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Short Note

4,4′-Difluoro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-Dioxide

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Abstract: 1,2,5-Oxadiazole oxides (furoxans) are well known nitric oxide donors; among them, 4-fluorofuroxans have recently been found to be important photoinduced nitric oxide donors. In this research, it was shown that the reaction of 4,4′-dinitro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide with fluoro-containing reagents (tetrabutylammonium fluoride or cesium fluoride) selectively gave the bis-substitution product 4,4′-difluoro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide. The structure of the synthesized compound was established by elemental analysis, ^{13}C, ^{19}F-NMR and IR spectroscopy, and mass-spectrometry.

Keywords: 1,2,5-oxadiazole oxides; 4-fluorofuroxans; nucleophilic substitution; cesium fluoride; tetrabutylammonium fluoride

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1. Introduction

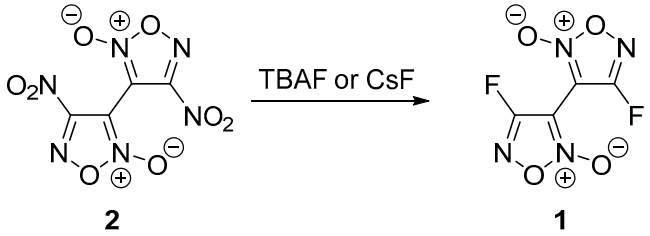
Furoxans (1,2,5-oxadiazole oxides) have been intensively investigated [1–3] as compounds that endogenously produce nitric oxide (NO), a gaseous signaling molecule, that mediates a variety of biological effects, such as vasodilation, inhibition of platelet aggregation, cell apoptosis, and neurotransmission [4]. Although many derivatives of this class are described in the literature, the furoxans with photoinduced nitric oxide donor ability are rare [5,6]. Photoinduced nitric oxide donors (PINODs) are used for the spatiotemporal control of the delivery of exogenous NO when light induces otherwise impossible reactivity without remaining in the system after completion. It has been recently found that fluorofuroxans exhibit PINOD character upon isomerization of thermodynamically stable 4-fluorine isomers to 3-isomers by UV irradiation. In the presence of a thiol cofactor as well as in its absence, 3-fluorofuroxans moderately release NO [7,8]. Herein, we report the selective synthesis of 4,4′-difluoro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **1** by the reaction of 4,4′-dinitro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **2** with tetrabutylammonium fluoride or cesium fluoride.

2. Results and Discussion

Treatment of 4,4′-dinitro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **2** with two equivalents of cesium fluoride in MeCN led to a bis-product **1** in a moderate yield of 64% (Scheme 1). The employment of tetrabutylammonium fluoride in THF, according to the reported procedure for 4-nitrofuroxans [8] at room temperature, increased the yield of 4,4′-difluoro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **1** to almost quantitative (93%). We attempted to synthesize monosubstituted 4-fluoro-4′-nitro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide. Surprisingly, when using one equivalent of tetrabutylammonium fluoride, a mixture of disubstituted derivative **1** and starting compound **2** is formed; our attempts to isolate the monosubstituted derivative were unsuccessful.

The structure of 4,4′-difluoro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **1** was fully confirmed by elemental analysis, ^{13}C, ^{19}F-NMR and IR spectroscopy, and mass-spectrometry. Elemental analysis confirm the brutto formula of compound **1**. The ^{13}C and ^{19}F-NMR

spectra of **1** showed characteristic signals for 4-fluorofuroxanes: singlet of ^{19}F (-114.2 ppm), two doublets of 4-F carbon atom 159.5 (J = 265.5 Hz), and 3-C carbon atom 93.8 (J = 31.2) [8].



2 **1**

Scheme 1. Synthesis of 4,4′-difluoro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **1**.

In conclusion, selective synthesis of 4,4′-difluoro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **1** was developed by the reaction of 4,4′-dinitro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **2** with tetrabutylammonium fluoride in THF or cesium fluoride in MeCN. The compound obtained may be considered as a potential photoinduced nitric oxide donor.

3. Materials and Methods

4,4′-Dinitro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **2** was prepared according to the published method [9]. The solvents and reagents were purchased from commercial sources and used as received. Elemental analysis was performed on a 2400 elemental analyzer (Perkin Elmer Inc., Waltham, MA, USA). Melting point was determined on a Kofler hot-stage apparatus and was uncorrected. ^{13}C and ^{19}F-NMR spectra were taken with a Bruker AM-300 machine (Bruker AXS Handheld Inc., Kennewick, WA, USA) at frequencies of 75 and 282.5 MHz, correspondingly. MS spectrum (EI, 70 eV) was obtained with a Finnigan MAT INCOS 50 instrument (Hazlet, NJ, USA). IR spectrum was measured with a Bruker "Alpha-T" instrument in KBr pellet.

Synthesis of 4,4′-difluoro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **1** (Supplementary Materials).

A solution of tetrabutylammonium fluoride hydrate (560 mg, 2 mmol) in THF (5 mL) was added to a solution of 4,4′-dinitro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **2** (260 mg, 1 mmol) in THF (5 mL). The reaction mixture was stirred for 3 h at room temperature. The solvent was distilled, the residue was extracted with CH_2Cl_2 (2 × 10 mL), washed with brine, and dried with $MgSO_4$. The solvent was removed and the residue was purified by column chromatography on silica gel (Silica gel Merck 60, eluent $CCl_4/CHCl_3$, 2:1, *v/v*). Yield 161 mg (78%), colorless oil, Rf = 0.78 ($CCl_4/CHCl_3$ 2:1). IR spectrum (KBr), ν, cm^{-1}: 1673 (C=N), 1619, 1556, 1456, 1380, 1178, 959, 819, 778, 674. ^{13}C-NMR ($CDCl_3$, ppm): 159.5 (C-4, J = 265.5 Hz), 93.8 (C-3, J = 31.2 Hz). ^{19}F-NMR ($CDCl_3$, ppm): δ −114.2. MS (EI, 70 Ev), m/z (I, %): 206 (M+, 15), 176 (M+—NO, 10), 112 (10), 86 (7), 30 (NO, 100). Anal. calcd. for $C_6F_2N_4O_4$: C, 23.31; N, 27.19. Found: C, 23.42; N, 27.33%.

A solution of cesium fluoride (304 mg, 2 mmol) in MeCN (3 mL) was added to a solution of 4,4′-dinitro-[3,3′-bi(1,2,5-oxadiazole)] 2,2′-dioxide **2** (260 mg, 1 mmol) in MeCN (3 mL). The reaction mixture was stirred for 3 h at room temperature. The solvent was distilled, the residue was extracted with CH_2Cl_2 (2 × 10 mL), washed with brine, and dried with $MgSO_4$. The solvent was removed and the residue was purified by silica gel column chromatography (Silica gel Merck 60, eluent $CCl_4/CHCl_3$, 2:1, *v/v*). Yield 132 mg (64%), colorless oil.

Supplementary Materials: Copies of ^{13}C, ^{19}F-NMR, IR, and mass-spectra for the compound **1**.

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Sample Availability: Samples of the compound **1** are available from the authors.

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