Three-Component Reactions of Halogenotrinitromethanes with Alkenes

Ekaterina M. Budynina, Olga A. Ivanova, Elena B. Averina, Yurii K. Grishin, Tamara S. Kuznetsova,* Nikolai S. Zefirov
Moscow State University, Chemistry Department, Leninskie gory, 119992 Moscow, Russia
Fax +7(095)9390290; E-mail: kuzn@org.chem.msu.ru
Received 2 July 2004; revised 22 September 2004

Abstract: Three-component one-pot reactions of bromotrinitromethane with bicyclobutylidene and methylenecyclobutanes provide a simple route to halogen-substituted isoxazolidines of mixed composition. With these same olefins, iodotrinitromethane gives adducts which decomposed rapidly to yield the corresponding isoxazolines. Reaction of bromotrinitromethane and bicyclobutylidene with electron-deficient alkenes produced isoxazolidines together with bromotrinitroalkanes as side products.

Key words: multi-component reaction, cycloaddition, heterocycles, small ring systems, polynitro compounds

The reactions of trinitromethane derivatives \([X\text{C(NO}_2\text{)}_3], \ X = \text{NO}_2, \ Br, \ I\) with unsaturated compounds are a powerful method for the construction of polynitro-substituted five-membered heterocycles.\(^1\) Recently we undertook the development of heterocyclizations of olefins which contain small rings using tetrinitromethane.\(^2\) Taking into account published data and our previous results we have elaborated a general scheme of interaction of tetrinitromethane and halogenotrinitromethanes with unsaturated compounds (Scheme 1). According to this scheme the addition of \(X\text{C(NO}_2\text{)}_3\) to double bond with the in situ generation of nitronic ester followed by [3+2]-cycloaddition gives 5-substituted dinitroisoxazolidines. It should be noted that in the known reactions\(^1,2\) the same alkene takes part in both steps of heterocyclization (A and B, Scheme 1).

The synthetic potential of these reactions may be extended by the application of two different olefins: the first olefin adds to \(X\text{C(NO}_2\text{)}_3\), to generate nitronic ester and the second one is employed in [3+2]-cycloaddition. Previously, we have succeeded in three-component one-pot reactions of tetrinitromethane with two different olefins in 1:1:1 ratio to yield \(N\)-alkoxy-3,3-dinitro-5-substituted isoxazolidines of mixed composition.\(^3\) Here we have studied \(X\text{C(NO}_2\text{)}_3\) (\(X = \text{Br, I}\)) in three-component tandem reactions with alkenes aiming at the preparation of a new group of highly functionalized isoxazolidines.

At first we found that both \(\text{BrC(NO}_2\text{)}_3\) and \(\text{IC(NO}_2\text{)}_3\) readily reacted with methylenecyclobutane (1a) in 1:2 ratio and yield expected isoxazolidines 2a,b (Scheme 2). These reactions proceeded with high regioselectivity to yield the corresponding 5-spirocyclobutane isoxazolidines as single products. Such a high regioselectivity is in a good accordance with previous results obtained by us in the reactions of methylenecyclobutanes with tetrinitromethane.\(^2,3\) Bicyclobutylidene (1b) reacts with bromotrinitromethane in 1:2 ratio and isoxazolidine 2c was isolated in a good yield.

---

**Scheme 1**

SYNTHESIS 2005, No. 2, pp 0286–0290
Advanced online publication: 01.12.2004
DOI: 10.1055/s-2004-834940; Art ID: Z13204SS
© Georg Thieme Verlag Stuttgart · New York
The structures of 2a–c were unambiguously established by 1H and 13C NMR spectra.

In the three-component reactions two different olefins were involved in the reaction with XC(NO₂)₃. According to our previous results bicyclobutylidene (1b) is an ideal precursor to generate nitronic ester in situ and thus we used olefin 1b as a main starting olefin.

