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Vicarious nucleophilic substitution in nitro derivatives of imidazo[1,2-*a*]pyridine

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Reactions of nitro derivatives of imidazo[1,2-*a*]pyridine with carbanions containing leaving groups and also with hydroxylamine in basic media give the products of vicarious nucleophilic substitution of hydrogen.

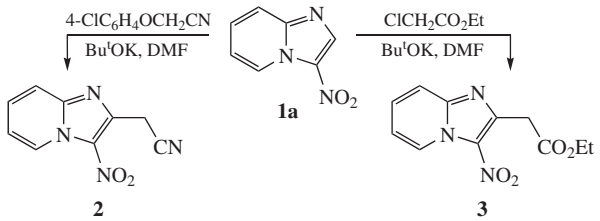
Vicarious nucleophilic substitution (VNS) of hydrogen provides a convenient method for the introduction of functional groups into aromatic[1–6] and heterocyclic rings.[7–10] This two-step reaction proceeds *via* addition of carbanions containing leaving groups X at the carbanionic center to the nitroaromatic ring followed by the base-induced β-elimination of HX from intermediate σ-adducts.[11] The products of VNS reactions are key intermediates in the synthesis of useful and new heterocyclic compounds.[12] The nitro derivatives of furan, pyrrole, thiophene,[13] imidazole,[14] pyridine,[15] indole,[16,17] quinoline[18] and benzimidazole[19] undergo VNS cyanomethylation with a variety of cyanoalkylating agents such as the carbanions of chloroacetonitrile, aryloxyacetonitriles,[20] arylthioacetonitrile, cyanomethyl dithiocarbamates[13] or trialkylammonium cyanomethylides.[21]

Pursuing our studies on nitroheterocycles,[19] we decided to explore the VNS reaction of nitro imidazo[1,2-*a*]pyridines to obtain new imidazo[1,2-*a*]pyridine derivatives as precursors for the synthesis of polyheterocyclic compounds of pharmacological importance. Imidazo[1,2-*a*]pyridines are widely used as anthelmintic, antifungal,[22] anti-inflammatory,[23] antibacterial[24] and antimalarial[25] agents and are useful for treatment of Alzheimer's disease.[26,27]

Treatment of 3-nitroimidazo[1,2-*a*]pyridine **1a** as the starting material with 4-chlorophenoxyacetonitrile in the presence of Bu^{t}OK in DMF resulted in VNS of hydrogen giving new 2-(3-nitro-*H*-imidazo[1,2-*a*]pyridin-2-yl)acetonitrile derivative **2**[†] in high yield (Scheme 1). Likewise, ethyl 2-(3-nitro-2,3-dihydroimidazo[1,2-*a*]pyridin-2-yl)acetate **3**,[‡] as the new derivative of imidazo[1,2-*a*]pyridine was synthesized from compound **1a** and ethyl chloroacetate in Bu^{t}OK and DMF *via* VNS (Scheme 1).

It is obvious that the presence of one nitro group and two nitrogen atoms in compound **1a** makes it a highly electron-deficient nitroarene. Therefore, it is a suitable precursor in VNS reactions. Nitro-activated polyaza heterocycles have been viewed as superelectrophilic Meisenheimer substrates, which are suitable for VNS.[28,29]

In order to evaluate the reactivity of C–H bonds or carbon atoms, alkylation of compound **2** was carried out under different conditions. Alkylation of **2** with various alkyl halides in K_2CO_3 and acetonitrile gave dialkyl derivatives **4a–f** (Scheme 2).[§] Note that methylene protons belonging to the alkyl groups in compounds **4b–f** are non-equivalent; therefore, they split each other in the ^{1}H NMR spectrum with J 13.7–17.1 Hz. For example, in compound **4f**, two doublet signals are observed at 3.75 and 3.99 ppm assignable to these protons.



Scheme 1

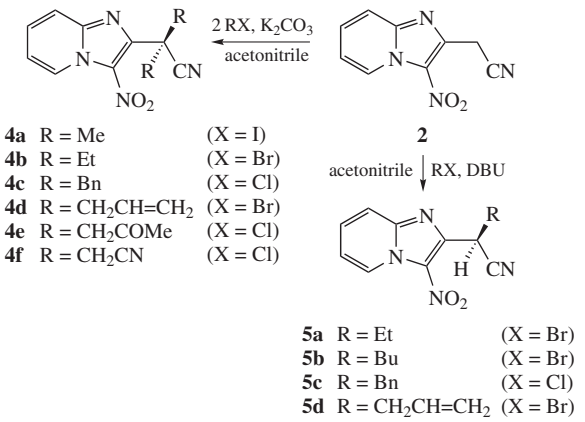
Racemic monoalkylated compounds **5a–d** were obtained from alkylation of compound **2** with various alkyl halides in DBU and acetonitrile.[¶] In this reaction, even with excess of alkyl halide, no dialkylated compound was obtained, which is a clear indication of the vital role of DBU in selective monoalkylation of compound **2**[30] (Scheme 2).

