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Synthesis of a new tricyclic 3-(tetrazol-5-yl)pyridine system from 2-(azidomethyl)nicotinonitriles

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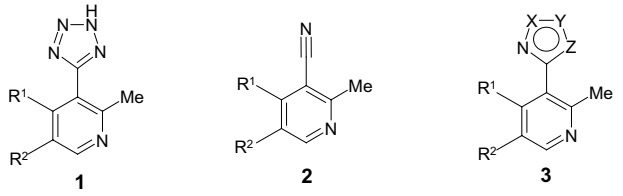
Abstract—2-Methyl-3-cyanopyridines were converted into the corresponding 2-azidomethyl derivatives, which then underwent an intramolecular cycloaddition reaction. A novel heterocyclic system containing a 3-(tetrazol-5-yl)pyridine unit was obtained in this way.

We have recently reported the synthesis of 3-(tetrazol-5-yl)pyridines **1** from sterically hindered nicotinonitriles **2**.[1] These polysubstituted nicotinonitriles **2** could be starting compounds in the synthesis of various core structures for combinatorial libraries (e.g., derivatives **3**). The core structures must contain two or more functional groups as derivatization points that could be positioned at C-4 of the aryl fragment 4-aryl (**3**, R^1) and/or on the 3-azolyl fragment. However, it would be of great interest to introduce an aliphatic functional group into the core system (Scheme 1).



R^1 = alkyl, aryl; R^2 = H; R^1R^2 = $(CH_2)_n$, $CH_2O(CH_2)_m$, etc.; X, Y, Z = N, O, S

Scheme 1. Nicotinonitriles **2** and their 3-azolyl derivatives **1**, **3**.

Keywords: Side chain oxidation; Methyl group functionalization; Intramolecular cycloaddition; Cyano group; Azidomethyl group; Fused tetrazole; Nicotinonitriles.
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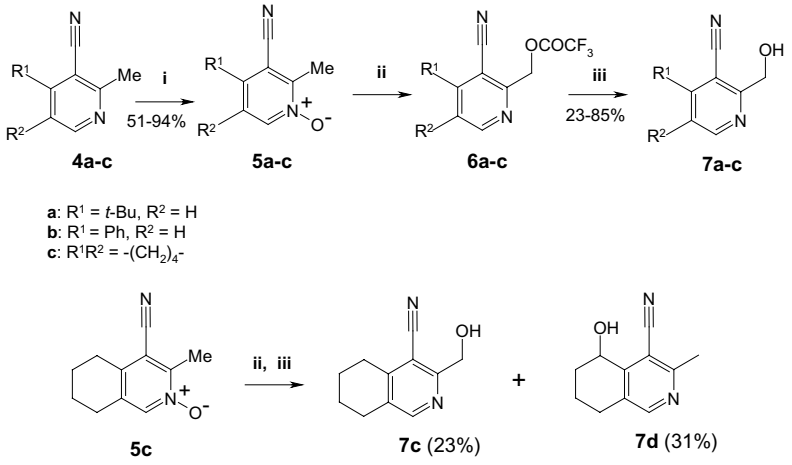
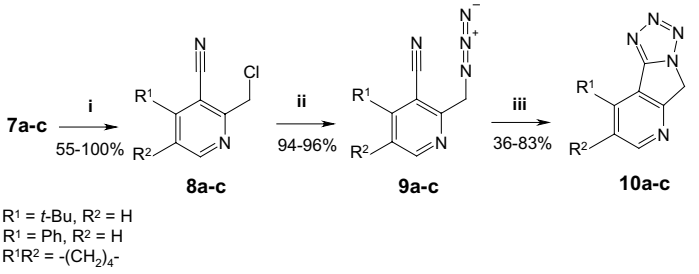
We describe here the functionalization of the 2-methyl group in structures **2** and the application of the derivatives thus obtained in the synthesis of the novel heterocyclic system **10**.

