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Ring opening of 1,1-dinitrocyclopropane by addition of C, N, O and S nucleophiles

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Abstract—Nucleophilic ring opening of 1,1-dinitrocyclopropane was studied with diverse C, N, O and S nucleophiles. A series of 3-X-substituted-1,1-dinitropropanes was obtained. Weak nucleophilic tertiary amines were also active in this reaction and afforded zwitterionic compounds.

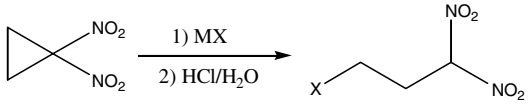
It is well known that cyclopropanes activated by two geminal electron-withdrawing substituents are capable of undergoing ring-cleavage reactions with various nucleophiles.[1] This transformation is known as the homologous version of the classical Michael addition and has been widely applied in organic synthesis for the formation of functionalized molecules with carbon skeletons, for example, those found in natural products.[1–4]

Recently we reported the first synthesis of 1,1-dinitrocyclopropane **1** by the reaction of trinitromethane and diazomethane.[5] Compound **1** is a novel, unique doubly activated cyclopropane, so we have studied its reactivity towards a wide range of C, N, O and S nucleophiles.

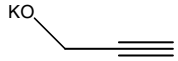
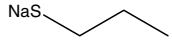
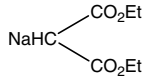
Treatment of **1** with a series of the inorganic salts, such as KCN, KSCN and NaN_3 readily afforded stable salts of dinitro-3-X-substituted propanes, which gave, after acidification, the corresponding dinitropropanes **2a**–**c**[6] (Table 1). Thiocyanate anions were found to be the most reactive nucleophiles: the reaction was complete in 4 h at 60 °C with the formation of dinitropropane **2c** in 75% yield.

The reaction of **1** with LiI in diethyl ether at room temperature afforded, however, a rearrangement product, 3-nitroisoxazoline *N*-oxide **3**[5,7] in quantitative yield (Scheme 1). Such isomerization was earlier observed for nitrocyclopropanecarboxylates by the action of halide ions as well as by heating.[2,3,8] It is interesting to note that **1** was thermally stable; heating at 150 °C for 2 h alone did not lead to *N*-oxide **3**.

Table 1.



1 **2a-g**

2	MX	Reaction time (h)	Solvent	Temperature (°C)	Yield[a] **2** (%)
a	NaN_3	16	CH_3CN/H_2O 1:1	60	52
b	NaCN	10	CH_3CN/H_2O 1:1	80	54
c	KSCN	4	CH_3CN/H_2O 1:1	60	75
d	NaOEt	1	EtOH	Reflux	84
e		24	THF	20	77
f		4	CH_3OH	20	54
g		2	EtOH	Reflux	82

[a] Yield of isolated product.

Keywords: Nucleophilic cyclopropane ring opening; Doubly activated cyclopropane; 1,1-Dinitrocyclopropane; 1,1-Dinitropropanes.
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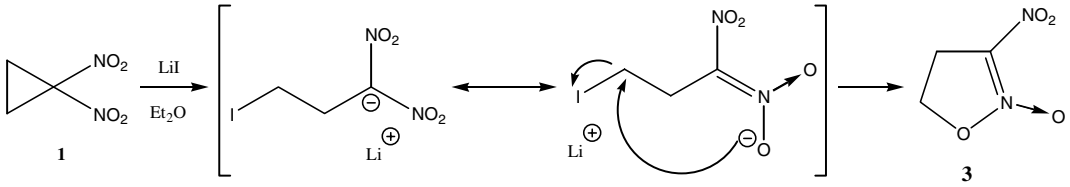
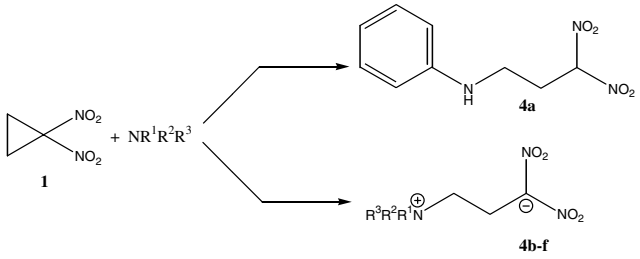


Scheme 1.

