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SULFURIC ACID MEDIATED HETEROCYCLIZATION OF *ORTHO*-CYANOMETHYLNITROARENES TO BENZO[C]ISOXAZOLES AND FUSED BENZO[C]ISOXAZOLES

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Abstract – The vicarious nucleophilic substitution of hydrogen (VNS) is used as the key step to convert substituted 5-nitrobenzimidazoles **1a-b** into their *ortho*-cyanomethyl derivatives **2a-b**. Conc. sulfuric acid mediated heterocyclization of these intermediates gave the novel 3*H*-imidazo[4',5':3,4]benzo[*c*]isoxazole-8-carboxamides **3a-b**. To generalize this synthetic strategy for benzo[*c*]isoxazoles syntheses, the VNS products of *para*-substituted nitrobenzene **4a-d** were successfully converted to the new benzo[*c*]isoxazoles derivatives **5a-d**.

INTRODUCTION

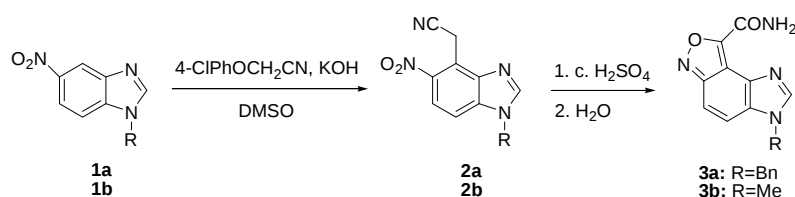
Benzo[*c*]isoxazoles (2,1-benzisoxazoles) derivatives are prescribed as antipsychotic risperidone drugs¹ and play a key role in many organic reactions,² notably those leading to anthranilic acids. There are several methods for the synthesis of these compounds. The formation of benzo[*c*]isoxazoles from *ortho* nitrobenzene derivatives is generally catalyzed both by acids and by bases and can also be initiated thermally or photochemically. A variety of *ortho*-nitrobenzylcarbonyl derivatives cyclize under both acidic and basic conditions and thermally, to afford the simple benzo[*c*]isoxazoles derivatives.³⁻⁵ The sole structural requirement for the success of these cyclizations appears to be depended upon the presence of a moderately acidic benzylic C-H group. Conversion of *ortho*-nitrobenzylcarboxylic acids in hot concentrated sulfuric acid to benzo[*c*]isoxazoles derivatives has been reported in early literature.⁶ To the best of our knowledge, heterocyclization of *ortho*-cyanomethylnitroarenes to benzo[*c*]isoxazoles have not

been investigated in conc. sulfuric acid. Owing to our growing interest in the synthesis of bioactive heterocycles and exploration of their synthetic pathways,⁷ we became interested in the transformation of *ortho* cyanomethyl nitroarenes to the new benzo[*c*]isoxazoles and fused benzo[*c*]isoxazoles. The vicarious nucleophilic substitution of hydrogen⁸ (VNS) is a highly efficient synthetic tool for the introduction of various functionalized substituents into the *ortho*-position relative to nitro group. Nitroarenes containing functionalized substituents in the *ortho*-position are valuable synthones in a variety of cyclocondensation reactions yielding potentially biologically active heterocycles such as indoles, benzimidazoles, quinolines, fused pyrimidines, fused pyrazines, etc (see a recent review and references cited therein).⁹

In this work, we have introduced the CH₂CN moiety into the *ortho*-position of nitro group in nitrobenzene derivatives (**4a-d**) and *N*-alkyl substituted 5-nitrobenzimidazoles (**1a-b**) with the aim to synthesize the new derivatives of benzo[*c*]isoxazoles (**5a-d**) and fused benzo[*c*]isoxazoles (**3a-b**) via conc. sulfuric acid catalysis at room temperature.