We have established that one-pot three-component reactions of XC(NO₂)₃ (X = Br, I) and bicyclobutylidene (1b) with methylenecyclobutanes 1a,c in 1:1:1 ratio proceeded with high regioselectivity and provided halogeno-3,3-dinitroisoxazolidines 3a–c in good yields (Scheme 3).

However, in contrast to the stable bromoisoxazolidine 3a, analogous iodoisoxazolidine derivative 3c spontaneously undergoes elimination to yield nitroisoxazoline 4a. Isoxazolidine 3d decomposed more rapidly, and cyanoisoxazoline 4b was the only product isolated. Previously isoxazolines 4a,b were obtained by the decomposition of 7-hydroxy-8-nitroisoxazolizidine in water in the presence of NaHCO₃ as a catalyst.

The structures of compounds 3a–c and 4a,b were established by 1H and 13C NMR spectra (see experimental part). Cyanoderivatives 3b and 4b were identified as mixtures of two stereoisomers in 4:1 ratio accordingly to NMR data.

Herein, we have found that three-component reactions of BrC(NO₂)₃, bicyclobutylidene (1b), and mono-substituted alkenes 5a–c with electron-withdrawing substituents yielded 5-substituted bromoisoxazolines 6a–c each as a mixture of a diastereomeric pair in the different ratios (Scheme 4). Besides isoxazolines 6a,b the products of the C-addition of BrC(NO₂)₃ to olefins 5a,b, bromotrinitropropanes 7a,b were also isolated. In the case of two-component reactions of BrC(NO₂)₃ with alkenes 5a,b bromotrinitromethanes 7a,b were obtained in quantitative yields. The analogous adduct of BrC(NO₂)₃ to olefin 5c was not formed due to a partial polymerization of 5c in the presence of BrC(NO₂)₃.

It is known that N-alkoxyisoxazolidines with bulky substituents possess high inversion barriers of nitrogen atom (60–120 kJ mol⁻¹). In the structures 6a–c besides this nitrogen center one more carbon asymmetrical center was created by [3+2]-cycloaddition. Therefore isoxazolines 6a–c were formed as mixtures of two diastereomers (dr, Scheme 4).

In conclusion, three-component one-pot reactions of XC(NO₂)₃ (X = Br, I) with bicyclobutylidene and olefins...
containing small ring and electron-withdrawing substituents represent a useful approach to novel halogen-substituted 3,3-dinitrosoxazolines of mixed composition.

NMR spectra were recorded on Varian VXR-400 and Bruker DPX-300 spectrometers at r.t. and the chemical shifts were measured in ppm with respect to solvent (1H: CDCl₃, δ = 7.24 ppm; 13C: CDCl₃, δ = 77.13 ppm). Melting points were measured on an electrothermal 9100 capillary melting point apparatus and the values are uncorrected. Column chromatography was performed on silica gel 60 (230–400 mesh, Merck). Bromotrinitromethane, 6 iodotrinitromethane, 3-methylencyclobutanecarbonitrile was synthesized by known procedures. Other olefins were commercially available. 

Caution: Although we have not experienced any problems in handling these compounds, full safety precautions should be taken due to their potentially explosive nature.

Preparation of Isoxazolidines 2a–c; General Procedure 1

Olefin 1 (5 mmol) was added to a cooled (0 °C) solution of X(NO₂)₃ (X = Br, I) (2.5 mmol) and bicyclobutylidene (2.5 mmol) in hexane (5 mL). The reaction mixture was warmed to r.t. and kept at that temperature for 24–48 h. The reaction mixture was concentrated and dissolved in CHCl₃. The products were isolated by column chromatography (CHCl₃–hexane, 1:2).

