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FUROXANS AS NITRILE OXIDE PRECURSORS: CYCLOADDITION REACTIONS OF BIS(BENZENESULFONYL)FUROXAN.

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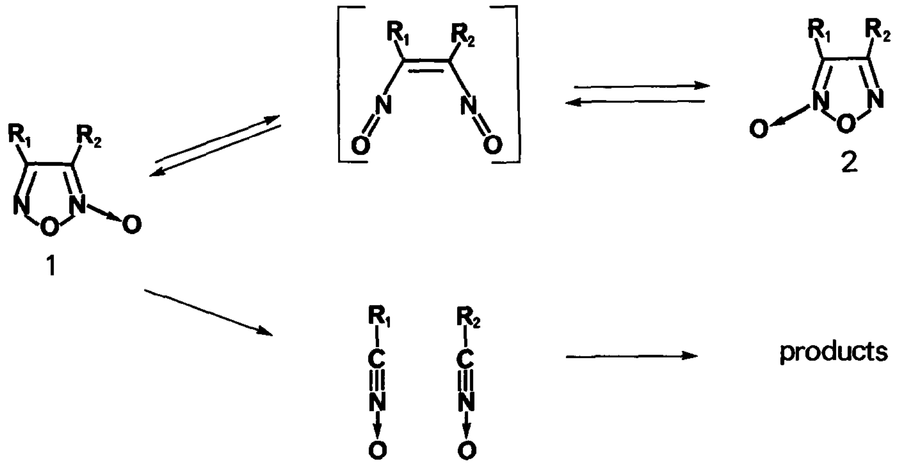
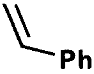
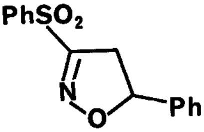
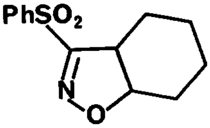
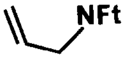
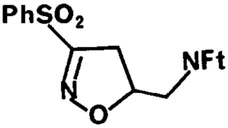
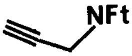
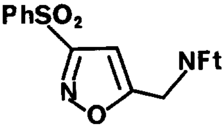
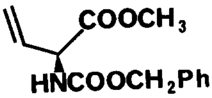
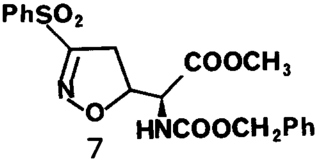
Summary: Bis(benzenesulfonyl)furoxan has been shown to undergo cycloaddition reactions with dipolarophiles in refluxing xylene to give benzenesulfonylnitrile oxide cycloadducts.

The addition of nitrile oxides to unsaturated carbon-carbon bonds is a well documented[1] procedure for the formation of isoxazoles and dihydroisoxazoles. An often troublesome competing reaction is the dimerization of the nitrile oxide to form a furoxan,with this process often being the limiting feature in the general utility of 1,3-dipolar cycloaddition reactions of certain nitriles oxides[2]. Recently several studies have been made of the behaviour of various furoxans (1) at elevated temperatures and the results can be summarized as follows: at very high temperatures (500-650°, flash vacuum pyrolysis) alkyl and aryl furoxans are fragmented to nitrile oxides which may be isolated and characterized[3]; at lower temperatures (111-257° depend on the nature of R_1 and R_2) and prolonged reaction times symmetrical alkyl, aryl and acyl furoxans have given reaction products, such as isocyanates or cycloadducts, characteristic of nitrile oxides[4]; in the temperature range 78-135° unsymmetrical furoxans undergo simple isomerization [(1)$\rightleftharpoons$(2)] with the rate of the reaction and the equilibrium constant being substituent dependent[5]. With various furoxans being readily available[4-9] either symmetrically or unsymmetrically substituted, it is of interest to ascertain their utility as precursors for



TABLE

dipolarophile	cycloadduct[13]	yield
	 3	46%
	 4	48%
	 5 mp. 148	34%
	 6 mp. 145	52%
	 7	28—50%

nitrile oxides with respect to cycloadduct formation. In this regard we have made a preliminary study with bis(benzenesulfonyl)furoxan[9] (1, $R_1=R_2=PhSO_2$) and have obtained cycloadducts as listed in the Table. A number of cycloadducts of benzenesulfonylnitrile oxide have been previously described[10] and were obtained in the traditional manner by dehydrohalogenation of the requisite bromo oxime in the presence of an excess of alkene.

Our procedure employs the dipolarophile as the limiting reagent with the reactions being conducted in xylene (0.1-0.3 M in dipolarophile) at reflux under a nitrogen atmosphere in the presence of one to four equivalents of bis(benzenesulfonyl)furoxan (an equivalent for 1 mmole of dipolarophile is 0.5 mmole of furoxan) for three to seven hours. Purification was performed by removal of the xylene under vacuum, decolourization with charcoal in ethyl acetate, then isolations of the cycloadduct by column chromatography (silica gel, hexane-ethyl acetate gradient elution) or by recrystallization. In this manner then styrene and cyclohexene reacted with one equivalent of bis(benzenesulfonyl)furoxan to give cycloadducts (3) and (4)[8] respectively which were obtained as oils, while N-allyl phthalimide and N-propargyl phthalimide gave the crystalline cycloadducts (5) and (6) respectively[13]. The assignment of the 3,5-disubstituted dihydroisoxazole structures was based on ^{1}H.m.r. spectra: (3) δ3.34 (H_{4A}, dd, J=17, 10Hz), 3.55 (H_{4B}, dd, J=17, 11Hz), 5.70 (H_5, dd, J=11, 10Hz); (5) δ3.27 (H_{4A}, dd, J=18, 7.4 Hz), 3.45 (H_{4B}, dd, J=18, 10.6 Hz), 5.10 (H_5, multiplet).

Recently the preparation of N-[benzyloxy)carbonyl]-D,L-vinylglycine methyl ester has been reported[11]. We have found this vinylglycine derivative to react under the conditions described to give the cycloadduct (7) in 28% yield when one equivalent of furoxan was employed. The yield was raised to 50% when an excess (four equivalents) of furoxan was used. Adduct (7) was obtained as an equal mixture of two diastereomers inseparable by chromatography. ^{1}H.m.r. data was similar to that described[12] for other 4,5-dihydro-5-isoxazoleacetic acid derivatives; (7) (two diastereomers) δ8.03-7.89 (2H, $PhSO_2$-), 7.77-7.42 (3H, $PhSO_2$-), 7.36 and 7.34 (5H, s, -Ph), 6.14 and 5.75 (1H, d, J=9Hz, -NH), 5.37 and 5.10 (1H, m, C_5-H), 5.08 and 5.06 (2H, s, $-CO_2CH_2Ph$), 4.60 (1H, m, $-CH-CO_2R$), 3.72 and 3.62 (3H, s, $-CO_2CH_3$), 3.80-3.22 (2H, m, H-C_4-H).

While the yields obtained by this method are only modest, the ready availability of bis(benzenesulfonyl)furoxan makes this a straightforward procedure. We are currently examining further this and other furoxans as nitrile oxide precursors in an effort to improve the yields of cycloadducts and to allow introduction of other functionalities at the 3-position of isoxazoles and dihydroisoxazoles.

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