Preparation of Novel Di-isoxazolines Using Bis(nitrile oxide) 1,3-Dipolar Cycloaddition Methodology

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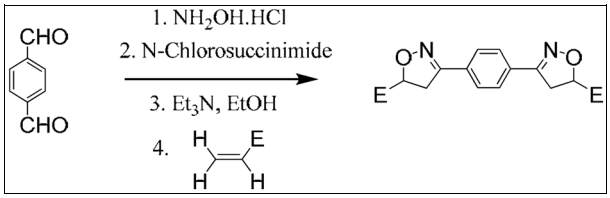

A general method for the synthesis of novel di-isoxazolines through a 1,3-dipolar cycloaddition reaction of *in situ* prepared bis (nitrile oxides) of terephthaldehyde and various olefins is described. The reactions are regiospecific and give high yields of products.

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INTRODUCTION

1,3-Dipolar cycloaddition reactions, also known as the Huisgen reactions, are important synthetic routes to preparation of heterocycles.

Many isoxazolines and their aromatic homologs are drugs with anti-inflammatory [1], antiplatelet [2], and anti-depressant [3] activity. Isoxazolines are also used in the synthesis of β-aminoalcohols and β-hydroxyketones [4].

The asymmetric 1,3-dipolar cycloaddition of nitrile oxides to alkenes provides a powerful tool for the stereo controlled synthesis of 4,5-dihydroisoxazoles [5,6]. Reports on the 1,3-dipolar cycloaddition reactions of bis (nitrile oxides) with olefins are limited [7,8].

RESULTS AND DISSCUSION

In this work, we have used terephthalaldehyde **1** to prepare the corresponding bis(nitrile oxides) **4** which upon reacting with selected olefins **5** gave the corresponding isoxazolines **6** (Scheme 1).

The reaction conditions were optimized by varying temperature, the type of solvent and the ratios of olefin **5** to terephthaloxime chloride **3** to triethylamine. The best yields were obtained when 1 eq. of **3** was mixed with 2 eq. of olefin **5** with slow addition of 4 eq. of triethyl amine at room temperature in ethanol for 24 h.

Nitrile oxides are prone to dimerization and polymerization. In our experiments formation of polymerized material was observed. We, however, made no attempt to identify the material thus formed.

Products were characterized by IR, ^{1}H and ^{13}C NMR and CHN analysis. A peak at 5.0–6.5 ppm (doublet of doublets) is assigned to hydrogen of the CH group in the isoxazoline ring. Hydrogens of the CH_2 group in isoxazoline ring are diastereotopic and appear at 3.5–4.0 ppm as two doublets of doublets. The peak around 156 ppm in ^{13}C NMR was assigned to the carbon of theisoxazoline ring with sp^2 hybridization. Results are tabulated in Table 1.

CONCLUSIONS

In conclusion, we wish to report an efficient procedure for the synthesis of di-isoxazolines via a 1,3-dipolar cycloaddition reaction. The yields are high and give five-substituted di-isoxazolines regiospecifically.

EXPERIMENTAL

General methods. The products were isolated and characterized by physical and spectral data. ^{1}HNMR spectra were recorded on a Bruker Avance-300 MHz spectrometer using tetramethylsilane as internal standard. IR spectra were recorded using a Perkin–Elmer RX1 Fourier transformation infrared spectrometer with KBr plates. Elemental analyses were doneusing a Perkin–Elmer 2400 series II CHN analyzer. Melting points were determined on a Barnstead Electrothermal 9200.

Preparation of terephthaldoxime. To a solution of terephthalaldehyde (10 mmol in 15 mL ethanol) and hydroxylamine hydrochloride (20 mmol in 15 mL water), sodium hydroxide (20 mmol, in 1.5 mL water) was added dropwise. After 30 minutes, the reaction mixture was neutralized by acetic acid and precipitate was filtered. Recrystallization in ethanol gave terephthaldoxime in 96% yield. m.p. 203–205°C; ^{1}H NMR (300 MHz, Acetone-d_6) δ (ppm):10.62 (2H, s), 8.15 (2H, s), 7.65 (4H, s). IR (KBr) ν_{max} (cm^{-1}): 3245, 3091, 1571, 1474, 822.