Table 2.



4	Amine ($NR^1R^2R^3$)	Reaction time (h)	Solvent	Temperature (°C)	Yield[a] 4 (%)
a	Aniline	4	CH_3CN	60	90
b	Piperidine	1	CH_3CN	20	67
c	Hydrazine	72	CH_3CN	20	48
d	Triethylamine	48	CH_3CN	20	79
e	Pyridine	24	CH_3CN	20	80
f	4-Aminopyridine	24	CH_3CN	20	88

[a] Yield of isolated product.

The formation of *N*-oxide **3** can be envisaged as two successive nucleophilic substitutions in which iodide anion initiates the sequence.

Compound **1** reacted easily with alcoholates and thiolates of alkali metals[9] under very mild conditions (**2e** and **2f**, Table 1). Similar reactions in the case of other doubly activated cyclopropanes could be achieved only after longer heating.[3,10]

Cyclopropane **1** underwent the ring-cleavage reaction with sodium diethylmalonate as a C-nucleophile forming dinitro-diester **2g**[11] (Table 1). This type of reaction was known previously as the first example of a 1,5-homoconjugate addition to an activated cyclopropane bearing two ethoxycarbonyl functionalities.[12] The reaction of dinitro-substituted cyclopropane **1** with sodium diethylmalonate proceeded under milder conditions and was complete after 2 h in boiling ethanol in contrast to that for diethylcyclopropane-1,1-dicarboxylate.[2a,12]

Primary and secondary amines also easily opened the cyclopropane ring of **1**[13] (Table 2). This cleavage occurred faster than in the cases of *gem*-disubstituted cyclopropanes bearing electron-withdrawing substituents such as COR or CN.[14] Thus, full conversion of **1** into the stable zwitterionic compound **4b** under the action of piperidine was complete in 1 h at room temperature. In the case of hydrazine, the formation of yellow betaine **4c** was observed. However, aniline did not give the corresponding zwitterion in reaction with **1** (Table 2) due to the low basicity of its nitrogen, conjugated as it is with an aromatic ring, instead, the product was amine **4a**.

In contrast, tertiary amines such as triethylamine, pyridine and 4-aminopyridine readily reacted with **1** to give the corresponding betaines **4d**–**f**[13] (Table 2). Previously, a similar reaction was reported only for the extremely activated *spiro*-acylal of Danishefsky (6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione).[10]

P-Nucleophiles such as triphenylphosphine and diethyl phosphite did not react with activated cyclopropane **1**.

The following main conclusion can be drawn from our results: the reactions of 1,1-dinitrocyclopropane **1** with diverse nucleophiles proceed via cyclopropane ring opening and with the retention of both nitro groups under mild conditions to yield various 3-substituted 1,1-dinitropropanes. Further studies of the reactivity of dinitrocyclopropane are currently in progress in our group.

