Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2010, **20**, 17–19
Mendeleev Communications

Stereoselective tandem [4 + 2]/[3 + 2] cycloaddition reactions of 3,3,3-trichloro(trifluoro)-1-nitropropenes and 2,3-dihydrofuran

Vladislav Yu. Korotaev,[a] Vyacheslav Ya. Sosnovskikh,*[a] Mikhail A. Barabanov,[a] Alexey Yu. Barkov[a] and Mikhail I. Kodess[b]

[a] *Department of Chemistry, A. M. Gorky Ural State University, 620083 Ekaterinburg, Russian Federation. Fax: +7 343 261 5978; e-mail: vyacheslav.sosnovskikh@usu.ru*
[b] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620041 Ekaterinburg, Russian Federation*

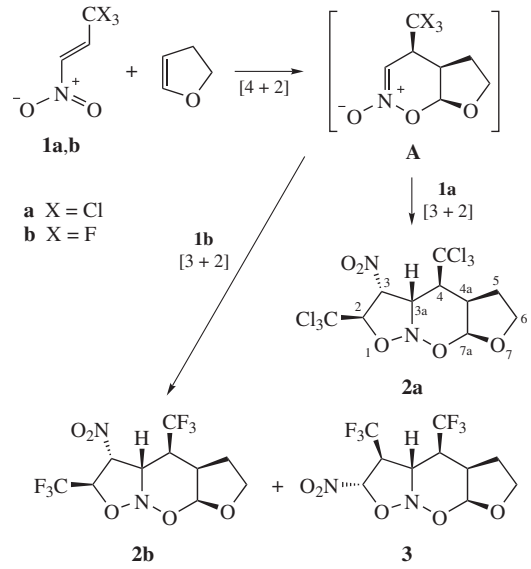
DOI: 10.1016/j.mencom.2010.01.007

The first example of the domino hetero-Diels–Alder/1,3-dipolar cycloaddition, in which 3,3,3-trichloro(trifluoro)-1-nitropropenes act as both the heterodiene and the dipolarophile in the reaction with 2,3-dihydrofuran, is described. The trichloromethylated nitroolefin gave tricyclic nitroso acetal as a single regio- and stereoisomer, while the trifluoromethylated derivative afforded a 3:1 mixture of two regioisomeric cycloadducts.

Trihalomethylated nitroolefins possess unique chemical reactivity toward both nucleophilic and cycloaddition reactions because of their reactive double bond. Owing to this, *trans*-3,3,3-trichloro(trifluoro)-1-nitropropenes **1** have attracted attention as excellent building blocks for the preparation of CCl_3- and CF_3-containing compounds.[1] Most pertinent to the present research is the 1,3-dipolar cycloaddition of benzonitrile oxide and nitrones to nitroalkenes **1** providing a straightforward route to isoxazolines[2] and isoxazolidines,[3] which can be considered as masked forms of various functionality including β-hydroxyketones, γ-aminoalcohols, *etc*.[4] Nitroalkenes **1** were also used as dienophiles in the Diels–Alder reaction.[5] However, published data on their participation in hetero-Diels–Alder reactions are lacking, a fact prompting us to investigate the cycloaddition of **1** to enol ethers.

It is known that nitroolefins in reactions with electron-rich alkenes can act as heterodienes in an inverse electron-demand Diels–Alder reaction.[6] However, without a catalyst, the cycloaddition involving these substrates often requires a large excess of enol ether, a long reaction time,[7] or activated nitroalkenes.[8] For example, the reaction of β-nitrostyrene with a large excess of ethyl vinyl ether (90 equiv.) at ambient pressure in ethanol as a solvent required five days to give the complete conversion of nitrostyrene, mainly to the tandem [4 + 2]/[3 + 2] adduct.[9] The use of high pressure allows some of these difficulties to be overcome.[9,10]

Here we report the cycloaddition reactions of *trans*-3,3,3-trichloro-1-nitropropene **1a** and *trans*-3,3,3-trifluoro-1-nitropropene **1b** with 2,3-dihydrofuran. Reaction of nitroolefin **1a** with an equimolar amount of 2,3-dihydrofuran at ~20 °C for 24 h afforded nitroso acetal **2a** in 45% yield with the regio- and stereochemistry shown in Scheme 1.† The yield was about 40–45% regardless of amounts of dienophile. Notably, compound **2a** contains six contiguous stereogenic centres, but only one diastereomer could be observed by ^{1}H NMR spectroscopy of the crude product. The observed difference in reactivity between **1a** and the above β-nitrostyrene is attributed to the presence of the powerful electron-withdrawing CCl_3 group in place of phenyl on the alkene moiety making nitroolefin **1a** more reactive mainly by lowering the LUMO energy level. Compound **2a** is thus formed as a result of [4 + 2] addition across the 4π heterodiene system of **1a** by 2,3-dihydrofuran, which acts as an activated



