

HETEROCYCLES, Vol. 71, No. 3, 2007, pp. 683 - 689. © The Japan Institute of Heterocyclic Chemistry
Received, 1st December, 2006, Accepted, 15th January, 2007, Published online, 15th January, 2007. COM-06-10961

OXIDATIVE AROMATIZATION OF 3,5-DISUBSTITUTED ISOXAZOLINES TO THE CORRESPONDING ISOXAZOLES WITH *N,N,N',N'*-TETRABROMOBENZENE-1,3-DISOLPHONAMIDE (TBBDS) AND 1,3-DIBROMO-5,5-DIMETHYLHYDANTOIN (DBH) AS EFFICIENT REAGENTS UNDER MILD REACTION CONDITIONS

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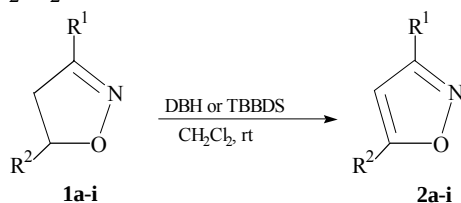
Abstract- The oxidation of 3,5-disubstituted isoxazolines to the corresponding isoxazoles has been carried out using *N,N,N',N'*-tetrabromobenzene-1,3-disolphonamide and 1,3-dibromo-5,5-dimethylhydantoin (DBH) as effective oxidizing agents under mild conditions at rt with good yields.

Among five-membered heterocycles, isoxazolines and their aromatic derivatives are biologically active natural products and synthetic compounds of medicinal interest.¹ The biological and medicinal importance of these heterocycles stem from their various chemotherapeutic properties.² Isoxazoles are also versatile intermediates in organic synthesis,³ used in the synthesis of a wide variety of natural products and pharmacophores in medicinal chemistry.⁴ Isoxazolines and isoxazoles are biologically active as fungicides, herbicides, antibacterial, ant-tubercular, antiviral and nicotinic acetylene receptor ligands.^{5,6} Isoxazolines, easily prepared from the cyclization of related chalcones with hydroxylamine, can be conveniently oxidized to isoxazoles.^{7,8} Oxidative aromatization of some five-membered heterocycles has been accomplished by various reagents including Pd/C/AcOH,⁹ activated carbon-O₂ system,¹⁰ cobalt soap of fatty acids,¹¹ Pb(OAc)₄,¹² mercury or lead oxide,¹³ MnO₂,⁷ potassium permanganate,^{14,15} silver nitrate,¹⁶ iodobenzene diacetate,¹⁷ zirconium nitrate,¹⁸ nickel peroxide,¹⁹ cromite,²⁰ NBS,²¹ Mn(OAc)₃,²² NaHCO₃/DMF,²³ DDQ,²⁴ Na₂CO₃/CH₃OH,²⁵ and tetrakispyridinenickel(II) dichromate.²⁶ However, most of these methods suffer from certain limitations such as long reaction times, high temperatures, side

product formation, and low yields. In addition, the presence of metal cations like Co(II), Pd(IV), Hg(II), Mn(IV or VII), Ag(I) and Zr(IV) added as catalysts, leave residual toxicity in the products. To tackle these drawbacks, we have previously reported some more convenient and easily available reagents for the oxidative aromatization of certain azolines including pyrazolines and isoxazolines.²⁷⁻³²

In continuation of our research to develop more robust and efficient oxidants, we were prompted to examine a simple, cheap and safe method for the oxidative aromatization of isoxazolines to isoxazoles. In this work, we have employed 1,3-dibromo-5,5-dimethylhydantoin (DBH) and *N,N,N',N'*-tetrabromobenzene-1,3-disulphonamide (TBBDS),³³ as efficient oxidizing agents to convert the isoxazolines **1a-i** to isoxazoles **2a-i** under mild conditions (Table 1).