To functionalize the methyl substituent, we used the well-known rearrangement[2] of pyridine *N*-oxides **5a–c** under acylation conditions as the key step. The use of trifluoroacetic anhydride gave rise to labile trifluoroacetates **6a–c**, very smoothly under mild conditions which were easily converted into alcohols **7a–c** by treatment with methanol.[3] Interestingly, two isomeric alcohols **7c** and **7d** were obtained from 3-methyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile **4c** in yields of 23% and 31%, respectively (Scheme 2). Introduction of a hydroxy group to an alkyl group at position 4 of a pyridine ring in that manner has been previously described.[4]

Compounds **7** were used to prepare azides **9** in which an intramolecular reaction between a cyano and an azido group, previously unknown in a heterocyclic series was accomplished (Scheme 3). The 2-azidomethyl-3-cyanopyridines **9a–c** were prepared in two steps, starting from the 2-hydroxymethyl derivatives **7a–c**. Treatment of the alcohols **7a–c** with mesyl chloride gave rise directly to the desired 2-chloromethyl intermediates **8a–c**. Reaction with NaN_3 gave 2-azidomethyl-3-cyanopyridines **9a–c** which were cyclized on heating in toluene solution at 130–140 °C.[5] It is significant to note that a high purity of the azides **9a–c** and a low concentration are crucial



Scheme 2. Functionalization of the methyl group in 2-methyl-3-cyanopyridines **4a**–**c**. Reagents and conditions: (i) H_2O_2, AcOH, 70 °C; (ii) $(CF_3CO)_2O$, CH_2Cl_2, 50 °C; (iii) MeOH, rt.



Scheme 3. Reaction pathway to tricyclic tetrazolylpyridine systems **10a**–**c**. Reagents and conditions: (i) MsCl, TEA, CH_2Cl_2, rt; (ii) NaN_3, DMSO, rt; (iii) PhMe, 130–140 °C.

for successful cyclization. Furthermore, the flexibility of the azidomethyl group is also very important because while azidomethylated intermediate **9c** was cyclized smoothly, no product of the intermolecular reaction in the corresponding azidomethylated compound prepared from isomer **7d** could be obtained under various conditions. Very few examples of similar intramolecular tetrazole formation reactions have been reported in the literature.[6]

As a result of this work, the new heterocyclic system, **10**, 5*H*-tetrazolo[1′,5′:1,5]pyrrolo[3,4-*b*]pyridine was obtained. This could serve not only as a template for combinatorial libraries but also as a very interesting subject for further investigation.[7] The structures of compounds **5a**–**c** to **10a**–**c** were confirmed by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. The assignment of the ^{1}H and ^{13}C NMR spectra involved HSQC and HMBC experiments. In addition, X-ray crystallographic analysis unequivocally confirmed the structure of compound **10a** (Fig. 1).[8] The IR spectrum of the 2-azidomethyl-3-cyanopyridine **9b** demonstrated two intense bands, assigned to the azido and cyano groups at 2110 and 2218 cm^{-1}, respectively. Both bands disappeared after cyclization.

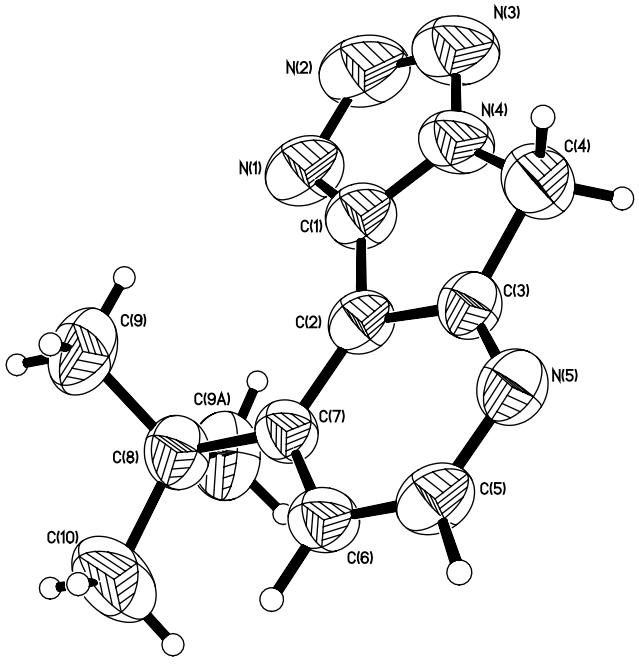


Figure 1. X-ray crystal structure of compound **10a**.

In conclusion, we have demonstrated a principle whereby an aromatic nitrile group undergoes an intramolecular reaction with an azido moiety attached to the aromatic ring through an alkyl chain.