Acknowledgements

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6. Dinitropropanes **2a**–**c**. Typical procedure. A solution of **1** (0.11 g, 0.83 mmol) in CH_3CN (5 ml) was added to a solution of the inorganic salt (0.83 mmol) (see Table 1) in H_2O (5 ml). The resulting mixture was stirred under the conditions indicated in Table 1. After that, the solution was concentrated under reduced pressure to afford yellow crystals of dinitropropanide. The crystals were dissolved in H_2O (5 ml) and the resulting solution was acidified with 0.1 N HCl to pH 4–5. The product was extracted with CH_2Cl_2 (3×5 ml), the extract was dried with $MgSO_4$ and concentrated. Pure product was obtained after column chromatography (SiO_2, elution with a 0→10% gradient of ethyl acetate in hexane).
1,1-Dinitro-3-thiocyanatopropane **2c**. Pale yellow oil; R_f 0.10 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.05–3.12 (m, 2H, CH_2), 3.14–3.19 (m, 2H, CH_2), 6.42 (t, $^3J = 6.6$, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.96 (CH_2), 31.16 (CH_2), 108.65 [$CH(NO_2)_2$], 109.73 (SCN). Anal. Calcd for $C_4H_4KN_3O_4S$: C, 20.96; H, 1.76; N, 18.33%. Found: C, 20.81; H, 1.42; N, 18.62.
(2) 1,1-Dinitro-3-thiocyanatopropane. Slight yellow oil; R_f 0.10 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.05–3.12 (m, 2H, CH_2), 3.14–3.19 (m, 2H, CH_2), 6.42 (t, $^3J = 6.6$, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.96 (CH_2), 31.16 (CH_2), 108.65 [$CH(NO_2)_2$], 109.73 (SCN). Anal. Calcd for $C_4H_4KN_3O_4S$: C, 20.96; H, 1.76; N, 18.33. Found: C, 20.81; H, 1.42; N, 18.62.
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9. 3-Ethoxy-1,1-dinitropropane **2d**. Na (0.06 g, 2.61 mmol) was dissolved in absolute EtOH (15 ml). To the resulting mixture, a solution of **1** (0.10 g, 0.76 mmol) in absolute EtOH (0.5 ml) was added. The reaction mixture was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was acidified with 0.1 N HCl to pH 4–5. The product was extracted with CH_2Cl_2 (3×5 ml) and the combined organic fractions dried with $MgSO_4$ and concentrated. Pure product was obtained as a colorless oil after column chromatography (SiO_2, elution with hexane/ethyl acetate 4:1). R_f 0.50 (hexane/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15 (t, $^3J = 7.0$ Hz, 3H, CH_3), 2.74 (dt, $^3J = 7.0$, 5.6 Hz, 2H, CH_2), 3.46 (q, $^3J = 7.0$ Hz, 2H, CH_2), 3.57 (t, $^3J = 7.0$ Hz, 2H, CH_2), 6.43 (t, $^3J = 5.6$ Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.73 (CH_3), 31.65 (CH_2), 63.90 (CH_2), 66.87 (CH_2), 110.06 [$CH(NO_2)_2$]. Anal. Calcd for $C_5H_{10}N_2O_5$: C, 33.71; H, 5.66. Found: C, 34.00; H, 5.79.
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11. 2-(3,3-Dinitropropyl)-malonic acid diethyl ester **2g**. Na (0.02 g, 0.87 mmol) was dissolved in absolute EtOH (1 ml). To the resulting solution diethyl malonate (0.15 g, 0.94 mmol) was added and the mixture was stirred for 5 min. After that, a solution of **1** (0.01 g, 0.76 mmol) in absolute EtOH (1 ml) was added and the resulting mixture was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was acidified with 0.1 N HCl to pH 4–5. The product was extracted with CH_2Cl_2 (3×5 ml) and the extract was dried with $MgSO_4$ and concentrated. Pure