Table 1. Oxidative aromatization of 3,5-disubstituted isoxazolines (**1a-i**) to the corresponding isoxazoles (**2a-i**) with DBH and TBBDS in CH₂Cl₂ at rt

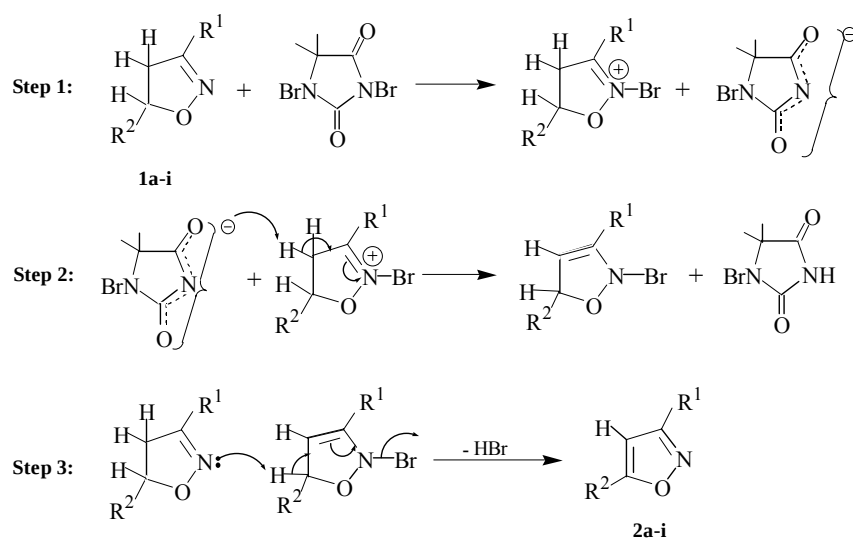


Substrate ^a	Product	R ¹	R ²	Yield (%) ^b		Time (h)		Mp (°C)
				DBH	TBBDS	DBH	TBBDS	
1a	2a	2-naphthyl	2-ClC ₆ H ₄	85	82	2.0	2.5	94-95
1b	2b	2-naphthyl	2-thienyl	80	68	2.2	2.8	118-120
1c	2c	2-naphthyl	4-CH ₃ OC ₆ H ₄	76	73	2.4	3.0	107-109
1d	2d	1-naphthyl	2-ClC ₆ H ₄	98	82	2.5	2.5	64-65
1e	2e	2-thienyl	4-ClC ₆ H ₄	84	72	2.5	2.3	192-194
1f	2f	2-naphthyl	3-ClC ₆ H ₄	70	65	2.0	3.2	90-92
1g	2g	2-furyl	4-ClC ₆ H ₄	75	67	2.8	3.5	124-125
1h	2h	2-pyrrolyl	4-ClC ₆ H ₄	92	85	2.3	2.8	185-187
1i	2i	2-naphthyl	2-styryl	94	88	2.0	3.0	165-167

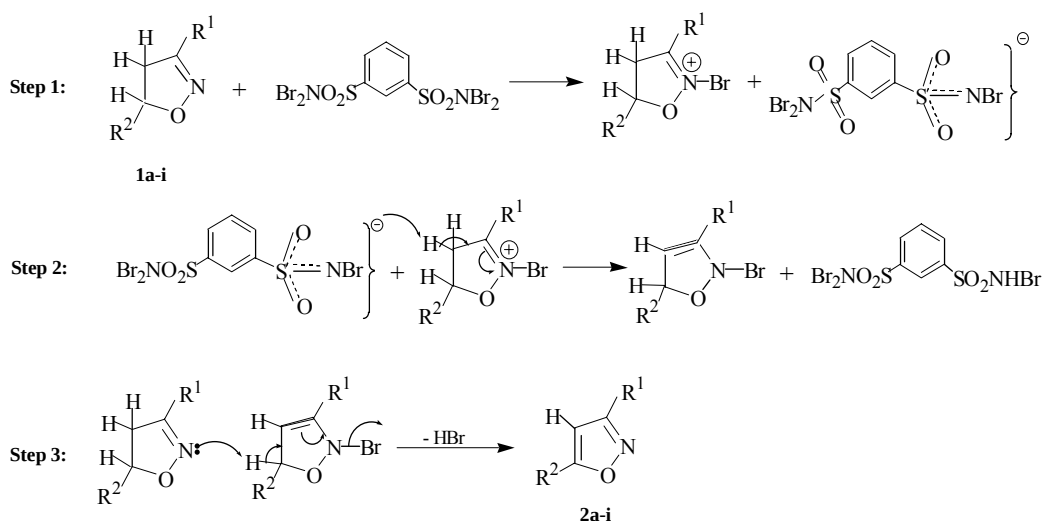
^a Isoxazolines were prepared according to the literature⁸ and characterized by their elemental analysis and IR, ¹H-NMR, ¹³C-NMR spectral and physical data. ^b Isolated yields.