Scheme 1

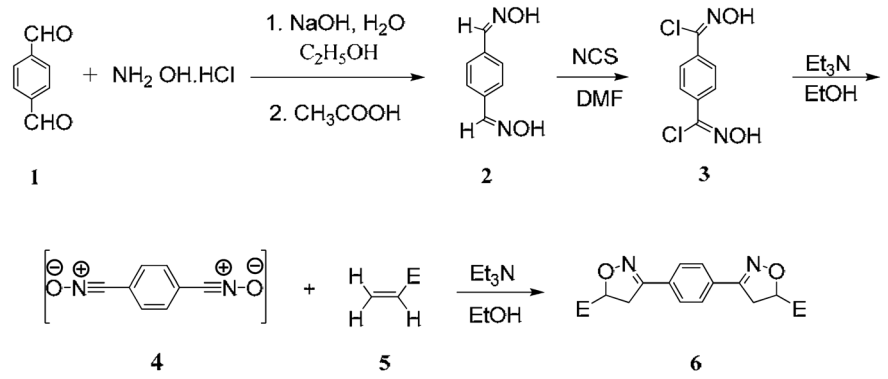
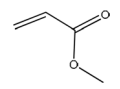
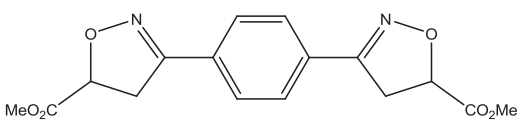
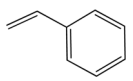
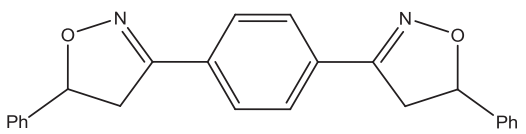
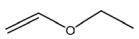
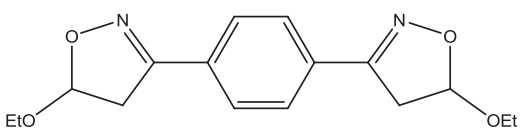
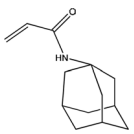
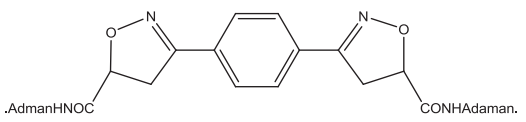
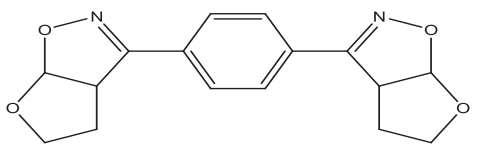
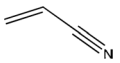
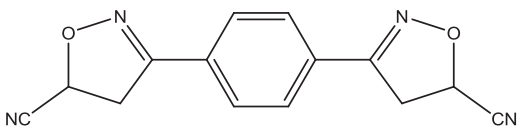


Table 1

Synthesis of 3,5-substituted di-isoxazolines.

Entry	Dipolarophile **5(a-f)**	Product **6(a-f)**	Yield (%)[a]	Melting Point °C
1			77%	169–170
2			82%	227–230
3			65%	160–162
4			70%	237–239
5			65%	227–230
6			72%	229–231

[a]Isolated yields.

Preparation of terephthaldoximechloride. Treatment of terephthaldoxime (10 mmol, in 5 mL *N, N*-dimethylformamide) with *N*-chlorosuccinimide gave terephthaldoxime chloride after 24 h (90% yields). m.p. 197–199°C; ^{1}H NMR (300 MHz, Acetone-d_6) δ (ppm):11.66 (2H, s), 7.96–7.92 (4H, s); ^{13}C NMR (300 MHz, Acetone-d_6) δ (ppm): 134.2, 134.5, 161.6; IR (KBr) ν_{max} (cm^{-1}): 3245, 3091, 1571, 1474, 822.

1,3-Dipolarcycloaddition reactions. To a solution of terephthaloxime chloride (1 mmol in 50 mL ethanol) and dipolarophile (2 mmol) was added triethylamine (4 mmol in 5 mL ethanol) dropwise over a period of 45 minutes to generate 4. The resulting mixture was stirred at room temperature for 24 h. Solid adducts were filtered off and recrystallization from ethanol gave the corresponding isoxazolines.

1,4-Bis-(methyl 4,5-dihydro-5-isoxazolecarboxylate-3-yl) benzene (5a). m.p. 168–170°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.76 (4H, s), 5.30 (2H, dd, *J* = 11.6 and 6.8 Hz), 3.80 (2H, dd, *J* = 17.4 and 11.7 Hz), 3.6 (2H, dd, *J* = 17.4 and 6.8 Hz), 3.70 (6H, s); ^{13}C NMR (300MHz, DMSO-d_6) δ (ppm) 170.3, 155.8,130.0,127.2,77.8, 52.4, 52.3; IR (KBr) ν_{max} (cm^{-1}): 3486, 3011, 2961, 1751, 1590, 1438, 1352, 1226, 1164, 1028, 833. Anal. Calcd. for $C_{16}H_{16}N_2O_6$: C, 57.83; N, 8.43; H, 4.82. Found: C, 57.90; N, 8.54; H, 4.76%.

