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Divergent Behaviour in the Isocyanate-induced and Thermal Generation of Nitrile Oxides from Ethyl Nitroacetate

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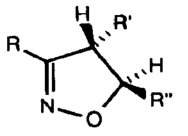
Abstract: Ethyl nitroacetate is a source of three nitrile oxides: thermolysis results in elimination of ethanol and carbon dioxide to generate formonitrile oxide ($HC{\equiv}N^{+}{-}O^{-}$), whereas treatment with phenyl isocyanate and a base gives either ethoxycarbonylformonitrile oxide ($EtO_2CC{\equiv}N^{+}{-}O^{-}$) or cyanoformanilide *N*-oxide ($PhNHCOC{\equiv}N^{+}{-}O^{-}$) depending on the reaction conditions.

One of the most versatile methods for the generation of nitrile oxides involves dehydration of nitromethyl compounds. Reagents that have been used for this purpose include phosphorus oxychloride,[1,2] *p*-toluenesulphonic acid,[3] *p*-toluenesulphonyl chloride,[4] and isocyanates with triethylamine.[5,6] While examining routes to ethoxycarbonylformonitrile oxide (**1**) we have observed that ethyl nitroacetate can provide a source, not only of the target ester nitrile oxide **1**, but also under appropriate conditions of two other nitrile oxides: formonitrile oxide (fulminic acid, **2**) and cyanoformanilide *N*-oxide (**3**).

$EtO_2C{-}C{\equiv}N^{+}{-}O^{-}$	$H{-}C{\equiv}N^{+}{-}O^{-}$	$PhNHCO{-}C{\equiv}N^{+}{-}O^{-}$
1	**2**	**3**

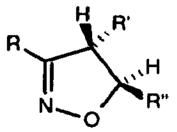
Treatment of ethyl nitroacetate with tolylene 2,4-diisocyanate (TDI) and a catalytic amount of triethylamine in 1,2-dichloroethane generated the expected ethoxycarbonylformonitrile oxide (**1**) which, in the presence of alkenes, was trapped as its 2-isoxazoline (4,5-dihydroisoxazole) cycloadducts **4**. For example, reaction with *trans*-dec-5-ene afforded *trans*-4,5-dibutyl-3-ethoxycarbonyl-2-isoxazoline (**4a**) in 48% yield.[7] The same nitrile oxide was also formed when ethyl nitroacetate was treated with *p*-toluenesulphonyl chloride/potassium carbonate/18-crown-6[4] and, in the presence of dec-1-ene, isoxazoline **4b** was isolated; in this case, however, the yield was low (16%) despite the higher reactivity of the dipolarophile.



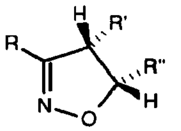
4a $R = CO_2Et, R' = R'' = Bu$
4b $R = CO_2Et, R' = H, R'' = (CH_2)_7CH_3$

In contrast, when an equimolar amount of potassium carbonate was used instead of catalytic triethylamine the reaction of ethyl nitroacetate with phenyl isocyanate yielded α-ethoxycarbonyl-α-nitroacetanilide [$PhNHCOCH(NO_2)CO_2Et$, **5**) as previously reported.[8-10] Subsequent thermolysis of this compound resulted in expulsion of ethanol and decarboxylation to give cyanoformanilide *N*-oxide (**3**), which could also be trapped as its 1,3-dipolar cycloadducts. Heating precursor **5** with *trans*- and *cis*-hex-3-enes in mesitylene under reflux (~165 °C) for 10 hours afforded *trans*- and *cis*-4,5-diethyl-3-anilinocarbonyl-2-isoxazolines (**4c**) and (**6a**) in 50% and 40% yields respectively. Other alkenes reacted similarly[11] and dec-5-yne gave the corresponding dibutylisoxazole **7** (42%). The structures of the products were established from their analytical and spectroscopic properties.[12] The isoxazolines all showed characteristic AX or ABX ^1H NMR signals for 4-H and 5-H at 3.2-3.5 and 4.2-4.6 ppm respectively, and ^{13}C NMR peaks at 154-156 (C-3), 37-51 (C-4) and 84-90 ppm (C-5). Using phenylene 1,4-diisocyanate rather than phenyl isocyanate yielded *p*-phenylene diamide derivative **8**, which was used as to prepare adducts of di(nitrile oxide) **9**.[13] Thermolysis with *cis*-dec-5-ene and dec-1-ene afforded, respectively, bis-isoxazolines **10** and **11**.

