*) 1.29 (t, 3H, CH_2*Me*, ^3J 7.1 Hz), 2.21 (s, 3H, Me), 2.64 (s, 3H, COMe), 4.27 (q, 2H, C*H*$_2$Me, ^3J 7.1 Hz), 5.40 (s, 1H, 2-H), 8.62 (d, 1H, 1-H, ^3J 13.7 Hz), 13.51 (d, 1H, NH, ^3J 13.7 Hz). MS, *m*/*z* (%): 242 ($M^{+\cdot}$, 17.01), 196 (19.32), 137 (13.94), 136 (28.32), 134 (10.82), 121 (35.93), 120 (19.93), 111 (10.77), 110 (29.49), 94 (16.26), 84 (19.78), 83 (12.43), 69 (11.55), 68 (14.45), 67 (15.54), 44 (18.16), 43 (68.30), 42 (18.98), 40 (100), 39 (15.76). Found (%): C, 49.92; H, 5.76; N, 11.36. Calc. for $C_{10}H_{14}N_2O_5$ (%): C, 49.58; H, 5.83; N, 11.56.