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## Isoxazoline derivatives from activated primary nitrocompounds and tertiary diamines

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Abstract—Activated nitrocompounds, in the presence of dipolarophiles and a tertiary diamine (e.g., DABCO), undergo dehydration to afford directly isoxazoline derivatives, formal cycloadducts of nitrile oxides; this mild procedure is very efficient for the synthesis of the reported isoxazolines.

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Primary nitrocompounds have become a common source of nitrile oxides since their dehydration with phenylisocyanate was first reported.<sup>1</sup> Several other dehydrating procedures subsequently described include treatment with strong acids or with other acylating agents. 'Activated' primary nitrocompounds, that is, those bearing an EWG geminal to the nitro group, are reported to undergo dehydration, too, by reaction with acids (sulfuric acid<sup>2</sup> or PTSA<sup>3-6</sup>) or in acylating condi-tions (aryl-sulfonyl chloride,<sup>7,8</sup> acetyl chloride,<sup>9</sup> ethyl chloroformate,<sup>8</sup> isocyanates<sup>10</sup>) or even on severe heating:10 cycloadducts are produced in the presence of dipolarophiles. Some activated nitrocompounds have also been reported to give the expected cycloadducts on treatment with an excess of Ce(III) ammonium nitrate in the presence of dipolarophiles.<sup>11</sup> Most reactions are carried out at elevated temperatures. The use of di-tert-butyl dicarbonate  $(Boc_2 \hat{O})^{12}$  or 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)<sup>13</sup> and catalytic amounts of N,N-dimethylaminopyridine (DMAP) allows the dehydration of nitroalkanes under much milder conditions.

Here we report the synthesis of isoxazoline derivatives from activated primary nitrocompounds (1a-d) and

dipolarophiles under mild conditions, by treatment with amines. Only tertiary amines can be used, since activated nitrocompounds are known to be cleaved by other amines.<sup>14</sup> As soon as these nitrocompounds are mixed in chloroform with tertiary amines, the salt is produced, as evidenced by <sup>1</sup>H NMR spectroscopy and as expected from their acid strength:<sup>15</sup> **1a**  $pK_a(H_2O) = 5.1$ ; **1b**,  $pK_a(H_2O) = 5.19$ ; **1c**,  $pK_a(H_2O) = 5.82$ ; **1d**,  $pK_a(MeOH H_2O$  = 5.69. With triethylamine (TEA), the addition of a dipolarophile such as norbornene (3) or styrene (4) causes the slow production of the dehydrated adducts 6a-b and 7a-b from nitroacetone (1a) as well as benzoylnitromethane (1b). In the same conditions, ethyl nitroacetate (1c) and phenylsulfonylnitromethane (1d) do not react with dipolarophiles 3 and 4. However, if tertiary diamines such as 1,4-diazabicyclo[2.2.2]octane (DABCO, 2) or N, N, N', N'-tetramethylethylenediamine (TMEDA) are employed, not only cycloadducts 6a-b and 7a-b, but 6c and 7c from 1c, as well as 6d from 1d are obtained, too, with the appropriate dipolarophiles. An induction period has been observed; for the reaction to go to completion, prolonged warming at 60 °C is required. Results are summarised in Table 1, together with the yields obtained with other procedures, shown for comparison.

Our method directly converts activated nitroalkanes 1a-d into isoxazolidines 6a-d and 7a-c with higher yields and an easier procedure compared to those previously reported. Normally, these procedures require an excess of dipolarophile to reduce the dimerisation of

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**D**<sup>1</sup>

Tab	le 1	. 1	Reacti	ion (	of son	ne n	itroal	kanes	with	di	ipol	arop	hil	es ii	n the	e p	resence	of	tertiar	y d	iamines <sup>1</sup>	0

		R <sup>1</sup> N 1a-d	$O_2 + R^2$	$R^3 \longrightarrow R^2$	N N	
Product <sup>a</sup>	$\mathbf{R}^1$	$\mathbb{R}^2$	R <sup>3</sup>	Conv. (%) <sup>b</sup>	Yield (%) <sup>c</sup>	Other methods (%)
6a	MeCO	L	7	Quantitative	(100) 90	_
7a	MeCO	Ph	Н	74	(77) 60	26 <sup>6</sup>
6b	PhCO	L	7	Quantitative	(91) 90 <sup>d</sup>	62, 83 <sup>17,18</sup>
7b	PhCO	Ph	Н	Quantitative	(75) 75 <sup>e</sup>	21; <sup>17,19</sup> 70; <sup>6,17</sup> 50; <sup>17,20</sup>
6c	EtOCO	L	$\sum_{i=1}^{n}$	Quantitative	(100) 100	83 <sup>17,21</sup>
7c	EtOCO	Ph	Н	Quantitative	(89) 91	66 <sup>21</sup>
6d	PhSO <sub>2</sub>	L	$\sum_{i=1}^{n}$	38	(39) 35	20-28 <sup>22</sup>
7d	PhSO <sub>2</sub>	Ph	Н		_	18-25 <sup>22,23</sup>