The experimental results indicate that the reactions proceed relatively rapidly within few hours at rt to afford the products **2a-i** in good yields (65-98%, Table 1). Numerous repetitions of the reactions under different molar conditions indicated that, the most effective conversions occur when the molar ratios of isoxazolines to DBH and TBBDS are 3 and 1 respectively. The possible mechanisms proposed for these transformations are presented in Schemes 1 and 2.

In conclusion, the advantages allocated to the DBH and TBBDS as oxidants include: low cost, easy accessibility, high stability, easy recovery of the reagents, mild reaction conditions and high yields of the products. These properties render them as efficient and convenient reagents to oxidize the isoxazolines to isoxazoles.



Scheme 1



Scheme 2

EXPERIMENTAL

Chemicals were purchased from Fluka and Merck companies. IR spectra were recorded using a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and NMR spectra were obtained using 90 MHz JEOL FT NMR spectrometer. Isoxazolines were all prepared as reported.⁸ The reagent *N,N,N',N'*-tetrabromobenzene-1,3-disulphonamide (TBBDS) was prepared as reported method.³³

Oxidation of 3,5-Disubstituted Isoxazolines; *General procedure:*

To a solution of isoxazolines **2a-i** (0.1 mmol) in CH₂Cl₂ (5 mL), was added DBH (0.3 mmol) or TBBDS (0.1 mmol), and the mixture was vigorously stirred for 2-3.5 h at rt (Table 1). The progress of the reaction was monitored by TLC using EtOAc/n-hexane (1/4), and slow liberation of hydrogen bromide was observed during the reaction. After the complete conversion of the substrate, the reaction mixture was filtered to remove the solid materials. The filtrate was then treated with saturated Na₂CO₃, washed with

water, dried over anhydrous sodium sulphate and filtered. After removal of the solvent under reduced pressure, the remaining crude solid product was recrystallized from ethanol to give the pure isoxazoles (**2a-i**) in 65-98% yields (Table 1). The isoxazoles **2a-I** were all characterized on the basis of their microanalysis and IR, ^1H NMR, ^{13}C NMR spectral analysis as given below.

5-(2-Chlorophenyl)-3-(2-naphthyl)isoxazole (2a): Yield: 85%; mp 94-95 °C (recrystallization from EtOH). IR (KBr): 3059, 1603, 1572, 1474, 1440, 1340, 751 cm^{-1} . ^1H NMR (90 MHz, CDCl_3) δ ppm 7.13 (1H, s, C4-H isoxazole), 7.21-7.87 (10H, m, Ar-H), 8.25 (1H, s, C1-H naphth.). ^{13}C NMR (22.5 MHz, CDCl_3) δ ppm 105.68 (C4 isoxazole), 123.88, 125.05, 125.58, 126.23, 126.80, 127.19, 127.74, 128.12, 129.12, 129.91, 130.61 (CH_{arom}), 132.12, 133.24, 134.26, 134.77, 136.08 (C_{arom}), 156.66 (C3 isoxazole), 165.80 (C5 isoxazole). Anal. Calcd for $\text{C}_{19}\text{H}_{12}\text{NOCl}$: C 74.63; H, 3.93; N, 4.58. Found: C 74.58; H, 3.90; N, 4.54.