References and notes

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3. *Typical procedure for* **7b**: 50% aqueous hydrogen peroxide (2 mL, 29.4 mmol) was added to a solution of nitrile **4b** (4.0 g, 20.6 mmol) in glacial acetic acid (10 mL), and the resulting mixture was heated at 70 °C for 24 h. Additional hydrogen peroxide solution (2 mL) was then added after which the mixture heated at 70 °C for a further 10 h. The addition of hydrogen peroxide and heating was repeated again, after which the reaction mixture was diluted with water (5 mL) and then evaporated at 80 °C/20 Torr. The oily residue was dissolved in chloroform (50 mL) and the solution washed with saturated aq Na_2CO_3. The aqueous layer was extracted with chloroform (3×20 mL) and the combined organic extracts were washed with brine, dried over magnesium sulfate and evaporated. The crude product (3.28 g, 75%) was purified by flash chromatography [silica gel Merck F60, ethyl acetate as initial eluent then a gradient system with THF (0–50% v/v)] to give analytically pure *N*-oxide **5b** (2.71 g, 63%), mp 158–163 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.62 (s, 3H, Me), 7.53–7.59 (m, 4H, Ph, 5-CH), 7.62–7.66 (m, 2H, Ph), 8.57 (d, $J = 7$ Hz, 6-CH).Trifluoroacetic anhydride (1 mL) was added dropwise to a boiling solution of *N*-oxide **5b** (1.7 g, 8.09 mmol) in anhydrous CH_2Cl_2 (10 mL). The reaction mixture was then stirred for 1 h at ambient temperature. Additional trifluoroacetic anhydride (1 mL) was added then the mixture was heated in sealed tube at 50 °C for 2 h. The reaction mixture was concentrated in vacuo, and the residue was mixed with methanol (10 mL). The solution was evaporated to dryness, and the operation was repeated several times. Subsequent purification on silica gel [hexane as initial eluent then a gradient system with ethyl acetate (30–100% v/v)] provided pure alcohol **7b** (1.45 g, 85%), mp 130–133 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.55 (br s, 1H, OH), 4.74 (s, 2H, CH_2), 7.54–7.58 (m, 4H, Ph, 5-CH), 7.61–7.65 (m, 2H, Ph), 8.79 (d, $J = 5$ Hz, 6-CH).
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5. *Typical procedure for* **10b**: methanesulfonyl chloride (0.38 mL, 4.9 mmol) was added dropwise to a solution of alcohol **7b** (1.0 g, 4.76 mmol) and triethylamine (TEA) (0.7 mL, 5 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then at ambient temperature for 2 h. Additional TEA (0.7 mL, 5 mmol) and MsCl (0.38 mL, 4.9 mmol) were added to the mixture which was then stirred for 10 h at ambient temperature. The resulting mixture was concentrated in vacuo, and the residue was subjected to chromatographic purification (silica gel, hexane–ethyl acetate = 3:1 as eluent) to give pure chloride **8b** (1.09 g, 100%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.98 (s, 2H, CH_2), 7.57–7.62 (m, 3H, Ph, 5-CH), 7.67–7.73 (m, 3H, Ph), 8.87 (d, $J = 6$ Hz, 6-CH).

