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 3H-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 drugs and play a key role in many organic reactions, 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. 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. To the best of our knowledge, heterocyclization of ortho-cyanomethylnitroarenens 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, 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 hydrogen (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).

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-1H-benzo[d]imidazol-4-yl)acetonitrile (2a) and 2-(1-methyl-5-nitro-1H-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](image)

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-3H-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 C=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).

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).

Alkylation of 3a with different alkyl halides in DMF and KOH gave the dialkyl derivatives 7a-c (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 $^1$H NMR (100MHz) spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constant $J$ 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[\textit{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-1H-benzo[\textit{d}]imidazol-4-yl)acetonitrile ($2a$).

Compound $2a$ was obtained as bright yellow crystals, yield (72%), mp 161-163 °C; $^1$H 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, DMSO-\textit{d}_6): δ 149.15, 143.50, 143.00, 137.61, 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 C$_{16}$H$_{12}$N$_4$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-1H-benzo[\textit{d}]imidazol-4-yl)acetonitrile ($2b$).

Compound $2b$ was obtained as bright yellow crystals, yield (70%), mp 188-190 °C; $^1$H NMR (100 MHz, DMSO-\textit{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 C$_{10}$H$_8$N$_4$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[\textit{c}]isoxazoes ($3a$-$b$) and benzo[\textit{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-3\textit{H}-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; \textsuperscript{1}H NMR (100MHz, DMSO-\textit{d}_6) δ 5.65 (s, 2H), 7.34 (s, 5H), 7.61 (d, \textit{J} = 12.0 Hz, 1H), 7.81 (d, \textit{J} =12.0 Hz,1H), 8.45 (br s, 1H), 8.61 (s, 1H), 9.55 (br s, 1H); \textsuperscript{13}C NMR (125MHz, DMSO-\textit{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\textsuperscript{-1} (NH\textsubscript{2}), 1698, 1670 cm\textsuperscript{-1} (C=O). MS, m/z (%): 292 (M\textsuperscript{+}, 31), 290 (99), 264 (26), 248 (40), 17 3 (45), 91 (100), 65 (62). Anal. Calcd for C\textsubscript{16}H\textsubscript{12}N\textsubscript{4}O\textsubscript{2} (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-3\textit{H}-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; \textsuperscript{1}H NMR (100MHz, DMSO-\textit{d}_6) δ 3.97 (s, 3H), 7.6 (d, \textit{J}=10.0 Hz, 1H), 7.9 (d, \textit{J}=10.0 Hz, 1H), 8.35 (br s, 1H), 8.45 (s, 1H), 9.55 (br s, 1H); IR (KBr): 3170, 3380 cm\textsuperscript{-1} (NH\textsubscript{2}), 1698, 1670 cm\textsuperscript{-1} (C=O). MS (m/z) 216 (M\textsuperscript{+}). Anal. Calcd for C\textsubscript{10}H\textsubscript{8}N\textsubscript{4}O\textsubscript{2} (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; \textsuperscript{1}H NMR (100MHz, DMSO-\textit{d}_6) δ 7.47 (d, \textit{J}=9.0 Hz, 1H), 7.86 (d, \textit{J}=9.0 Hz, 1H), 7.95 (s, 1H), 8.25 (br s, 1H), 8.69 (br s, 1H); IR (KBr): 3185, 3390 cm\textsuperscript{-1} (NH\textsubscript{2}), 1690, 1665 cm\textsuperscript{-1} (C=O). MS (m/z) 197 (M\textsuperscript{+}). Anal. Calcd for C\textsubscript{8}H\textsubscript{5}ClN\textsubscript{2}O\textsubscript{2} (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; \textsuperscript{1}H NMR (100MHz, DMSO-\textit{d}_6) δ 7.60 (d, \textit{J}=10.0 Hz, 1H), 7.80 (d, \textit{J}=10.0 Hz, 1H), 8.16 (s, 1H), 8.24 (br s, 1H), 8.67 (br s, 1H); IR (KBr): 3185, 3390 cm\textsuperscript{-1} (NH\textsubscript{2}), 1690, 1665 cm\textsuperscript{-1} (C=O). MS (m/z) 241 (M\textsuperscript{+}). Anal. Calcd for C\textsubscript{8}H\textsubscript{5}BrN\textsubscript{2}O\textsubscript{2} (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; \textsuperscript{1}H NMR (100MHz, DMSO-\textit{d}_6) δ 3.96 (s, 3H), 7.29 (d, \textit{J}=10.0 Hz, 1H), 7.35 (s, 1H),7.50 (d, \textit{J}=10.0 Hz, 1H), 8.15 (br s, 1H), 8.78 (br s, 1H); IR (KBr): 3185, 3390 cm\textsuperscript{-1} (NH\textsubscript{2}), 1690, 1665 cm\textsuperscript{-1} (C=O). MS (m/z) 192 (M\textsuperscript{+}). Anal. Calcd for C\textsubscript{9}H\textsubscript{8}N\textsubscript{2}O\textsubscript{3} (192.2): C, 56.25; H, 4.20; N, 14.58. Found: C, 55.95; H, 4.16; N, 14.42.

2.6. 5-(Benzzyloxy)benzo[c]isoxazole-3-carboxamide (5d). Compound 5d was obtained as colorless crystals (acetone), yield (69%), mp 228-230 °C; \textsuperscript{1}H NMR (100MHz, DMSO-\textit{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\(^{-1}\) (C=O). MS (m/z) 268 (M\(^+\)). Anal. Calcd for C\(_{15}H_{12}N_2O_3\) (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-3\(^H\)-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 °C; \(1^H\) NMR (100MHz, DMSO-d\(_6\)) \(\delta\) 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); 13C NMR (125MHz, DMSO-d\(_6\)): \(\delta\) 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 C\(_{32}H_{20}N_8O_2\) (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-3\(^H\)-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 °C; \(1^H\) NMR (100MHz, CDCl\(_3\)) \(\delta\) 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 C\(_{20}H_{12}N_8O_2\) (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-3\(^H\)-imidazo[4',5':3,4]benzo[c]isoxazole-8-carboxamide (7a). Compound 7a was obtained as yellow crystals (EtOH), yield (65%), mp 184-187 °C; \(1^H\) NMR (100MHz, CDCl\(_3\)) \(\delta\) 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 C\(_{20}H_{20}N_4O_2\) (348.4): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.73; H, 5.65; N, 15.92.

Compound 7b was obtained as yellow crystals (EtOH), yield (67%), mp 129-132 °C; \(1^H\) NMR (100MHz, CDCl\(_3\)) \(\delta\) 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 C\(_{22}H_{24}N_4O_2\) (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-3\(^H\)-imidazo[4',5':3,4]benzo[c]isoxazole-8-carboxamide (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