Use of Diisocyanates for in Situ Preparation of Nitrile Oxides: Preparation of Isoxazoles and Isoxazolines

Eric J. Kantorowski, Sean P. Brown, and Mark J. Kurth*

Department of Chemistry, University of California, Davis, Davis, California 95616

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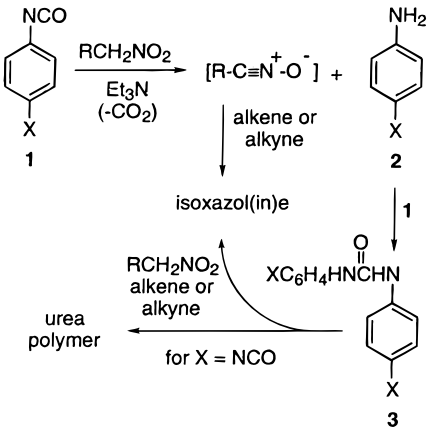
Isoxazole and isoxazoline heterocycles have been employed for a wide variety of uses in chemistry. Typically, these ring systems are derived from the [3 + 2] cycloaddition of a nitrile oxide to an alkyne or alkene, respectively.[1] The nitrile oxide 1,3-dipole is generated in situ from the corresponding primary nitroalkane[2] or hydroximoyl chloride.[3] Other methods have also been utilized.[4]

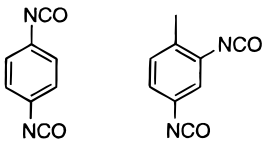
The primary nitroalkane → nitrile oxide reaction requires the use of a dehydrating agent with phenyl isocyanate (**1a**, X = H) being the most popular. It is necessary to use 2 equiv of **1a** as the second equivalent serves to trap aniline (**2**, X = H) which is formed during the course of the reaction. The resulting byproduct, 1,3-diphenylurea (**3**, X = H), exhibits only moderate solubility in organic solvents and low solubility in water (acidic, neutral, or basic). Consequently, product isolation and purification is often complicated by contamination with **3** (X = H).[5]

We have recently demonstrated[6] that polymer-bound nitrile oxide cycloaddition reactions employing phenyl isocyanate have the experimental advantage of removing the urea byproduct by simply washing the resin with solvent. This observation, coupled with our general interest[7] in the [3 + 2] cycloaddition reactions of 1,3-dipoles, and an intriguing literature report[8] prompted us to explore the use of aryl diisocyanates for generating nitrile oxides from primary nitroalkanes.

By employing 1,4-phenylene diisocyanate (**1b**) in place of phenyl isocyanate, the aniline (**2**, X = NCO) + isocyanate reaction initially gives **3** (X = NCO) and, ultimately, a polyurea which may be removed from product by simple filtration (Scheme 1). We found it necessary to employ more than the theoretical amount of diisocyanate **1b** (i.e., 1 mol equiv, Table 1) which may be attributed to reduced reactivity between **2** (X = NCO) and the growing polymer chain. The polyurea derived from **3** (X = NCO) was insoluble in the reaction solvent (THF, CH_2C1_2, or PhH), and the reaction worked well at either reflux or ambient temperatures. The dimer of $CH_3C{\equiv}N^+{-}O^-$ was a minor side product (∼5%) in some reactions even when excess dipolarophile was used (entry 4). Nitrile oxide dimers were not observed for the other primary nitroalkanes employed. When diisocyanate **4** was employed, yields were lower and the polyurea was partially soluble and thus not completely removed by filtration.

Scheme 1





The utility of **1b** ($OCNC_6H_4NCO$) is well-demonstrated in **5** → **6** (Scheme 2). In the conventional reaction (**5** + $THPOCH_2CH_2NO_2$ + C_6H_5NCO), the product (**6**) and 1,3-diphenylurea (from C_6H_5NCO) have near-identical R_f values.[6] Multiple precipitations of diphenylurea were attempted, but proved inefficient and time-consuming as did chromatographic methods of separation. Alternatively, when **1b** was employed, purification was greatly expedited. Filtration and a single chromatographic application provided pure **6** in 74% yield (Table 1, entry 14). The yield was comparable to the solution-phase results (Table 1, entry 13), but more importantly, isolation of the product was simplified.

Experimental Section

General Procedures. 1,4-Phenylene diisocyanate was purchased from Aldrich and used as received. Solvents were purified as follows: tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl; methylene chloride (CH_2Cl_2) was distilled from CaH_2; benzene was distilled from potassium. All reactions, unless otherwise stated, were conducted under an inert atmosphere of N_2. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 and 75 MHz, respectively, and chemical shifts are reported in ppm downfield from internal tetramethylsilane. Thin-layer chromatography (TLC) was performed on silica gel plates, and components were visualized by UV light or by iodine or by heating the plates after treatment with a phosphomolybdic acid reagent (1:1 in EtOH).