1,4-Bis-(5-phenyl-4,5-di hydroxazole-3-yl) benzene (5b). m.p. 230–233°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.72 (4H, s), 7.38–7.26 (10H, m), 5.73 (1H, dd, *J* = 11.0 and 8.4 Hz), 3.37 (1H, dd, *J* = 16.6 and 11.0 Hz), 3.30 (1H, dd, *J* = 16.6 and 8.4 Hz); IR (KBr) ν_{max} (cm^{-1}) 3038, 2978, 2941, 1588, 1476, 1383, 1172, 1037,836; ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 155.5, 140.5, 130.9, 128.7, 128.2, 126.9, 125.8, 82.8,45.7; Anal. Calcd. for $C_{24}H_{20}N_2O_2$: C, 78.26; N, 7.61; H, 5.43. Found: C, 76.51; N, 8.15; H, 5.43%.

1,4-Bis-(4,5-dihydro-5-isoxazol-3-yl ethyl ether) benzene (5c). m.p: 160–162°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.77 (4H, s), 5.76 (2H, d, *J* = 6.7 Hz), 3.59–3.76 (4H, m), 3.5–3.6 (4H, m), 1.12 (6H, m); ^{13}C NMR (300 MHz, DMSO-d_6) δ (ppm): 156.7, 130.5, 127.1, 103.1, 62.9, 40.6,15.09; IR (KBr) ν_{max} (cm^{-1}) 3057, 2977, 2929, 1599, 1442, 1358, 1199, 1154, 1094, 1028, 844; Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.16; N, 9.21; H, 6.58 Found: C, 63.17; N, 9.21; H, 6.69%.

1,4-Bis (*N*5-tricyclo[3.3.1.1^{3,7}]dec-1-yl-4,5-dihydro-5-isoxazolecarboxamide-3-yl) benzene (5d). m.p. 237–240°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.74 (4H, s), 6.45 (2H, s), 5.05 (2H, dd, *J* = 11.0 and 6.7 Hz), 3.58-3.74 (4H, m), 2.09 (6H), 2.02 (12H), 1.69 (12H); IR (KBr) ν_{max} (cm^{-1}) 3397, 3054, 2907, 2850, 1682, 1589, 1523, 1437, 1358, 1151, 1012, 856; ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 156.5, 130.5, 127.4, 79.4, 52.0, 41.4, 39.2, 36.2, 29.4; Anal. Calcd. for $C_{34}H_{42}N_4O_4$: C, 71.57; N, 9.82; H, 7.37 Found: C, 69.50; N, 9.64; H, 7.36%.

1,4-Bis-(3a,4,5,6a-tetrahydrofuro[3,2-d]isoxazole-3-yl) benzene (5e). m.p. 227–230°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.81(4H, s), 6.29 (2H, d, *J* = 6.2 Hz), 4.45 (2H, m), 3.97 (2H, m), 3.34 (2H, m), 2.01(2H, m), 1.97(2H, m); IR (KBr) ν_{max} (cm^{-1}) 3433, 3052, 2996, 2955, 2893, 1715, 1579, 1473, 1448, 1368, 1353, 1184, 1088, 881, 834; ^{13}C NMR (300 MHz, DMSO-d_6) δ (ppm) 157.5, 129.8, 127.4, 109.2, 66.1, 50.8, 30.2; Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 64.0; N, 9.33; H, 5.33. Found: C, 63.77; N, 9.56; H, 5.33%.

1,4-Bis-(4,5-dihydro-5-isoxazolecarbonitrie-3-yl)benzene (5f). m.p. 229–231°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 7.81 (4H, s), 5.84 (2H, dd, *J* = 10.7 and 5.9 Hz), 3.89 (4H,m); IR (KBr) ν_{max} (cm^{-1}) 3055, 2973, 1594, 1431, 1354, 1168, 1038, 851; ^{13}C NMR (300 MHz, DMSO-d_6) δ (ppm) 157.1, 129.7, 127.7, 118.2, 67.2; Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; N, 21.05; H, 3.76 Found: C, 62.58; N, 20.43; H, 3.87%.

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