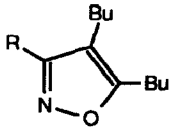
The occurrence of two divergent pathways in the reactions of ethyl nitroacetate is attributed to the ambident nature of the intermediate nitronate anion. With equimolar potassium carbonate in toluene attack on the isocyanate is by the carbon of the nitronate, whereas in 1,2-dichloroethane with catalytic triethylamine reaction takes place at the oxygen terminus (Scheme).



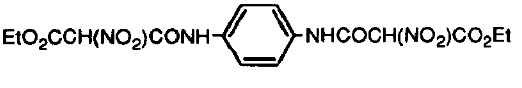
4c R = PhNHCO, R' = R" = Et
4d R = PhNHCO, R' = R" = Bu
4e R = PhNHCO, R' = R" = $(CH_2)_5CH_3$
4f R = PhNHCO, R' = H, R" = $(CH_2)_7CH_3$
4g R = PhNHCO, R' = H, R" = $(CH_2)_{11}CH_3$
4h R = H, R' = R" = Bu
4i R = R' = H, R" = $(CH_2)_7CH_3$



6a R = PhNHCO, R' = R" = Et
6b R = PhNHCO, R' = R" = Bu
6c R = H, R' = R" = Bu



7 R = PhNHCO



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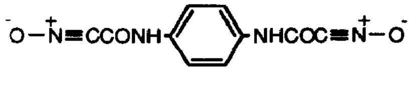

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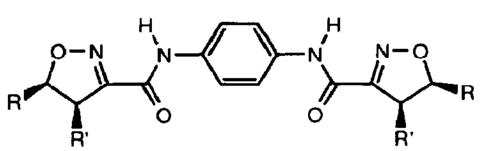
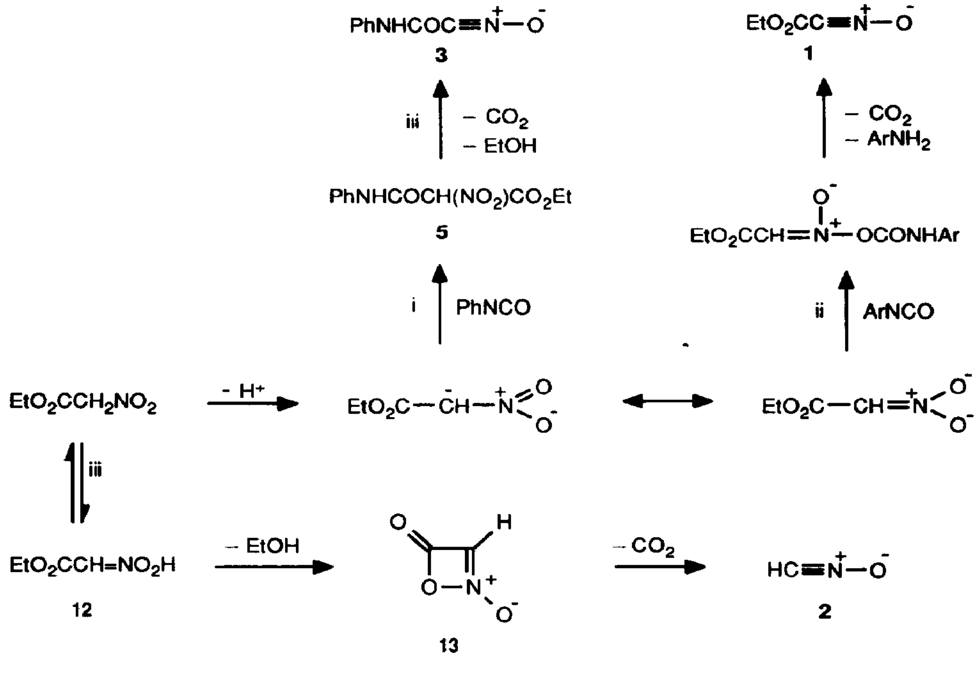