RESULTS AND DISCUSSION

The key intermediates 2-(1-benzyl-5-nitro-1*H*-benzo[*d*]imidazol-4-yl)acetonitrile (**2a**) and 2-(1-methyl-5-nitro-1*H*-benzo[*d*]imidazol-4-yl)acetonitrile (**2b**) were obtained via the VNS reaction of *N*-benzyl- and *N*-methyl-5-nitrobenzimidazoles **1a-b** with 4-chlorophenoxyacetonitrile in basic DMSO solution. The compounds **2a-b** were cyclized to fused benzo[*c*]isoxazoles **3a-b** in conc. sulfuric acid at room temperature (Scheme 1).

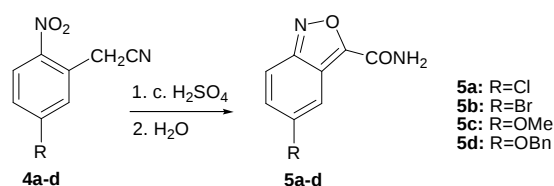


Scheme 1

The structural assignments of compounds **3a-b** were based on the analytical and spectral data. For example, in the ¹³C NMR spectrum of 3-benzyl-3*H*-imidazo[4',5':3,4]benzo[*c*]isoxazole-8-carboxamide (**3a**), the signal at 17.39 ppm attributed to CH₂CN carbon atom of compound **2a** is absent but instead there is a signal at 131.57 ppm for an aromatic carbon atom which is a clear indication of the cyclization step which led to the formation of the third aromatic ring. In the ¹H NMR spectrum of **3a** the signal at 4.64 ppm assignable to cyanomethyl protons of compound **2a** is not present but instead two signals attributed to two exchangeable protons (amide NH₂ group) appeared at 8.45 and 9.55 ppm which is a

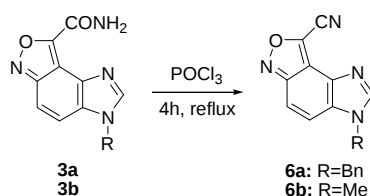
further indication of the heterocyclization step. Moreover, the FT-IR spectrum of **3a** in KBr showed two different absorption bands at 3170 cm^{-1} and 3380 cm^{-1} assignable to amide NH_2 group, 1698 cm^{-1} and 1670 cm^{-1} assignable to $\text{C}=\text{O}$ group. All this evidence plus the molecular ion peak at m/z 292 and microanalytical data strongly support the cyclic structure of compound **3a**.

Heterocyclization of *ortho*-cyanomethylnitrobenzenes **4a-d** in conc. sulfuric acid afforded the new derivatives of benzo[*c*]isoxazoles **5a-d** (Scheme 2).



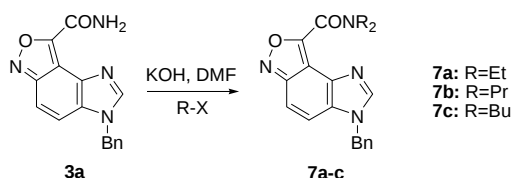
Scheme 2

Dehydration of **3a-b** compounds in boiling POCl_3 gave the new derivatives of 3-benzyl-3*H*-imidazo[4',5':3,4]benzo[*c*]isoxazol-8-yl cyanide (**6a**) and 3-methyl-3*H*-imidazo[4',5':3,4]benzo[*c*]isoxazol-8-yl cyanide (**6b**).



Scheme 3

Alkylation of **3a** with different alkyl halides in DMF and KOH gave the dialkyl derivatives **7a-c** (Scheme 4).



Scheme 4

In summary, this research has demonstrated that the sequential VNS reaction of nitroarenes and heterocyclization of the *ortho* substituted products in the presence of conc. sulfuric acid is a reliable strategy for the synthesis of new benzo[*c*]isoxazoles and fused benzo[*c*]isoxazoles. This work can be extended to the synthesis of other novel heterocyclic compounds.

EXPERIMENTAL

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 ^{13}C NMR (125MHz) spectra were recorded on a Bruker Avance DRX-500 Fouriertransformer spectrometer. The ^1H NMR (100MHz) spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constance J are given in Hertz. 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,¹⁰ compounds **1a-b**¹¹ and **4a-d**¹² were obtained according to the published methods. Other reagents were commercially available.

