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Alumina promoted cyclization of α-nitro-oximes: a new entry to the synthesis of 1,2,5-oxadiazoles *N*-oxides (furoxans)

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Abstract

A convenient method for the synthesis of 1,2,5-oxadiazole-*N*-oxides (furoxans) from α-nitro-ketoximes using acidic alumina as catalyst is described.

Only few years ago furoxan derivatives were found to play an important pharmacological role, as they are able to increase the cytosolic level of cGMP in human platelets,[1] to activate the rat liver soluble guanylate cyclase and to release NO when treated with thiol compounds under physiological conditions[2] resulting in a potent vasodilating effect.[3] Very recently it has also been discovered that furoxan derivatives exert anti-HIV1, antitrypanosomal and cytotoxic activities.[4–7]

Furoxans have been synthesized by oxidation of α-dioximes with sodium or *t*-butyl hypochlorite,[8,9] by thermolysis of *o*-nitro-azides, by dimerization of nitrile-*N*-oxides, by oxidation of aromatic *o*-amino-nitro derivatives and by reaction of alkenes with N_2O_3.[10,11] Unfortunately many of these procedures suffer some limitations such as difficulty of handling, high temperatures, use of strong oxidating agents and hazardous materials. Best results were obtained by treatment of readily available α-nitro-oximes or β-nitro-nitroso derivatives with polyphosphoric acid at 110°C, but there are only few examples of the application of this reaction.[12]

Surface-mediated solid phase reactions are of growing interest because of their advantages of ease of set-up, mild conditions, rapid reactions, selectivity, increased yields, high purity of compounds and low cost compared with their homogeneous counterpart.[13–21] Based on our previous experience in the use of alumina as the solid surface,[22–27] we found that acidic alumina

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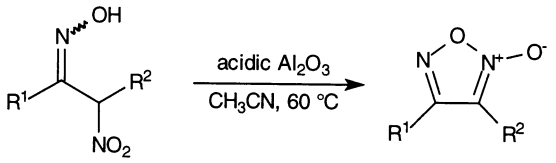
is an excellent heterogeneous catalyst for the conversion of α-nitro-oximes into their corresponding 1,2,5-oxadiazoles *N*-oxides (furoxans) (Scheme 1).



Scheme 1.

The reaction was carried out by adding a solution of the α-nitro-oxime in acetonitrile to a suspension of acidic alumina (Brockmann I) in acetonitrile at 60°C. The reaction takes from 1 to 5 hours (see Table 1) and after a simple work-up affords furoxan derivatives in good yield from both cyclic and acyclic α-nitro-oximes. All furoxans showed absorptions, in IR their spectra, in the range of 1600–1620 cm^{-1} and a typical fragmentation pattern in their mass spectra (M^+, M^+-30, M^+-60).[28] The mechanism of the reaction probably involves an initial tautomeric equilibrium of the α-nitro-oxime with the β-nitro-nitroso isomer and subsequent elimination of water with the formation of the furoxan ring system.[4,12]

In summary, acidic alumina, has proved to be a useful reagent for the preparation of furoxans from readily available α-nitro-oximes and the reported method represents the first example of the application of heterogeneous catalysis in this area.

Experimental. Typical procedure: To a well stirred suspension of acidic Al_2O_3 (4 g) in acetonitrile (25 ml) a solution of α-nitro ketoxime[29] (4 mmol) in acetonitrile (5 ml) was added and the resulting mixture was stirred at 60°C for the appropriate time (see Table 1). The mixture was filtered under vacuum and the solution was evaporated under reduced pressure. The crude material was purified by flash chromatography on SiO_2 (eluent CH_2Cl_2) affording the desired furoxan.

4,5,6,7-Tetrahydro-2,1,3-benzoxadiazol-*N*-oxide (**1b**): yellow oil; IR (CH_2Cl_2): $\nu = 1620$ cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.65–1.82 (m, 4H), 2.42–2.51 (m, 2H), 2.63–2.75 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 156.20, 113.04, 22.06, 21.21, 20.99, 19.38; GC/MS: $M^+ = 140$.

6-(*tert*-Butyl)-4,5,6,7-tetrahydro-2,1,3-benzoxadiazol-*N*-oxide (**2b**): yellow oil; IR (CH_2Cl_2): $\nu = 1625$ cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (s, 9H), 1.05–3.02 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 156.33, 114.11, 44.22, 32.58, 27.07, 23.32, 22.52, 21.22; GC/MS: $M^+ = 196$.