5-Hexyl-4,5-dihydro-3-methylisoxazole. 1,4-Phenylene diisocyanate (**1b**) (0.992 g, 6.19 mmol), nitroethane (0.150 g, 2.00 mmol), and 1-octene (0.225 g, 2.00 mmol) were dissolved in benzene (20 mL). Triethylamine (5−10 drops) was added, and

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(3) Christl, M.; Huisgen, R. *Chem. Ber.* **1973**, *106*, 3345−3367.

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(5) 1,3-Diphenylurea crystallizes from various solvents (EtOH, THF, CH_2Cl_2); however, in practice, complete crystallization is never fully realized.

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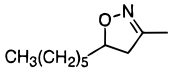
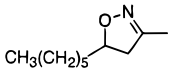
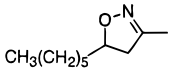
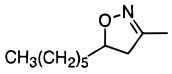
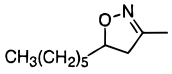
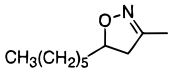
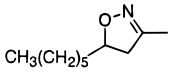
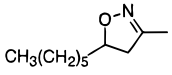
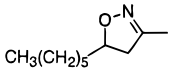
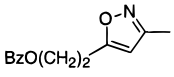
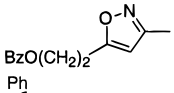
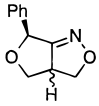
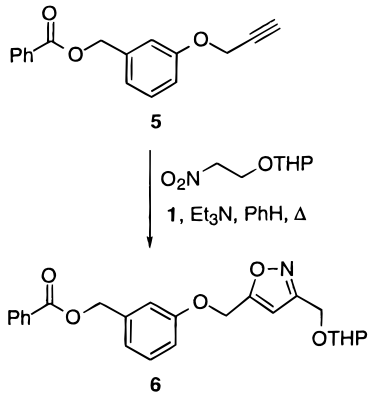
Table 1. 1,4-Phenylene Diisocyanate-Mediated Preparation of Isoxazolines and Isoxazoles

entry	reaction solvent	temperature (°C)	isocyanate (mol equiv)[a]	nitro compound[b]	dipolarophile (mol equiv)	product	yield (%)
1	THF	reflux	**1b** (1.0)	$EtNO_2$	1-octene (1.0)		31
2	THF	reflux	**1b** (4.9)	$EtNO_2$[c]	1-octene (1.0)		45
3	THF	reflux	**1b** (2.0)	$EtNO_2$	1-octene (1.0)		65
4	THF	reflux	**1b** (3.0)	$EtNO_2$	1-octene (5.0)		78
5	CH_2Cl_2	ambient	**1b** (1.0)	$EtNO_2$	1-octene (1.0)		22
6	CH_2Cl_2	reflux	**1b** (1.0)	$EtNO_2$	1-octene (1.0)		38
7	CH_2Cl_2	reflux	**1b** (2.0)	$EtNO_2$	1-octene (1.0)		61
8	PhH	reflux	**1b** (3.0)	$EtNO_2$	1-octene (1.0)		74
9	PhH	reflux	C_6H_5NCO (2.0)	$EtNO_2$	1-octene (1.0)		86
10	PhH	reflux	**1b** (1.0)	$EtNO_2$	$BzO(CH_2)C{\equiv}CH$ (1.0)		34
11	PhH	reflux	**1b** (3.0)	$EtNO_2$	$BzO(CH_2)C{\equiv}CH$ (1.0)		72
12	PhH	reflux	**1b** (3.0)	$O_2NCH_2CH(Ph)OCH_2CH{=}CH_2$[d]			88
13[e]	PhH	reflux	C_6H_5NCO (2.0)	$THPOCH_2CH_2NO_2$	**5**	**6**	73
14	PhH	reflux	**1b** (3.1)	$THPOCH_2CH_2NO_2$	**5**	**6**	74

[a] **1b** = $OCNC_6H_4NCO$; 2 −NCO/mol equiv (except entry 9). [b] 1.0 mol equiv. [c] 2.9 equiv. [d] Intramolecular 1,3-dipolar cycloaddition; 1.0 mol equiv. [e] See ref 6.