1. General procedure for the synthesis of *ortho* disubstituted benzo[d]imidazol-4-yl)acetonitrile **2a-b**.

To a solution of the *N*-substituted 5-nitrobenzimidazoles **1a-b** (19.7 mmol) and 4-chlorophenoxyacetonitrile (20 mmol) in DMSO (90 mL), powdered KOH (5.6 g, 100 mmol) was added. The reaction mixture was stirred for 3 h at rt, and then poured onto crushed ice containing (10 mL) hydrochloric acid. The precipitate was collected by filtration and recrystallized from EtOH to give the pure products **2a-b**.

1.1. 2-(1-Benzyl-5-nitro-1*H*-benzo[d]imidazol-4-yl)acetonitrile (2a). Compound **2a** was obtained as bright yellow crystals, yield (72%), mp 161-163 °C; ^1H NMR (100 MHz, CDCl_3) δ 4.64 (s, 2H), 5.43 (s, 2H), 7.2-7.4 (m, 6H), 8.15 (s, 1H), 8.23 (d, $J=10.9$ Hz, 1H); ^{13}C NMR (125MHz, $\text{DMSO}-d_6$): δ 149.15, 143.50, 143.00, 137.61, 136.97, 129.72, 128.92, 128.36, 120.93, 119.92, 118.23, 112.24, 49.07, 17.34; IR (KBr): 1350, 1525 (NO_2), 2250 cm^{-1} (CN). MS, m/z (%): 292 (M^+ , 33), 273 (42), 251(12), 207 (38), 127 (34), 91 (100), 65 (53). Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_2$ (292.3): C, 64.74; H, 3.62; N, 20.13. Found: C, 64.92; H, 3.59; N, 20.09.

1.2. 2-(1-Methyl-5-nitro-1*H*-benzo[d]imidazol-4-yl)acetonitrile (2b). Compound **2b** was obtained as bright yellow crystals, yield (70%), mp 188-190 °C; ^1H NMR (100 MHz, $\text{DMSO}-d_6$) δ 3.92 (s, 3H), 4.58 (s, 2H), 7.9 (d, $J=14$ Hz, 1H), 8.2 (d, $J=14$ Hz, 1H), 8.55 (s, 1H); IR (KBr): 1350, 1525 (NO_2), 2250 cm^{-1} (CN). MS (m/z) 216 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_8\text{N}_4\text{O}_2$ (216.2): C, 53.47; H, 2.99; N, 27.71. Found: C, 53.38; H, 2.85; N, 27.54.

2. General procedure for the synthesis of fused benzo[c]isoxazoes (**3a-b**) and benzo[c]isoxazoes (**5a-d**).

To concentrated sulfuric acid (6 mL), which was kept in an ice-bath, compounds **2a-b** and **4a-d** (6.8 mmol) was gradually added, with stirring. The inside temperature was kept between 15-20 °C. The

addition was accomplished over a period of 1 h, the solution was stirred at rt for further 4 h, then water (8 mL) was added to the solution in an ice-bath and it was stirred for further 2 h before it was poured onto crushed ice, and finally it was neutralized with dilute aqueous NaOH. The reaction mixture which was allowed to reach 50-70 °C during the neutralization, was cooled to rt, filtered and washed with water and then CH₂Cl₂, to give the pure products **3a-b**.

2.1. 3-Benzyl-3H-imidazo[4',5':3,4]benzo[c]isoxazole-8-carboxamide (3a). Compound **3a** was obtained as colorless crystals (1,4-dioxane), yield (90%), mp 260-263 °C; ¹H NMR (100MHz, DMSO-*d*₆) δ 5.65 (s, 2H), 7.34 (s, 5H), 7.61 (d, *J* = 12.0 Hz, 1H), 7.81 (d, *J* = 12.0 Hz, 1H), 8.45 (br s, 1H), 8.61 (s, 1H), 9.55 (br s, 1H); ¹³C NMR (125MHz, DMSO-*d*₆): δ 157.93, 157.79, 155.39, 142.85, 137.36, 131.57, 130.31, 129.74, 128.92, 128.26, 120.74, 111.97, 111.13, 49.24; IR (KBr): 3170, 3380 cm⁻¹ (NH₂), 1698, 1670 cm⁻¹ (C=O). MS, *m/z* (%): 292 (M⁺, 31), 290 (99), 264 (26), 248 (40), 173 (45), 91 (100), 65 (62). Anal. Calcd for C₁₆H₁₂N₄O₂ (292.3): C, 65.75; H, 4.14; N, 19.17. Found: C, 65.54; H, 4.11; N, 18.94.