   Compound **8b** (1.09 g, 4.8 mmol) was dissolved in anhydrous DMSO (5 mL), and dry NaN_3 (0.62 g, 9.53 mmol) was added. After stirring at ambient temperature for 1 h the reaction mixture was diluted with water (20 mL) and extracted with diethyl ether (4×20 mL). The combined ether extracts were washed with brine, dried over magnesium sulfate and evaporated. Purification of the residue on silica gel (hexane–ethyl acetate = 4:1 as eluent) provided analytically pure azide **9b** (1.08 g, 96%), with mp 88–90 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.80 (s, 2H, CH_2), 7.58–7.63 (m, 3H, Ph), 7.66–7.70 (m, 3H, Ph, 5-CH), 8.87 (d, $J = 6$ Hz, 6-CH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 53.4 (CH_2), 106.6 (3-C), 115.7 (CN), 123.5 (5-C), 128.6 (3′-C, 5′-C, phenyl), 129.0 (2′-C, 6′-C, phenyl), 130.2 (4′-C, phenyl), 135.5 (1′-C, phenyl), 152.3 (6-C), 152.9 (4-C), 159.6 (2-C). IR (film, ν/cm^{-1}): 2922, 2853, 2218 (C≡N), 2110 (N_3), 1577, 1539, 1462, 1394, 1286, 1083, 930, 858, 755, 695, 592. A solution of azide **9b** (100 mg, 0.42 mmol) in anhydrous toluene (10 mL) was heated in a sealed tube at 130–140 °C for 90 h. The resulting mixture was concentrated at 80 °C/20 Torr, and the residue was purified using column chromatography [hexane as initial eluent then a gradient system with ethyl acetate (30–100% v/v)]. Pure **10b** (83 mg, 83%) was isolated as well as some starting azide **9b** (16 mg, 16%). Compound **10b**: mp 208–210 °C (dec). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.71 (s, 2H, CH_2), 7.59–7.67 (m, 3H, Ph), 7.80 (d, $J = 6$ Hz, 1H, 5-CH), 7.97–8.01 (m, 2H, Ph), 8.80 (d, $J = 6$ Hz, 1H, 6-CH). ^{13}C NMR (DMSO-d_6,100 MHz): δ 51.0 (CH_2), 115.9 (3-C, pyridine ring), 122.9 (5-C, pyridine ring), 128.6 (2′-C, 6′-C, phenyl), 128.8 (3′-C, 5′-C, phenyl), 130.0 (4′-C, phenyl), 134.6 (1′-C, phenyl), 144.3 (4-C, pyridine ring), 151.2 (6-C, pyridine ring), 159.3 (5″-C, tetrazole ring), 164.8 (2-C, pyridine ring). IR (film, ν/cm^{-1}): 2922, 2852, 1567, 1517, 1473, 1443, 1350, 1256, 1199, 1160, 1123, 958, 863, 751, 645. Anal. Calcd for $C_{13}H_9N_5$ (235.25) (%): C, 66.37; H, 3.86; N, 29.77. Found (%): C, 66.51; H, 3.91; N, 29.61.
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7. Three products were obtained: **10a**, 9-*tert*-butyl-5*H*-tetrazolo[1′,5′:1,5]pyrrolo[3,4-*b*]pyridine, ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.55 (s, 9H, *t*-Bu), 5.65 (s, 2H, CH_2), 7.56 (d, $J = 5$ Hz, 1H, 5-CH), 8.68 (d, $J = 5$ Hz, 1H, 6-CH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 28.2 [$(CH_3)_3C$], 35.4 [$(CH_3)_3C$], 50.9 (CH_2), 116.8 (3-C, pyridine ring), 120.4 (5-C, pyridine ring), 151.6 (6-C, pyridine ring), 156.1 (4-C, pyridine ring), 160.0 (5′-C, tetrazole ring), 164.6 (2-C, pyridine ring); **10b**, 9-phenyl-5*H*-tetrazolo[1′,5′:1,5]pyrrolo[3,4-*b*]pyridine (vide supra); **10c**, 2,3,4,7-tetrahydro-1*H*-tetrazolo[1′,5′:1,5]pyrrolo[3,4-*c*]isoquinoline, ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.79–1.91 (m, 4H, 6-CH_2, 7-CH_2), 2.80–2.87 (m, 2H, 8-CH_2), 3.06–3.13 (m, 2H, 5-CH_2) (all the protons in tetrahydroisoquinoline unit), 5.57 (s, 2H, CH_2, pyrrole ring), 8.44 (s, 1H, 1-CH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.1, 21.7 (both 6-C, 7-C, tetrahydroisoquinoline unit), 25.5, 26.0 (both 5-C, 8-C, tetrahydroisoquinoline unit), 51.1 (CH_2, pyrrole ring), 117.2 (4-C, tetrahydroisoquinoline unit), 133.2 (4′-C, pyridine ring), 142.1 (5′-C, pyridine ring), 151.4 (1-C, tetrahydroisoquinoline unit), 158.9 (5″-C, tetrazole ring), 160.8 (3-C, tetrahydroisoquinoline unit).
8. Crystallographic data for compound **10a**: $C_{11}H_{13}N_5$, monoclinic, space group *P*2(1)/*m*, $a = 9.222(5)$, $b = 6.636(3)$, $c = 9.268(4)$ Å, $\alpha = 90°$, $\beta = 102.43(3)°$, $\gamma = 90°$, volume 553.9(5) Å^3, $T = 293(2)$ K, $Z = 2$, $D_c = 1.291$ Mg/m^3, $\mu = 0.084$ mm^{-1}, $\theta_{max} = 25.11°$, 1089 reflections measured

and 1012 unique (R_{int} = 0.0853) reflections, full matrix least-squares refinement on F^2, R_1(obs) = 0.0590, and wR_2 (all data) = 0.1934. Supplementary data in the form of a CIF file has been deposited with the Cambridge Crystallographic Data Centre (CCDC 248520). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].