6-[1-Bromomethylcyclobutyloxy]-7,7-dinitro-5-oxa-6-azaspiro[3.4]octane (2a)

Yield: 0.40 g (44%); colorless plates; mp 69–70 °C; Rf 0.80

1H NMR (300 MHz, CDCl₃): δ = 1.50–2.90 (m, 12 H, cy-Bu), 3.33 [d, J = 15.1 Hz, 1 H, CH₂C(NO₂)₃], 3.53 [dd, J = 0.9, 11.4 Hz, 1 H, CH₂Br], 3.70 [dd, J = 1, 11.4 Hz, 1 H, CH₂Br], 3.90 [d, J = 15.1 Hz, 1 H, CH₂C(NO₂)₃].

13C NMR (100.6 MHz, CDCl₃): δ = 29.18, 34.25, 34.93, 35.30, 39.28 (CH₂, cy-Bu), 44.39 [C(NO₂)₃].

Anal. Calcd for C₁₄H₂₀BrN₃O₆: C, 41.39; H, 4.96; N, 10.34. Found: C, 41.45; H, 4.19; N, 12.90.

1H NMR (300 MHz, CDCl₃): δ = 1.45–2.88 (m, 12 H, cy-Bu), 3.33 [d, J = 15.0 Hz, 1 H, CH₂C(NO₂)₃], 3.36 [dd, J = 1.0, 11.2 Hz, 1 H, CH₂H], 3.50 [dd, J = 1.4, 11.2 Hz, 1 H, CH₂H], 3.85 [d, J = 15.0 Hz, 1 H, CH₂C(NO₂)₃].

13C NMR (100.6 MHz, CDCl₃): δ = 12.03, 13.23 (CH₃, cy-Bu), 13.39 (CH₃), 31.21, 31.56, 34.33, 38.93 (CH₂, cy-Bu), 43.84 [CH₂C(NO₂)₃], 84.89, 89.21 (C, cy-Bu), 128.38 [C(NO₂)₃].


Preparation of Isoxazolidines 3a–d, 5a–c of Mixed Composition

6-[(1-Iodomethylcyclobutyl)oxy]-7,7-dinitro-5-oxa-6-azaspiro[3.4]octane (3a)

Yield: 0.47 g (46%); colorless plates; mp 85–86 °C (MeOH).

1H NMR (400 MHz, CDCl₃): δ = 1.35–2.82 (m, 18 H, cy-Bu), 3.29 [d, J = 15.2 Hz, 1 H, CH₂C(NO₂)₃], 3.88 [d, J = 15.2 Hz, 1 H, CH₂C(NO₂)₃].

13C NMR (75.4 MHz, CDCl₃): δ = 11.85, 13.33, 16.63, 28.30, 29.18, 34.25, 34.93, 35.30, 39.28 (CH₂, cy-Bu), 44.39 [CH₂C(NO₂)₃], 71.25 (CBr), 89.37, 90.58 (C, cy-Bu), 128.29 [C(NO₂)₃].

Anal. Calcd for C₁₆H₂₁BrN₄O₆: C, 43.19; H, 4.96; N, 10.34. Found: C, 41.41; H, 5.15; N, 9.94.

6-[(1-Iodomethylcyclobutyl)oxy]-1-yl]oxy]-7,7-dinitro-5-oxa-6-azaspiro[3.4]octane (3b)

Mixture of stereoisomers (5:1); yield: 0.81 g (75%); colorless plates; mp 72–73 °C; Rf 0.50 (CHCl₃).

1H NMR (400 MHz, CDCl₃): δ (major isomer) = 1.42–2.90 (m, 16 H, cy-Bu), 3.33 (m, 1 H, CHCN), 3.47 [d, J = 15.6 Hz, 1 H, CH₂C(NO₂)₃], 4.01 [d, J = 15.6 Hz, 1 H, CH₂C(NO₂)₃].

13C NMR (100.6 MHz, CDCl₃): δ (major isomer) = 11.52 (CH₃, cy-Bu), 15.92 (CH₃CN), 16.40, 27.77, 29.22, 34.47, 35.11, 37.71, 42.31 (CH₂, cy-Bu), 44.19 [CH₂C(NO₂)₃], 71.19 (CBr), 87.65, 90.95 (C, cy-Bu), 121.16 (CN), 127.68 [C(NO₂)₃].