2.2. 3-Methyl-3H-imidazo[4',5':3,4]benzo[c]isoxazole-8-carboxamide (3b). Compound **3b** was obtained as colorless crystals (1,4-dioxane), yield (86%), mp 270-272 °C; ¹H NMR (100MHz, DMSO-*d*₆) δ 3.97 (s, 3H), 7.6 (d, *J* = 10.0 Hz, 1H), 7.9 (d, *J* = 10.0 Hz, 1H), 8.35 (br s, 1H), 8.45 (s, 1H), 9.55 (br s, 1H); IR (KBr): 3170, 3380 cm⁻¹ (NH₂), 1698, 1670 cm⁻¹ (C=O). MS (*m/z*) 216 (M⁺). Anal. Calcd for C₁₀H₈N₄O₂ (216.2): C, 55.56; H, 3.73; N, 25.91. Found: C, 55.95; H, 3.57; N, 25.77.

2.3. 5-Chlorobenzo[c]isoxazole-3-carboxamide (5a). Compound **5a** was obtained as colorless crystals (acetone), yield (75%), mp 226-227 °C; ¹H NMR (100MHz, DMSO-*d*₆) δ 7.47 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.95 (s, 1H), 8.25 (br s, 1H), 8.69 (br s, 1H); IR (KBr): 3185, 3390 cm⁻¹ (NH₂), 1690, 1665 cm⁻¹ (C=O). MS (*m/z*) 197 (M⁺). Anal. Calcd for C₈H₅ClN₂O₂ (196.6): C, 48.88; H, 2.56; N, 14.25. Found: C, 48.49; H, 2.51; N, 14.03.

2.4. 5-Bromobenzo[c]isoxazole-3-carboxamide (5b). Compound **5b** was obtained as colorless crystals (acetone), yield (55%), mp 235-237 °C; ¹H NMR (100MHz, DMSO-*d*₆) δ 7.60 (d, *J* = 10.0 Hz, 1H), 7.80 (d, *J* = 10.0 Hz, 1H), 8.16 (s, 1H), 8.24 (br s, 1H), 8.67 (br s, 1H); IR (KBr): 3185, 3390 cm⁻¹ (NH₂), 1690, 1665 cm⁻¹ (C=O). MS (*m/z*) 241 (M⁺). Anal. Calcd for C₈H₅BrN₂O₂ (241.0): C, 39.86; H, 2.09; N, 11.62. Found: C, 39.64; H, 1.99; N, 11.45.

2.5. 5-Methoxybenzo[c]isoxazole-3-carboxamide (5c). Compound **5c** was obtained as colorless crystals (acetone), yield (59%), mp 232-234 °C; ¹H NMR (100MHz, DMSO-*d*₆) δ 3.96 (s, 3H), 7.29 (d, *J* = 10.0 Hz, 1H), 7.35 (s, 1H), 7.50 (d, *J* = 10.0 Hz, 1H), 8.15 (br s, 1H), 8.78 (br s, 1H); IR (KBr): 3185, 3390 cm⁻¹ (NH₂), 1690, 1665 cm⁻¹ (C=O). MS (*m/z*) 192 (M⁺). Anal. Calcd for C₉H₈N₂O₃ (192.2): C, 56.25; H, 4.20; N, 14.58. Found: C, 55.95; H, 4.16; N, 14.42.