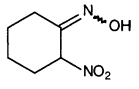
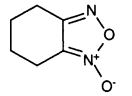
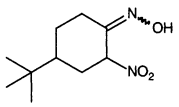
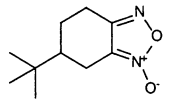
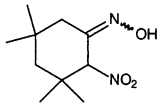
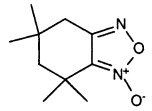
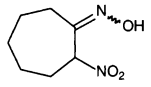
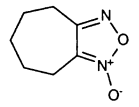
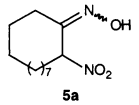
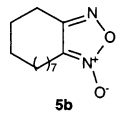
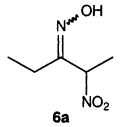
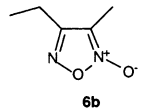
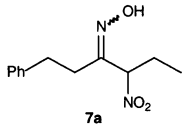
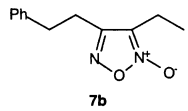
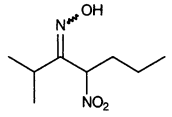
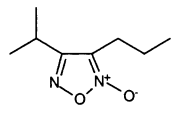
5,5,7,7-Tetramethyl-4,5,6,7-tetrahydro-2,1,3-benzoxadiazol-*N*-oxide (**3b**): yellow oil; IR (CH_2Cl_2): $\nu = 1620$ cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10, 1.13, 1.17, 1.39 (4s, 12H), 1.68 (s, 2H), 2.52 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 155.31, 117.46, 46.21, 42.15, 39.87, 33.22, 28.12, 26.65, 25.99, 25.45; GC/MS: $M^+ = 196$

5,6,7,8-Tetrahydro-4*H*-cyclohepta[*c*][1,2,5]oxadiazol-*N*-oxide (**4b**): yellow oil; IR (CH_2Cl_2): $\nu = 1620$ cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18–1.63 (m, 6H), 2.32–2.47 (m, 2H), 2.61–2.73 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 153.67, 115.21, 28.10, 27.42, 26.29, 26.01, 24.79; GC/MS: $M^+ = 154$.

4,5,6,7,8,9,10,11,12,13-Decahydrocyclododeca[*c*][1,2,5]oxadiazol-*N*-oxide (**5b**): yellow oil; IR (CH_2Cl_2): $\nu = 1620$ cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.05–1.60 (m, 16H), 2.07–2.26 (m, 2H), 2.48–2.61 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 152.89, 111.13, 25.79, 24.94, 24.75, 24.63, 24.62, 23.49, 23.19, 22.66, 21.94; GC/MS: $M^+ = 224$.

3-Ethyl-4-methyl-1,2,5-oxadiazol-*N*-oxide (**6b**): yellow oil; IR (CH_2Cl_2): $\nu = 1610$ cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32–1.45 (t, 3H, $J = 7.6$ Hz), 2.17 (s, 3H), 2.65–2.78 (q, 2H, $J = 7.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 159.17, 112.76, 19.27, 10.62, 7.51; GC/MS: $M^+ = 128$.

Table 1
Al_2O_3 promoted synthesis of furoxans from α-nitro-oximes

Substrate	Product	Time (h)	Yield %[a]
 **1a**	 **1b**	1	93
 **2a**	 **2b**	1	93
 **3a**	 **3b**	5	75
 **4a**	 **4b**	3	89
 **5a**	 **5b**	3	82
 **6a**	 **6b**	3	91
 **7a**	 **7b**	4	83
 **8a**	 **8b**	4	85

[a]Yields of pure isolated products, characterized by IR, GC-MS, ^{1}H NMR and ^{13}C NMR.

3-Ethyl-4-phenethyl-1,2,5-oxadiazol-*N*-oxide (**7b**): yellow oil; IR (CH_2Cl_2): $\nu = 1615$ cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.94–1.05 (t, 3H, $J = 6.5$ Hz), 2.12–2.95 (m, 6H), 7.05–7.20 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 155.84, 141.11, 128.56, 128.26, 126.32, 109.43, 32.44, 31.93, 29.44, 8.61; GC/MS: $M^+ = 218$.

4-Isopropyl-3-propyl-1,2,5-oxadiazol-*N*-oxide (**8b**): yellow oil; IR (CH_2Cl_2): $\nu = 1615$ cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.89–1.07 (t, 3H, $J = 7.1$ Hz), 1.32–1.42 (d, 6H, $J = 7.0$ Hz), 1.75–3.02 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 150.02, 114.11, 26.48, 24.49, 20.39, 18.88, 13.72; GC/MS: $M^+ = 170$.

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