1H NMR (400 MHz, CDCl₃): δ (minor isomer) = 1.42–2.90 (m, 16 H, cy-Bu), 3.15 (m, 1 H, CHCN), 3.36 [d, J = 15.3 Hz, 1 H, CH₂C(NO₂)₃], 3.90 [d, J = 15.3 Hz, 1 H, CH₂C(NO₂)₃].

13C NMR (100.6 MHz, CDCl₃): δ (minor isomer) = 13.24 (CH₃, cy-Bu), 14.39 (CH₃CN), 17.37, 27.89, 29.08, 35.58, 38.61, 38.11, 43.55 (CH₂, cy-Bu), 44.96 [CH₂C(NO₂)₃], 70.95 (CBr), 88.18, 90.36 (C, cy-Bu), 120.21 (CN), 128.02 [C(NO₂)₃].


7-Nitro-5-oxa-6-azaspiro[3.4]octane (3c)

Yield: 0.76 g (67%); a slightly yellow oil; Rf 0.44 (CHCl₃).

1H NMR (400 MHz, CDCl₃): δ = 1.50–2.90 (m, 18 H, cy-Bu), 3.33 [d, J = 15.1 Hz, 1 H, CH₂C(NO₂)₃], 3.91 [d, J = 15.1 Hz, 1 H, CH₂C(NO₂)₃].

13C NMR (100.6 MHz, CDCl₃): δ = 10.87, 12.87, 17.07, 33.91, 36.46, 36.89, 37.22, 37.24, 39.04 (CH₂, cy-Bu), 43.73 [CH₂C(NO₂)₃], 54.23 (C), 88.85, 91.30 (C, cy-Bu), 127.70 [C(NO₂)₃].


7-Nitro-5-oxa-6-azaspiro[3.4]octane (3d)

Storage of 3c (0.76 g) at 0 °C for a week gave 4a (0.23 g, 86%) as colorless plates; mp 52–53 °C; Rf 0.47 (CHCl₃).
1H NMR (400 MHz, CDCl 3): δ = 1.70 (m, 1 H, cy-Bu), 1.94 (m, 1 H, cy-Bu), 2.32 (m, 2 H, cy-Bu), 2.62 (m, 2 H, cy-Bu), 3.54 [s, 2 H, CH 2C(NO 2) 2].

13C NMR (100.6 MHz, CDCl 3): δ = 12.38 (CH 3-Cy, Cy-Bu), 36.83 (2× CH 2cy-Bu), 40.80 [CH 2C(NO 2) 2], 94.07 (Cspiro), 163.04 [C(NO 2)].


7-Nitro-5-oxa-6-azaspiro[3.4]oct-6-ene-2-carbonitrile (4b)
Mixture of stereoisomers (1:4); yield: 0.16 g (36%); colorless plates; mp 85–102 °C; R f 0.16 (CHCl 3).

1H NMR (300 MHz, CDCl 3): δ (major isomer) = 2.75–2.94 (m, 4 H, cy-Bu), 3.36 (m, 1 H, CHCN), 89.94 [C (spiro)], 121.82 (CN), 164.35 [C (spiro)].

13C NMR (75.4 MHz, CDCl 3): δ (minor isomer) = 2.75–2.94 (m, 4 H, cy-Bu), 3.11 (m, 1 H, CHCN), 36.88 [s, 2 H, CH 2C(NO 2) 2].


5-Acetyl-2-{1′-[bromo-1,1′-bicyclobutyl]-1-yl}oxy]-3,3-dinitroisoxazolidine (6a)
Mixture of diastereomers (10:9); yield: 0.41 g (40%); colorless plates; mp 47–48 °C; R f 0.50 (CHCl 3).