2.6. 5-(Benzyloxy)benzo[c]isoxazole-3-carboxamide (5d). Compound **5d** was obtained as colorless crystals (acetone), yield (69%), mp 228-230 °C; ¹H NMR (100MHz, DMSO-*d*₆) δ 5.45 (s, 2H), 7.21 (s,

5H), 7.29 (s, 1H), 7.37 (d, $J=10.0$ Hz, 1H), 7.54 (d, $J=10.0$ Hz, 1H), 8.26 (br s, 1H), 8.77 (br s, 1H); IR (KBr): 3185, 3390 cm^{-1} (NH_2), 1690, 1665 cm^{-1} ($\text{C}=\text{O}$). MS (m/z) 268 (M^+). Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_3$ (268.3): C, 67.16; H, 4.51; N, 10.44. Found: C, 66.88; H, 4.49; N, 10.37.

3. General procedure for the synthesis of 6a-b from 3a-b.

The mixture of **3a-b** (0.2 g, 0.68 mmol) and POCl_3 (3 mL) was refluxed with stirring for 3 h. After cooling to rt the product poured into crushed ice and neutralized with ammonia solution. The product was extract with EtOAc (2×50 mL). The extract was dried, and evaporated to give pure **6a-b**.

3.1. 3-Benzyl-3H-imidazo[4',5':3,4]benzo[c]isoxazol-8-yl cyanide (6a). Compound **6a** was obtained as pale yellow crystals, yield (75%), mp 182-184 $^\circ\text{C}$; ^1H NMR (100MHz, $\text{DMSO}-d_6$) δ 5.65 (s, 2H), 7.33 (s, 5H), 7.67 (d, $J=10.0$ Hz, 1H), 7.95 (d, $J=10.0$ Hz, 1H), 8.56 (s, 1H); ^{13}C NMR (125MHz, $\text{DMSO}-d_6$): δ 157.71, 144.51, 137.39, 133.22, 131.92, 130.53, 129.79, 128.89, 128.20, 121.96, 119.00, 111.73, 110.58, 49.09; IR (KBr): 2220 cm^{-1} (CN). MS (m/z) 274 (M^+). Anal. Calcd for $\text{C}_{32}\text{H}_{20}\text{N}_8\text{O}_2$ (274.3): C, 70.07; H, 3.67; N, 20.43. Found: C, 70.33; H, 3.72; N, 20.56.

3.2. 3-Methyl-3H-imidazo[4',5':3,4]benzo[c]isoxazol-8-yl cyanide (6b). Compound **6b** was obtained as pale yellow crystals, yield (72%), mp 128-130 $^\circ\text{C}$; ^1H NMR (100MHz, CDCl_3) δ 3.95 (s, 3H), 7.65 (d, $J=9.5$ Hz, 1H), 7.85 (d, $J=9.5$ Hz, 1H), 7.92 (s, 1H); IR (KBr): 2220 cm^{-1} (CN). MS (m/z) 198 (M^+). Anal. Calcd for $\text{C}_{20}\text{H}_{12}\text{N}_8\text{O}_2$ (198.18): C, 60.61; H, 3.05; N, 28.27. Found: C, 60.55; H, 3.05; N, 28.39.

4. General procedure for the synthesis of 7a-c from 3a.

To a solution of **3a** (0.68 mmol) in DMF (5 mL), alkyl halide (1.4 mmol) and KOH (0.34 g, 6 mmol) was added. The mixture was stirred for 1 day and then poured into water. The precipitate was collected by filtration, washed with water and air-dried to give **7a-e**.

4.1. N,N-Diethyl-3-benzyl-3H-imidazo[4',5':3,4]benzo[c]isoxazole-8-carboxamide (7a). Compound **7a** was obtained as yellow crystals (EtOH), yield (65%), mp 184-187 $^\circ\text{C}$; ^1H NMR (100MHz, CDCl_3) δ 1.4 (t, $J=8.0$ Hz, 3H), 1.6 (t, $J=8.0$ Hz, 3H), 3.6 (q, $J=6.7$ Hz, 2H), 4 (q, $J=6.7$ Hz, 2H), 5.45 (s, 2H), 7.1-7.5 (m, 7H), 7.95 (s, 1H). MS (m/z) 348 (M^+). Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_2$ (348.4): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.73; H, 5.65; N, 15.92.