<sup>a</sup> General conditions: dipolarophile (40 mg, 0.425 mmol), nitrocompound (1.06 mmol), base (0.216–0.318 mmol) in CHCl<sub>3</sub> (1.4 mL) at 60 °C (sealed tube), 20–40 h.

<sup>b</sup> Conversion of dipolarophile determined by <sup>1</sup>H NMR.

<sup>c</sup> Isolated yields, based on dipolarophile, spectroscopic yields (in parentheses) determined by <sup>1</sup>H NMR using an internal standard.

<sup>d</sup> Quantitative yield including a side product (10%).

<sup>e</sup> Quantitative yield including a side product (25%).

the intermediate nitrile oxide. For example the reaction of styrene (4) with nitroacetone (1a) in the presence of DABCO gives isoxazolidine 7a in one step and 60% yield as compared to the lower yield (26%) of the reported transformation of **1a** into **7a** using a nitronic ester intermediate. Furthermore the reaction of styrene (4) with ethyl nitroacetate (1c) in the presence of DAB-CO gives isoxazolidine 7c in one step and 91% yield (66% yield in previously reported synthesis). Cycloadducts can be easily isolated from the reaction mixture after usual work-up and the amine completely recovered. However, in the reactions of benzoylnitromethane (1b) minor side products were obtained and the isolation of the adducts required an additional chromatographic separation. These side products are not isomers of adducts 6b and 7b and their structure is at present under investigation.

In the extensive literature on dehydration of primary nitro compounds (hinted at the beginning) the identification of nitrile oxides as possible intermediates has received the attention of several authors.<sup>24,6</sup> In the absence of dipolarophile, either the spectroscopic identification of the nitrile oxide<sup>25</sup> or the isolation of its dimer, the corresponding furoxan.<sup>2,3</sup> have been taken as evidence for the formation of the nitrile oxide as an intermediate. When furoxan is not detected in the absence of dipolarophile, the problem actually exists and it has been discussed in detail.<sup>24,6</sup> In the present reaction, does the dehydration step precede or follow cycloaddition? In other words, is the nitrile oxide a reaction intermediate? Minor amounts of furoxan 8a have been observed beside adducts 6a and 7a only in the reactions of nitroacetone 1a, while furoxans were not detected in the reactions of 1b-d, even in the absence of dipolarophile.



While cycloadditions of nitronic esters are widely described in the literature,<sup>26</sup> reports of nitronate or nitronic acid cycloadditions are not common.<sup>27</sup> In fact, the cycloadducts produced in the presence of strong acids usually derive from intermediate nitrile oxides.<sup>6</sup> Recently an intramolecular 1,3-dipolar cycloaddition of nitronic acids to unactivated double bonds has been reported.<sup>28</sup>

Scheme 1 is based on the observations reported above: a pre-equilibrium is slowly established between the nitronate (possibly H-bonded to the ammonium ion) and the dipolarophile, thus accounting for the induction period. Adduct 5 is assumed to be in equilibrium with its tautomers and with the conjugated acid 5' (nitronic acid cycloadduct). The dehydration, requiring heterolysis of the hexocyclic N–O bond, can then be explained by the interaction of one of the N-hydroxy species 5 or 5' with the ammonium ion. The success of the reaction with tertiary diamines when triethylamine fails, deserves a comment. The  $pK_a$  values for TEA and DABCO are quite close, in water as well as in other solvents, even though their ion-pair basicity differs.<sup>29</sup> Both data, however, refer to equilibrium conditions (thermodynamic basicity), while the irreversible dehydration step leading to the final cycloadducts 6 and 7 depends on the Transition State (TS): the release of a proton from the ammonium ion to deliver water is much easier for the diamine that loses a proton from one N atom while binding another proton to the other N atom (the TS is illustrated with curly arrows). Further investigations are necessary to add support to this mechanism.

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