1H NMR (300 MHz, CDCl 3): δ (major isomer) = 1.41–3.00 (m, 12 H, cy-Bu), 2.36 (s, 3 H, CH 3), 3.41 [dd, J = 5.9, 15.5 Hz, 1 H, CH 2C(NO 2) 2], 3.92 [dd, J = 9.3, 15.5 Hz, 1 H, CH 2C(NO 2) 2], 5.37 (dd, J = 5.9, 9.3 Hz, 1 H, CH(OEt)).

1H NMR (300 MHz, CDCl 3): δ (minor isomer) = 1.41–3.00 (m, 12 H, cy-Bu), 2.27 (s, 3 H, CH 3), 3.36 [dd, J = 8.9, 15.4 Hz, 1 H, CH 2C(NO 2) 2], 4.17 [dd, J = 6.3, 15.4 Hz, 1 H, CH 2C(NO 2) 2], 4.81 (dd, J = 6.3, 8.9 Hz, 1 H, CH(OEt)).

13C NMR (75.4 MHz, CDCl 3): δ (for two diastereomers) = 11.53, 11.80, 16.18, 16.53 (CH 3, cy-Bu), 26.85, 26.94 (CH 3), 28.04, 28.14 (2×), 28.15, 29.63, 32.48, 34.24, 34.97 (CH 3, cy-Bu), 34.99, 35.05 [CH 2C(NO 2) 2], 70.52, 71.82 (CBr), 84.44, 85.21 (CHO), 91.17, 91.19 (C, cy-Bu), 127.11, 127.54 [C(NO 2)], 201.32, 202.07 (CO).


2-{1′-[Bromo-1,1′-bicyclobutyl]-1-yl}oxy]-5-diethoxymethyl-3,3-dinitroisoxazolidine (6b)
Mixture of diastereomers (15:1); yield: 0.65 g (56%); slightly yellow plates; mp 59–60 °C; R f 0.67 (CHCl 3).

1H NMR (400 MHz, CDCl 3): δ (major isomer) = 1.49–2.95 (m, 12 H, cy-Bu), 1.12 (t, J = 7.0 Hz, 3 H, CH 3), 1.81 (t, J = 7.0 Hz, 3 H, CH 3), 3.33 [dd, J = 4.5, 15.2 Hz, 1 H, CH 2C(NO 2) 2], 3.48 (m, 2 H, CH 3-O), 3.66 (m, 2 H, CH 3-O), 3.76 [dd, J = 9.0, 15.2 Hz, 1 H, CH 2C(NO 2) 2], 4.46 [d, J = 2.3 Hz, 1 H, CH(OEt)], 4.90 (dd, J = 2.3, 4.5, 9.0 Hz, 1 H, CH(OEt)).

1C NMR (100.6 MHz, CDCl 3): δ (major isomer) = 11.81 (CH 3, cy-Bu), 14.65, 15.02 (CH 3), 16.34, 27.99, 28.52, 33.16, 34.94 (CH 3, cy-Bu), 35.05 [CH 2C(NO 2) 2], 63.84, 65.86 (CH 3-O), 71.80 (CBr), 82.35 (CHO), 90.23 (C), 99.63 [CH(OEt)], 127.50 [C(NO 2)].

13C NMR (100.6 MHz, CDCl 3): δ (minor isomer) = 11.60 (CH 3, cy-Bu), 15.15, 15.43 (CH 3), 16.48, 27.49, 29.88, 30.37, 34.36 (CH 3, cy-Bu), 35.33 [CH 2C(NO 2) 2], 63.28, 63.84 (CH 3-O), 82.83 (CHO), 90.78 (C), 103.39 [CH(OEt)].

Acknowledgment
This work was supported by the International Science and Technical Center (Project 1151).

References


(4) The scope of the stated method is restricted to nucleophilic and hindered olefins like tri- and tetrasubstituted alkyl or aryl cycloalkenes, which form nitronic esters in situ. For analogues see ref. 3.