4.2. N,N-Dipropyl-3-benzyl-3H-imidazo[4',5':3,4]benzo[c]isoxazole-8-carboxamide (7b).

Compound **7b** was obtained as yellow crystals (EtOH), yield (67%), mp 129-132 $^\circ\text{C}$; ^1H NMR (100MHz, CDCl_3) δ 0.9 (t, $J=8.0$ Hz, 3H), 1.15 (t, $J=8.0$ Hz, 3H), 1.6-2 (m, 4H), 3.4-3.8 (m, 4H), 5.45 (s, 2H), 7.15-7.6 (m, 7H), 7.95 (s, 1H). MS (m/z) 376 (M^+). Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_2$ (376.5): C, 70.19; H, 6.43; N, 14.88. Found: C, 70.45; H, 6.20; N, 15.16.

4.3. N,N-Dibutyl-3-benzyl-3H-imidazo[4',5':3,4]benzo[c]isoxazole-8-carboxamidz (7c).

Compound **7c** was obtained as yellow crystals (EtOH), yield (60%), mp 91-94 °C; ¹H NMR (100MHz, CDCl₃) δ 0.8-1.95 (m, 14H), 3.35-3.8 (m, 4H), 5.4 (s, 2H), 7.1-7.5 (m, 7H), 7.9 (s, 1H). MS (m/z) 404 (M⁺). Anal. Calcd for C₂₄H₂₈N₄O₂ (404.5): C, 71.26; H, 6.98; N, 13.85. Found: C, 71.49; H, 6.79; N, 13.64.

REFERENCES

1. A. Szarfman, J. Tønning, J. Levine, and P. Doraiswamy, *Pharmacotherapy*, 2006, **26**, 748.
2. J. D. Loudon and G. Tennant, *Quart. Rev.*, 1964, **18**, 389.
3. S. S. Joshi and I. R. Gambhir, *J. Am. Chem. Soc.*, 1956, **78**, 2222.
4. M. P. Cava and M. V. Lakshimikantham, *J. Org. Chem.*, 1970, **35**, 1867.
5. H. G. Garg, *J. Org. Chem.*, 1962, **27**, 3683.
6. D. R. Eckroth and T. G. Cochran, *J. Chem. Soc. C*, 1970, 2660.
7. M. Bakavoli, B. Feizyadeh, and M. Rahimizadeh, *Tetrahedron Lett.*, 2006, **47**, 8965; M. Bakavoli, M. Nikpour, and M. Rahimizadeh, *J. Heterocycl. Chem.*, 2006, **43**, 1327; A. Davoodnia, M. Bakavoli, A. Vahedinia, M. Rahimizadeh, and M. Roshani, *Heterocycles*, 2006, **68**, 801; M. Bakavoli, A. Davoodnia, M. Rahimizadeh, and M. M. Heravi, *Mendeleev Commun.*, 2006, **16**, 29; M. Bakavoli, M. Nikpour, M. Rahimizadeh, M. R. Saberi, and H. Sadeghian, *Bioorg. Med. Chem.*, 2007, **15**, 2120.
8. M. Mąkosza and J. Winiarski, *Acc. Chem. Res.*, 1987, **20**, 282.
9. M. Mąkosza and K. Wojciechowski, *Chem. Rev.*, 2004, **104**, 2631.
10. E. Grochowski and Z. Eckstein, *Bull. Acad. Pol. Sci.; Ser. Sci. Chim.*, 1963, 443 (*Chem. Abstr.*, 1964, **60**, 2815).
11. B. Aliprandi, F. Cacace, and E. Possagno, *Ann. Chim. (Italy)*, 1958, **48**, 1349.
12. M. Makosza and J. Winiarski, *J. Org. Chem.*, 1984, **49**, 1494.