[†] Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrometer and only noteworthy absorptions are listed. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in ppm downfield from TMS as an internal standard. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

4-Chlorophenoxyacetonitrile[34] and compounds **1a**,**b**[35] were obtained according to published methods.

*Synthesis of 2-(3-nitro-*H*-imidazo[1,2-*a*]pyridin-2-yl)acetonitrile* **2** *from 3-nitroimidazo[1,2-*a*]pyridine* **1a**. To a mixture of Bu^{t}OK (16.83 g, 150 mmol) in DMF (150 ml), a solution of compound **1a** (12.2 g, 47.3 mmol) and *p*-chlorophenoxyacetonitrile (8.32 g, 49.65 mmol) in DMF (50 ml) was added dropwise at –20 °C. The mixture was stirred at this temperature for 15 min and poured onto an ice-cold dilute solution of hydrochloric acid. The resulting precipitate was filtered and washed with water, air dried and recrystallized from EtOH and acetone (50:50) as bright yellow crystals, yield 92%, mp 215–217 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 4.82 (s, 2H), 7.50 (dd, 1H, H-6, $J_{6,5}$ 6.8 Hz, $J_{6,7}$ 6.0 Hz), 7.87 (dd, 1H, H-7, $J_{7,8}$ 9.1 Hz, $J_{7,6}$ 6.0 Hz), 8.03 (d, 1H, H-8, $J_{8,7}$ 9.1 Hz), 9.37 (d, 1H, H-5, $J_{5,6}$ 6.8 Hz). IR (KBr, ν/cm^{-1}): 1350, 1525 (NO_2), 2250 (CN). MS, *m*/*z*: 202 (M$^+$). Found (%): C, 53.38; H, 2.85; N, 27.54. Calc. for $C_9H_6N_4O_2$ (202.2) (%): C, 53.47; H, 2.99; N, 27.71.

[‡] *Synthesis of ethyl 2-(3-nitro-*H*-imidazo[1,2-*a*]pyridin-2-yl)acetate* **3** *from 3-nitroimidazo[1,2-*a*]pyridine* **1a**. To a mixture of Bu^{t}OK (8.42 g, 75 mmol) in DMF (70 ml), a solution of compound **1a** (6.1 g, 23.6 mmol) and ethyl chloroacetate (3.04 g, 24.8 mmol) in DMF (25 ml) was added dropwise at –30 °C. The mixture was stirred at this temperature for 15 min and poured onto an ice-cold diluted solution of hydrochloric acid. The resulting precipitate was filtered and washed with water, air-dried and recrystallized from EtOH. Compound **5** was obtained as bright yellow crystals, yield 75%, mp 145–147 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.25 (t, 3H, J 7.1 Hz), 4.24 (q, 2H, J 7.1 Hz), 4.28 (s, 2H), 7.36 (dd, 1H, H-6, $J_{6,5}$ 8.0 Hz, $J_{6,7}$ 6.5 Hz), 7.67 (dd, 1H, H-7, $J_{7,8}$ 9.0 Hz, $J_{7,6}$ 6.5 Hz), 7.88 (d, 1H, H-8, $J_{8,7}$ 9.0 Hz), 9.42 (d, 1H, H-5, $J_{5,6}$ 8.0 Hz), IR (KBr, ν/cm^{-1}): 1350, 1525 (NO_2), 1735 (C=O). MS, *m*/*z*: 249 (M$^+$). Found (%): C, 52.81; H, 4.35; N, 16.73. Calc. for $C_{11}H_{11}N_3O_4$ (249.2) (%): C, 53.01; H, 4.45; N, 16.86.



4a R = Me (X = I)
4b R = Et (X = Br)
4c R = Bn (X = Cl)
4d R = $CH_2CH{=}CH_2$ (X = Br)
4e R = CH_2COMe (X = Cl)
4f R = CH_2CN (X = Cl)

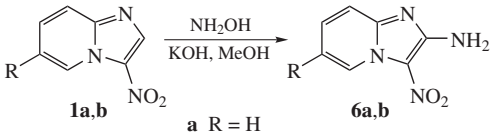
2

5a R = Et (X = Br)
5b R = Bu (X = Br)
5c R = Bn (X = Cl)
5d R = $CH_2CH{=}CH_2$ (X = Br)

Scheme 2

Direct amination of nitroarenes with hydroxylamine through VNS mechanism, has been known for many years,[31] but it is limited to highly electron-deficient nitroarenes such as dinitroarenes[32] and nitronaphthalene.[33] Compounds **1a**,**b** are susceptible to this reaction due to their highly electron-deficient character. In the presence of hydroxylamine, compounds **1a**,**b** were directly aminated in basic MeOH–EtOH in high yields to produce 3-nitro-*H*-imidazo[1,2-*a*]pyridin-2-amine **6a** and 6-chloro-3-nitro-*H*-imidazo[1,2-*a*]pyridin-2-amine **6b** (Scheme 3).††

Compounds **6a**,**b** can be used as precursors in the synthesis of new heterocyclic compounds.