Scheme 2



the reaction mixture was heated to reflux; shortly thereafter the reaction mixture became turbid, and a precipitate was observed. After 20 h at reflux the reaction mixture was cooled, the reaction quenched with H_2O (~1 mL), and the mixture stirred for an additional 1 h. The polymer was removed by filtration, and the filtrate was dried ($MgSO_4$), filtered, and concentrated to provide 0.262 g of the nearly pure (per ^1H NMR) heterocycle which was contaminated with trace amounts of the methylnitrile oxide dimer. Column chromatography (30% EtOAc in petroleum ether) provided the known[9] isoxazoline (0.251 g, 74%): ^1H NMR δ 0.85−0.90 (m, 3H), 1.23−1.76 (m, 10H), 1.97 (s, 3H), 2.54 (dd, 1H, J = 16.8, 8.3 Hz), 2.96 (dd, 1H, J = 16.8, 9.8 Hz), 4.47−4.57 (m, 1H); ^{13}C NMR δ 13.26, 13.98, 22.48, 25.47, 29.05, 31.65, 35.21, 43.70, 80.34, 155.12.

2-(3-Methylisoxazol-5-yl)ethyl Benzoate. Following the procedure described above, **1b** (0.101 g, 0.58 mmol), nitroethane (0.044 g, 0.59 mmol), and 3-butynyl benzoate (0.281 g, 1.75 mmol) in benzene (6 mL) provided, after column chromatography (30% EtOAc in petroleum ether), the pure isoxazole (0.097 g, 72%): FTIR (thin film) 2243, 1720, 1273 cm^{-1}; ^1H NMR δ 2.25 (s, 3H), 3.19 (t, 2H, J = 6.5 Hz), 4.58 (t, 2H, J = 6.5 Hz), 5.96 (s, 1H), 7.39−7.57 (m, 3H), 7.99−8.02 (m, 2H); ^{13}C NMR δ 11.11, 26.43, 61.61, 102.43, 128.20, 129.38, 129.68, 132.90, 159.58, 165.97, 169.00; HRMS (FAB) calcd for $C_{13}H_{14}NO_3$ 232.0974, found 232.0966 (M + H).

3a,4,6,6a-Tetrahydro-3-phenylfuro[3,4-*d*]isoxazole. Following the procedure described above, **1b** (7.70 g, 48.11 mmol) and 2-nitro-1-phenyl-1-(prop-2-enyloxy)ethane (3.11 g, 15.05 mmol) in benzene (100 mL) provided, after column chromatography (33% EtOAc in hexane), the known[10] isoxazolines (4.21 g, 88%) as a 9:1 mixture of syn:anti diastereomers. Syn diastereomer: FTIR (neat) 3006, 2914, 2862, 2335, 1651, 1458, 1009, 976, 802, 754, 698 cm^{-1}; ^1H NMR δ 3.71−3.77 (m, 1H), 3.96−4.03 (m, 1H), 4.14−4.20 (m, 1H), 4.33−4.39 (m, 1H), 4.48−4.54 (m, 1H), 5.55 (s, 1H), 7.32−7.38 (m, 5H); ^{13}C NMR δ 54.55, 69.88, 73.13, 73.62, 125.77, 128.35, 128.67, 137.83, 169.96. Anti diastereomer: mp 97.0−98.0 °C; FTIR (KBr) 1491, 1450, 1036, 1026 cm^{-1}; ^1H NMR δ 3.83−3.91 (m, 1H), 3.98−4.06 (m, 1H),

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4.28−4.42 (m, 1H), 4.53−4.62 (m, 1H), 5.59 (s, 1H), 7.29−7.46 (m, 5H); ^{13}C NMR δ 55.61, 68.93, 72.72, 73.70, 126.16, 128.05, 128.23, 137.23, 170.23.

(3-((3-((2-Oxanyloxy)methyl)isoxazol-5-yl)methoxy)-phenyl)methyl Benzoate (6). Following the procedure described above, **1b** (0.762 g, 4.76 mmol), tetrahydropyranyl-2-nitroethanol (0.270 g, 1.54 mmol), and (3-(2-propynyloxy)phenyl)-methyl benzoate (0.411 g, 1.54 mmol) in benzene (35 mL) provided, after radial chromatography (30% EtOAc in hexanes), the known[6] isoxazole (0.481 g, 74%): FTIR (thin film) 1718, 1603, 1587, 1452, 1271, 1119, 1070, 1038, 714; ^{1}H NMR δ 1.50−1.86 (m, 6H), 3.54 (m, 1H), 3.86 (m, 1H), 4.61 (d, 1H, J = 12.9 Hz), 4.70 (t, 1H, J = 3.2 Hz), 4.77 (d, 1H, J = 12.9 Hz), 5.15 (s, 2H), 5.34 (s, 2H), 6.41 (s, 1H), 6.91−8.08 (m, 9H); ^{13}C NMR δ 19.19, 25.31, 30.35, 60.31, 61.46, 62.23, 66.26, 98.40, 102.93, 114.45, 114.63,121.44, 128.39, 129.71, 129.84, 130.11, 133.04, 135.56, 138.02, 158.09, 161.77, 167.91.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and FTIR spectra for 2-(3-methylisoxazol-5-yl)ethyl benzoate (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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