3-(2-Naphthyl)-5-(2-thienyl)isoxazole (2b): Yield: 80%; mp 118-120 °C. IR (KBr): 3056, 1594, 1499, 1447, 1410, 792 cm^{-1} . ^1H NMR (90 MHz, CDCl_3) δ ppm 7.19 (1H, s, C4-H isoxazole), 7.32-7.95 (9H, m, Ar-H), 8.41 (1H, s, C1-H naphth.). ^{13}C NMR (22.5 MHz, CDCl_3) δ ppm 98.76 (C4 isoxazole), 122.19, 123.75, 124.21, 125.70, 126.33, 126.99, 127.12, 127.42, 128.95, 129.98 (CH_{arom}), 133.03, 134.10, 140.51, 142.20 (C_{arom}), 156.51 (C3 isoxazole), 168.32 (C5 isoxazole). Anal. Calcd for $\text{C}_{17}\text{H}_{11}\text{NOS}$: C 73.65; H 3.97; N 5.05. Found: C 73.62; H, 3.95; N, 4.98.

5-(Methoxyphenyl)-3-(2-naphthyl)isoxazole (2c): Yield: 76%; mp 107-109 °C. IR (KBr): 3052, 2963, 1611, 1505, 1420, 1396, 803 cm^{-1} . ^1H NMR (90 MHz, CDCl_3) δ ppm 3.79 (3H, s, OCH_3), 7.04 (1H, s, C4-H isoxazole), 7.20-7.87 (10H, m, Ar-H), 8.31 (1H, s, C1-H naphth.). ^{13}C NMR (22.5 MHz, CDCl_3) δ ppm 54.97 (OCH_3), 110.34 (C4 isoxazole), 120.87, 123.43, 124.57, 125.54, 126.23, 127.06, 128.43, 129.21, 130.67, 131.92 (CH_{arom}), 133.21, 137.71, 138.92, 142.50, 142.85 (C_{arom}), 150.28 (C3 isoxazole), 162.56 (C5 isoxazole). Anal. Calcd for $\text{C}_{20}\text{H}_{15}\text{NO}_2$: C 79.73; H, 4.98; N, 4.65. Found: C 79.68; H, 4.92; N, 4.63.

5-(2-Chlorophenyl)-3-(1-naphthyl)isoxazole (2d): Yield: 98%; mp 64-65 °C. IR (KBr): 3053, 1602, 1580, 1471, 1428, 1375, 774 cm^{-1} . ^1H NMR (90 MHz, CDCl_3) δ ppm 6.94 (1H, s, C4-H isoxazole), 7.28-8.46 (11H, m, Ar-H). ^{13}C NMR (22.5 MHz, CDCl_3) δ ppm 110.32 (C4 isoxazole), 122.76, 123.43, 124.44, 125.89, 126.23, 126.95, 127.45, 128.32, 129.36, 129.99, 130.87 (CH_{arom}), 131.14, 133.65, 134.56, 139.67, 143.12 (C_{arom}), 150.09 (C3 isoxazole), 160.32 (C5 isoxazole). Anal. Calcd for $\text{C}_{19}\text{H}_{12}\text{NOCl}$: C 74.63; H, 3.93; N, 4.58. Found: C 74.62; H, 3.85; N, 4.56.

5-(4-Chlorophenyl)-3-(2-thienyl)isoxazole (2e): Yield: 84%; mp 192-194 °C. IR (KBr): 3087, 1607, 1570, 1488, 1430, 1391, 781 cm^{-1} . ^1H NMR (90 MHz, CDCl_3) δ ppm 6.59 (1H, s, C4-H isoxazole), 7.11-7.70 (7H, m, Ar-H). ^{13}C NMR (22.5 MHz, CDCl_3) δ ppm 103.11 (C4 isoxazole), 126.43, 127.14, 127.98, 128.61, 129.45, 130.17, 131.27 (CH_{arom}), 132.65, 133.69, 138.88 (C_{arom}), 151.81 (C3 isoxazole), 164.46

(C5 isoxazole). Anal. Calcd for $C_{13}H_8NOClS$: C 59.65; H, 3.06; N, 5.35. Found: C 59.48; H, 3.10; N, 5.25.

