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THE FORMATION OF FUROXAN-3,4-DICARBOXAMIDES FROM NITROACETAMIDES

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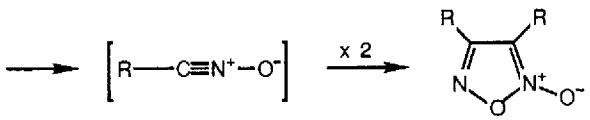
Summary : Secondary and tertiary nitroacetamides are converted by treatment with thionyl chloride alone into furoxan-3,4-dicarboxamides.

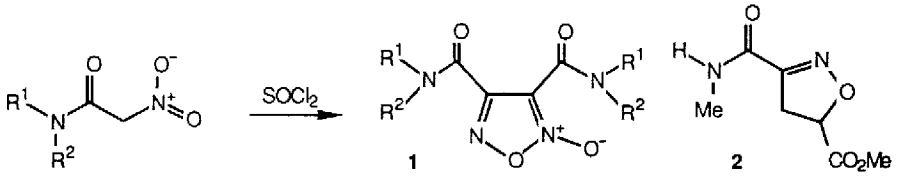
It is well known[1] that nitrile oxides dimerise, unless intercepted by a dipolarophile, and thus produce 3,4-disubstituted 1,2,5-oxadiazole-2-oxides (furoxans) (Scheme 1). Nitrile oxides have been generated in a number of ways : the most frequently used methods involve the direct oxidation of syn



Scheme 1

aldoximes with hypohalites[2] or lead tetracetate[3], dehydrohalogenation[4] of hydroxyiminoyl chlorides (1-chlorooximes)[5], and the triethylamine-catalysed dehydration of nitromethylene precursors (RCH_2NO_2) using phenyl isocyanate[6]. Of direct relevance to our results below are some isolated reports of the production of nitrile oxides from nitro-containing precursors under acidic conditions, or using other, base-catalysed dehydrating conditions, thus boron trifluoride/acetic anhydride at 120°C[7] or concentrated sulphuric acid at -5°C[8] (in each case only with ethyl nitroacetate), hot mineral acids[9] (with 2-nitroketones). and the combinations sulphur trioxide/triethylamine[10], acetic anhydride/triethylamine,[11a] and phosphorus oxychloride/triethylamine[11] generate nitrile oxides as intermediates.

In an attempt to convert N-methyl nitroacetamide into its iminochloride[12,13] it was treated at room temperature with phosphorus oxychloride; none of the desired product was obtained but instead the furoxan-3,4-dicarboxamide **1a** was produced; thionyl chloride gave the same product, more cleanly. That there was a nitrile oxide intermediate involved was demonstrated by trapping : addition of methyl acrylate to the thionyl chloride reaction mixture led to the isolation of dipolar cycloadduct, isoxazoline **2**, in moderate yield.

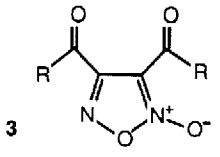


The simplicity and mildness of this method for the formation of furoxan **1a** led us to explore its generality. A range of nitroacetamides were subjected to thionyl chloride and in each case the corresponding furoxan **1** was obtained (Table) with the exception that from nitroacetamide itself, no product could be isolated.

Table

Furoxan-dicarboxamide	R^1	R^2	Yield	m.p (°C)
1a	H	Me	50	163-65
1b	H	H	-	
1c	Me	Me	22	125-27
1d	H	Ph	52	190-93
1e	$(CH_2)_4$		51	99-104

In looking to expand the range of nitro-compounds to which this dehydrative procedure might apply we treated 2-nitro-1-phenylethanone and ethyl nitroacetate with thionyl chloride. The ketone was smoothly converted, at room temperature, into furoxan **3a**, however with the ester no reaction took place; indeed ethyl nitroacetate could be recovered from reflux with thionyl chloride.



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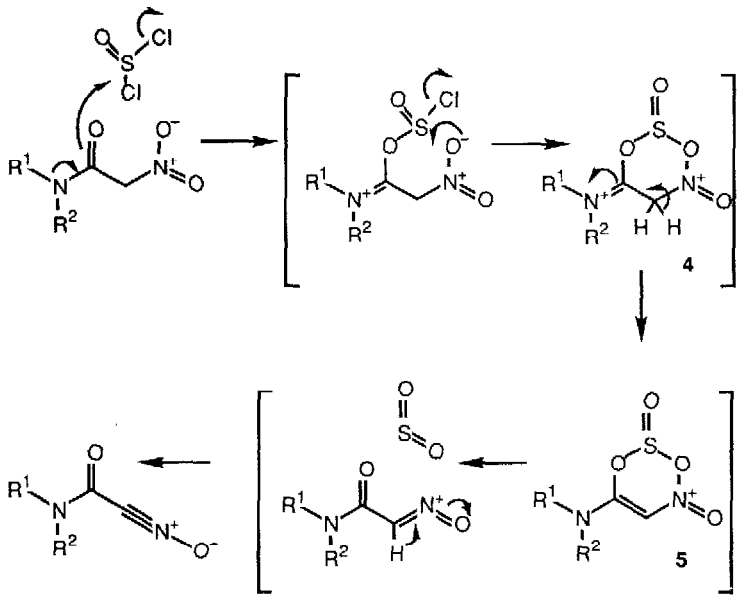
R	
a	Ph
b	OEt

The formation of diethyl furoxan-3,4-dicarboxylate, **3b** (46 %), could be achieved however, and at room temperature, by incorporating a mol equivalent of pyridine into the reaction. Since the ester methylene is more acidic that the amide methylene it was clear that the relative acidities of the methylene groups in the nitroacetate and nitroacetamides could not be the factor allowing the latter to react easily, and without the need for added base. We suggest that the amide reactivity can be explained (Scheme 2) by an initial interaction of the reagent with amide carbonyl, followed by intramolecular delivery of sulfur to nitro-group oxygen. This would produce an intermediate **4** with a sufficiently acidic central methylene to obviate the need for added base to produce **5**. One may then visualise an electrocyclic loss of sulphur dioxide from **5** leading on to the nitrile oxide and thence the furoxan.



Scheme 2

Typical Procedure

2-Nitro-1-phenylethanone (227 mg) was dissolved in thionyl chloride (15 ml) and the solution stirred at room temperature for 16 h (most reactions were complete after 0.5 h; overnight reaction caused no deterioration in quality or yield of product). Evaporation of the thionyl chloride under reduced pressure, addition of aqueous $NaHCO_3$ and extraction of product with $CHCl_3$ gave pure furoxan, **3a** (163 mg; 80%), as a colourless oil which crystallised, m.p. 80-85°C (87°C[9b]).

References and Footnotes

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12 Our interest in this halide was a potential precursor to MeNH(MeS)C:CHNO$_2$, an intermediate useful for the synthesis of ranitidine. It was reported[14] that the iminochloride will react directly with appropriate amine to afford ranitidine.

13 The iminochloride has been reported[14] only once, in the Patent literature, existing as its enamine tautomer, MeNH(Cl)C:CHNO$_2$, and synthesised by reaction of 2,2-dichloronitroethene with methylamine. We are grateful to Dr. A. Alcaide for sending us details for its preparation.

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