product was obtained as a colorless oil after column chromatography (SiO_2, elution with hexane/ethyl acetate 4:1). R_f 0.30 (hexane/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (t, $^3J = 7.1$ Hz, 6H, 2×CH_3), 2.06 (td, $^3J = 7.3$, 7.1 Hz, 2H, CH_2), 2.62 (td, $^3J = 7.3$, 7.0 Hz, 2H, CH_2), 3.45 (t, $^3J = 7.0$ Hz, 1H, CH), 4.18–4.30 (m, 4H, 2×CH_2), 6.31 (t, $^3J = 7.0$ Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.92 (2×CH_3), 23.02 (CH_2), 28.46 (CH_2), 50.43 (CH), 62.04 (2×CH_2), 111.26 [$CH(NO_2)_2$], 168.23 (2×C). Anal. Calcd for $C_{10}H_{16}N_2O_8$: C, 41.10; H, 5.52. Found: C, 41.13; H, 5.67.
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13. (3,3-Dinitropropyl)-phenylamine **4a**. A solution of **1** (0.11 g, 0.83 mmol) in CH_3CN (2 ml) was added to a solution of aniline (0.08 g, 0.83 mmol) in CH_3CN (5 ml). The resulting mixture was stirred for 4 h at 60 °C. Concentration under reduced pressure and purification by column chromatography (SiO_2, elution with hexane/ethyl acetate 4:1 gave the product as a dark red oil). R_f 0.25 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.80 (dt, $^3J = 7.0$, 6.3 Hz, 2H, CH_2), 3.42 (t, $^3J = 6.3$ Hz, 2H, CH_2), 3.75 (br. s, 1H, NH), 6.35 [t, $^3J = 7.0$ Hz, 1H, $CH(NO_2)_2$], 6.60 (d, $^3J = 7.8$ Hz, 2H, *o*-CH, Ph), 6.79 (t, $^3J = 7.4$ Hz, 1H, *p*-CH, Ph), 7.17–7.23 (m, 2H, *m*-CH, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.22, 39.05 (CH_2), 110.04 [$CH(NO_2)_2$], 113.15 (2×*o*-CH, Ph), 119.18 (*p*-CH, Ph), 129.58 (2×*m*-CH, Ph), 146.43 (C, Ph).
Dinitropropanides **4b**–**f**. Typical procedure. A solution of **1** (0.13 g, 0.98 mmol) in CH_3CN (2 ml) was added to a solution of the amine (1.47 mmol) (see Table 2) in CH_3CN (5 ml). The resulting mixture was stirred under the conditions indicated in Table 2. The mixture was then concentrated under reduced pressure to afford yellow crystals, which were washed with small portions of cold EtOH and then dried.
1,1-Dinitro-3-(piperidinium)-propan-3-ide **4b**. Yellow plates; mp 120.5–120.8 °C (with decomposition). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.35–1.42 (m, 1 H), 1.55–1.74 (m, 3 H), 1.75–1.85 (2 H), 2.82–2.96 (m, 2 H), 3.19 (t, $^3J = 7.1$ Hz, 2H, CH_2), 3.37 (t, $^3J = 7.1$ Hz, 2H, CH_2), 3.49–3.58 (m, 2 H), 8.86 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.61 (CH_2), 22.96 (2×CH_2), 25.10 (CH_2), 52.83 (2×CH_2), 53.61 (CH_2), 130.65 [$C(NO_2)_2$]. Anal. Calcd for $C_8H_{15}N_3O_4$: C, 44.23; H, 6.96; N, 19.34. Found: C, 43.71; H, 6.89; N, 19.18.
1,1-Dinitro-3-(pyridinium)-propan-1-ide **4e**. Yellow plates; mp 130–131 °C (with decomposition). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.61 (t,$^3J = 6.1$ Hz, 2H, CH_2), 4.80 (t, $^3J = 6.1$ Hz, 2H, CH_2), 8.07 (dd, $^3J = 7.8$, 6.6 Hz, 2H, *m*-CH, Py), 8.56 (t, $^3J = 7.8$ Hz, 1H, *p*-CH, Py), 8.98 (d, $^3J = 6.6$ Hz, 2H, *o*-CH, Py). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.02 (CH_2), 59.05 (CH_2), 128.18 (2×*m*-CH, Py), 129.49 [$C(NO_2)_2$], 145.40 (*p*-CH, Py), 145.88 (2×*o*-CH). UV (DMSO): λ_{max} 371.5 nm. Anal. Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.27; N, 19.91. Found: C, 45.15; H, 4.10; N, 19.61.
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