5-(3-Chlorophenyl)-3-(2-naphthyl)isoxazole (2f): Yield: 70%; mp 90-92 °C. IR (KBr): 3113, 3062, 1585, 1562, 1483, 1448, 1408, 788 cm^{-1} . 1H NMR (90 MHz, $CDCl_3$) δ ppm 6.85 (1H, s, C4-H isoxazole), 7.17-7.85 (10H, m, Ar-H), 8.17 (1H, s, C1-H naphth.). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ ppm 108.96 (C4 isoxazole), 123.47, 123.95, 125.97, 126.79, 127.02, 127.15, 128.31, 128.53, 129.38, 130.06, 131.52 (CH_{arom}), 132.89, 134.61, 135.76, 137.62, 138.43 (C_{arom}), 156.17 (C3 isoxazole), 159.68 (C5 isoxazole). Anal. Calcd for $C_{19}H_{12}NOCl$: C 74.63; H, 3.93; N, 4.58. Found: C 74.61; H, 3.90; N, 4.45.

5-(4-Chlorophenyl)-3-(2-furyl)isoxazole (2g): Yield: 75%; mp 124-125 °C. IR (KBr): 3131, 1663, 1594, 1486, 1460, 1396, 774 cm^{-1} . 1H NMR (90 MHz, $CDCl_3$) δ ppm 5.96 (1H, s, C4-H isoxazole), 7.24-7.71 (7H, m, Ar-H). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ ppm 110.12 (C4 isoxazole), 112.57, 113.45, 126.67, 127.11, 129.85, 131.74, 132.71 (CH_{arom}), 136.98, 138.70, 144.24 (C_{arom}), 148.17 (C3 isoxazole), 169.11 (C5 isoxazole). Anal. Calcd for $C_{13}H_8NO_2Cl$: C 63.54; H, 3.26; N, 5.70. Found: C 63.48; H, 3.22; N, 5.68.

5-(4-Chlorophenyl)-3-(2-pyrrolyl)isoxazole (2h): Yield: 92%; mp 185-187 °C. IR (KBr): 3259, 3049, 1602, 1494, 1446, 1350, 756 cm^{-1} . 1H NMR (90 MHz, $CDCl_3$) δ ppm 7.06 (1H, s, C4-H isoxazole), 7.21-8.01 (7H, m, Ar-H), 9.87 (1H, s br, N-H). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ ppm 103.23 (C4 isoxazole), 109.66, 112.82, 126.96, 127.38, 128.99, 130.67, 131.83 (CH_{arom}), 134.42, 136.78, 139.37 (C_{arom}), 151.81 (C3 isoxazole), 167.41 (C5 isoxazole). Anal. Calcd for $C_{13}H_9N_2OCl$: C 63.80; H, 3.68; N, 11.45. Found: C 63.75; H, 3.65; N, 11.38.

3-(2-Naphthyl)-5-(2-styryl)isoxazole (2i): Yield: 94%; mp 165-167 °C. IR (KBr): 3052, 1636, 1599, 1542, 1492, 1477, 1363, 714 cm^{-1} . 1H NMR (90 MHz, $CDCl_3$) δ ppm 6.96 (1H, s, C4-H isoxazole), 7.12-7.92 (13H, m, Ar-H and vinyl), 8.35 (1H, s, C1-H naphth.). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ ppm 104.32 (C4 isoxazole), 123.37, 124.21, 126.29, 126.55, 127.12, 128.94, 129.32, 131.28, 131.74, 132.38, 133.06, 133.67, 134.74, 135.31 (CH_{arom}), 136.95, 141.51, 143.30, 144.20 (C_{arom} and vinyl), 156.48 (C3 isoxazole), 162.34 (C5 isoxazole). Anal. Calcd for $C_{21}H_{15}NO$: C 84.85; H, 5.05; N, 4.71. Found: C 84.78; H, 5.03; N, 4.68.

ACKNOWLEDGEMENT

We wish to thank the Research Council of Bu-Ali-Sina University, Hamadan, Iran, for financial support to carry out this research.

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