10 R = R' = Bu
11 R = Bu, R' = H

Finally we have found that ethyl nitroacetate can also be used as a source of fulminic acid, the parent nitrile oxide. Thermolysis in the absence of isocyanate of a 1:1 mixture of ethyl nitroacetate and *trans*-dec-5-ene in mesitylene (reflux, 10 h) afforded *trans*-4,5-dibutyl-2-isoxazoline (**4h**) (36%) as a colourless oil. The product was identified by its characteristic NMR spectra. The ^1H NMR spectrum shows, in addition to signals for the butyl substituents at the 4- and 5-positions, a distinctive absorption at 7.0 ppm for the proton at the 3-position with a small coupling (1.7 Hz) to 4-H. The chemical shifts for 4-H (2.8 ppm) and 5-H (4.3 ppm) are typical of 4,5-disubstituted 2-isoxazolines. In the ^{13}C NMR spectrum there are peaks at 149.5, 53.7 and 84.3 ppm which are characteristic for C-3, C-4 and C-5 of the isoxazoline ring. Dec-1-ene and *cis*-dec-5-ene reacted similarly.[14] The reaction pathway (Scheme) is assumed to be similar to that proposed by Shimizu *et al*[3,10] for the formation of ester nitrile oxide **1** from diethyl nitromalonate and of alkyl nitrile oxides from α-substituted nitroacetates, *ie* involving initial loss of ethanol from *aci*-nitro tautomer **12**, followed by extrusion of carbon dioxide from the resulting oxazetinone *N*-oxide **13**. This represents a novel approach for generating formonitrile oxide which differs markedly from traditional methods based on fulminate salts,[15] the dehydroiodination of formohydroximoyl iodide (HCI=NOH),[16] or the hydrolysis of trimethylsilylformonitrile oxide.[17] It has the advantage of affording the cycloadducts, albeit in low to moderate yields (*ca* 20-40%) with such unreactive dipolarophiles, in one step from a readily accessible starting material.



Scheme

Reagents and conditions: (i) K_2CO_3, toluene, 60-65 °C, 6 h; (ii) Et_3N, $ClCH_2CH_2Cl$, reflux, 1.5 h; (iii) mesitylene, reflux, 10 h.

References and Notes

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7. A solution of ethyl nitroacetate (10 mmol) in 1,2-dichloroethane (5 ml) was added over 1.5 h to a solution of *trans*-dec-5-ene (35 mmol), Et_3N (5 mmol) and TDI (25 mmol) in 1,2-dichloroethane under reflux. After cooling and dilution with Et_2O (5 ml), 1,2-diaminoethane (30 mmol) was added dropwise to remove unreacted isocyanate. The resulting polymeric urea was removed by filtration, the filtrate concentrated and chromatographed (silica, hexane-Et_2O/9:1) to afford isoxazoline **4a** as a clear oil (Found: *m/z* 256.19128. $C_{14}H_{25}NO_3$ requires M+1 256.19126); ν_{max}/cm^{-1} (film) 1720 (C=O); selected NMR data: δ_H/ppm ($CDCl_3$, 200 MHz) 4.42 (1 H, m, 5-H), 4.31 (2 H, q, *J* 7.0 Hz, OCH_2), 3.08 (1 H, ddd, *J* 8.9, 5.1, 3.6 Hz, 4-H), 1.34 (3 H, t, *J* 7.0 Hz, CH_3); δ_C/ppm ($CDCl_3$, 50 MHz) 153.69 (C-3), 88.9 (C-5), 51.17 (C-4).
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11. The procedure is illustrated for the preparation of isoxazole **7**: Heating a mixture of α-ethoxycarbonyl-α-nitroacetanilide (**5**)[8] (0.79 mol) and dec-5-yne (0.79 mol) in mesitylene (5 ml) under reflux for 10 h followed by dry flash chromatography (silica, hexane-Et_2O/4:1) of the product yielded isoxazole **7** as a pale yellow liquid (Found: *m/z* 301.19160. $C_{18}H_{24}N_2O_2$ requires 301.19159); ν_{max}/cm^{-1} (film) 3300-3400 (NH), 1690 (C=O); δ_H/ppm ($CDCl_3$, 360 MHz) 8.57 (1 H, s, NH), 7.1-7.6 (5 H, m, PhH), 2.74 (2 H, t CH_2Pr), 2.65 (2 H, m, CH_2Pr), 1.2-1.7 (8 H, m CH_2), 0.95 (3 H, t, CH_3), 0.92 (3 H, t, CH_3). Isoxazolines **4c** (50%), **4d** (36%), **4e** (20%), **4f** (21%), **4g**[10] (31%), **6a** (20%) and **6b** (19%) were prepared similarly.
12. The elemental compositions of all new compounds were established by combustion analysis and/or high resolution mass spectrometry.
13. It is presumed that the bis-cycloadducts are formed by stepwise generation and reaction of the individual nitrile oxide moieties rather than *via* the di(nitrile oxide) itself.
14. The procedure is illustrated for the preparation of isoxazoline **6d**: A solution of ethyl nitroacetate (10 mmol) and *trans*-dec-5-ene (10 mmol) in mesitylene (20 ml) was heated under reflux for 20 h. Concentration of the mixture and chromatography (silica, hexane-Et_2O/4:1) afforded **6c** (19%) as a clear liquid (Found: *m/z* 184.17013. $C_{11}H_{21}NO$ requires M+1 184.17013). **6a** (40%) and **6b** (20%) were prepared similarly.
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