1a,**b** **6a**,**b**

a R = H
b R = Cl

Scheme 3

In summary, we have presented the first vicarious nucleophilic substitution in nitro derivatives of imidazo[1,2-*a*]pyridines and have synthesized new derivatives, which are very difficult to obtain by other ways.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2009.05.017.

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§ *General procedure for the synthesis of* **4a**–**f**. To a solution of compound **2** (0.14 g, 0.68 mmol) in acetonitrile (5 ml), alkyl halide (1.4 mmol) and K_2CO_3 (4 mmol) were added. The mixture was stirred for 2 days and then poured into water. The product was extracted with 2×20 ml CH_2Cl_2. The extract was dried, treated with charcoal and evaporated to give crude **4a**–**f**.

2-Methyl-2-(3-nitro-H-*imidazo[1,2*-a*]pyridin-2-yl)propanenitrile* **4a**: colourless crystals (MeOH), yield 75%, mp 123–125 °C. ^{1}H NMR ($CDCl_3$) δ: 1.98 (s, 6H), 7.34 (dd, 1H, H-6, $J_{6,5}$ 7.0 Hz, $J_{6,7}$ 6.1 Hz), 7.70 (dd, 1H, H-7, $J_{7,8}$ 7.1 Hz, $J_{7,6}$ 6.1 Hz), 7.89 (d, 1H, H-8, $J_{8,7}$ 7.1 Hz), 9.54 (d, 1H, H-5, $J_{5,6}$ 7.0 Hz). IR (KBr, ν/cm^{-1}): 2250 (CN). MS, *m*/*z*: 230 (M^+). Found (%): C, 57.25; H, 4.25; N, 24.14. Calc. for $C_{11}H_{10}N_4O_2$ (230.2) (%): C, 57.39; H, 4.38; N, 24.34.

For characteristics of compounds **4b**–**f**, see Online Supplementary Materials.

¶ *General procedure for the synthesis of* **5a**–**d**. To a solution of **2** (0.27 g, 1.36 mmol) in acetonitrile (10 ml), alkyl halide (1.4 mmol) and DBU (2 mmol) were added. The solution was stirred for a day and then poured into water. The product was extracted with 2×20 ml CH_2Cl_2. The extract was washed with 2×20 ml dilute HCl, and then it was dried, treated with charcoal and evaporated to give crude **5a**–**d**.

2-(3-Nitro-H-*imidazo[1,2*-a*]pyridin-2-yl)butanenitrile* **5a** was passed through silica gel column ($CHCl_3$–MeOH, 19:2) to give analytical sample of **5a** as a colourless crystal (MeOH), yield 45%, mp 119–121 °C. ^{1}H NMR ($CDCl_3$) δ: 1.05 (t, 3H, *J* 7.4 Hz), 2.04–2.38 (m, 2H), 4.88 (t, 1H, *J* 7.1 Hz), 7.35 (dd, 1H, H-6, $J_{6,5}$ 7.3 Hz, $J_{6,7}$ 6.3 Hz), 7.78 (dd, 1H, H-7, $J_{7,8}$ 8.9 Hz, $J_{7,6}$ 6.3 Hz), 7.91 (d, 1H, H-8, $J_{8,7}$ 8.9 Hz), 9.47 (d, 1H, H-5, $J_{5,6}$ 7.3 Hz). IR (KBr, ν/cm^{-1}): 2250 (CN). MS, *m*/*z*: 230 (M^+). Found (%): C, 57.24; H, 4.29; N, 23.97. Calc. for $C_{11}H_{10}N_4O_2$ (230.2) (%): C, 57.39; H, 4.38; N, 24.34.

For characteristics of compounds **5b**–**d**, see Online Supplementary Materials.

†† *General procedure for the synthesis of* **6a**,**b**. Compounds **1a**,**b** (22.7 mmol) and hydroxylamine hydrochloride (142 mmol) were dissolved in absolute ethanol (200 ml). The solution was cooled to 5–8 °C and then potassium hydroxide (350 mmol) in methanol (50 ml) was added dropwise during 1 h. The resulting yellow suspension was stirred for 5 h and then neutralized by concentrated hydrochloric acid to pH 7–8. The precipitate was collected by filtration, washed with water and dried to give **6a**,**b** in 80 and 65% yields, respectively.

For characteristics of compounds **6a**,**b**, see Online Supplementary Materials.