Scheme 1 Tandem [4 + 2]/[3 + 2] cycloaddition reactions of nitroalkenes **1a**,**b** and 2,3-dihydrofuran.

dienophile, and then intermediate **A** undergoes the second [3 + 2] cycloaddition reaction across the nitronate function by a

† *2,3*-trans-*3,3a*-cis-*3a,4*-trans-*4,4a*-cis-*4a,7a*-cis-*3-Nitro-2,4-bis(trichloromethyl)octahydrofuro[3,2*-e*]isoxazolo[2,3*-b*][1,2]oxazine* **2a**. A mixture of 3,3,3-trichloro-1-nitropropene **1a** (0.76 g, 4.0 mmol) and 2,3-dihydrofuran (0.14 g, 2.0 mmol) was kept for 24 h at ~20 °C (TLC). After that, the mixture was concentrated under reduced pressure and the solid formed was recrystallized from toluene. Yield 0.41 g (45%), colourless crystals, mp 189–190 °C. ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: 2.02 (dddd, 1H, H-5, *J* 12.0, 9.2, 6.9, 2.4 Hz), 2.28 (dddd, 1H, H-5′, *J* 12.0, 11.2, 9.1, 8.9 Hz), 3.14 (dddd, 1H, H-4a, *J* 11.2, 9.2 Hz, $J_{4a,7a}$ 6.7 Hz, $J_{4a,4}$ 4.7 Hz), 3.76 (ddd, 1H, H-6, *J* 9.1, 8.4, 7.0 Hz), 3.78 (dd, 1H, H-4, $J_{4,3a}$ 6.9 Hz, $J_{4,4a}$ 4.7 Hz), 4.16 (ddd, 1H, H-6′, *J* 9.0, 8.4, 2.4 Hz), 4.33 (dd, 1H, H-3a, $J_{3a,3}$ 7.9 Hz, $J_{3a,4}$ 6.9 Hz), 5.42 (d, 1H, H-7a, *J* 6.7 Hz), 5.95 (dd, 1H, H-3, $J_{3,3a}$ 7.9 Hz, $J_{3,2}$ 3.8 Hz), 6.23 (d, 1H, H-2, *J* 3.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.76 (C-5), 38.81 (C-4a), 53.36 (C-4), 69.22 (C-6), 73.03 (C-3a), 89.49 (C-3), 94.55 (2-CCl_3), 95.48 (C-2), 99.32 (4-CCl_3), 102.73 (C-7a). IR (KBr, ν/cm^{-1}): 1567, 1487, 1442, 1359, 1339. Found (%): C, 26.59; H, 2.25; N, 6.14. Calc. for $C_{10}H_{10}Cl_6N_2O_5$ (%): C, 26.64; H, 2.24; N, 6.21.

Table 1 Selected ^{1}H NMR chemical shifts and coupling constants of **2a**,**b** and **3** in [$^2H_6$]DMSO.

Adduct	^{1}H NMR, δ/ppm					
	H-2	H-3	H-3a	H-4	H-4a	H-7a
2a	6.23 (d, *J* 3.8 Hz)	5.95 (dd, *J* 7.9, 3.8 Hz)	4.33 (dd, *J* 7.9, 6.9 Hz)	3.78 (dd, *J* 6.9, 4.7 Hz)	3.14 (dddd, *J* 11.2, 9.2, 6.7, 4.7 Hz)	5.42 (d, *J* 6.7 Hz)
2b	6.22 (qd, *J* 6.8, 4.1 Hz)	6.36 (dd, *J* 8.3, 4.1 Hz)	4.42 (t, *J* 8.3 Hz)	3.14 (qdd, *J* 8.9, 8.3, 4.2 Hz)	2.86 (tdd, *J* 10.2, 6.8, 4.2 Hz)	5.36 (d, *J* 6.8 Hz)
3	7.06 (d, *J* 2.0 Hz)	4.64 (quint. d, *J* 10.0, 2.0 Hz)	4.37 (t, *J* 9.0 Hz)	3.23 (quint. d, *J* 8.8, 4.0 Hz)	2.89 (m)	5.41 (d, *J* 7.0 Hz)

second molecule of **1a** to give tricyclic product **2a**. This reaction is consistent with the reactivity of cyclic nitronates as an electron-rich 1,3-dipole[6,8,9] (Scheme 1).

The regio- and stereochemistry of this adduct can be explained by assuming that [4 + 2] inverse electron-demand cycloaddition of 2,3-dihydrofuran over the nitroalkene system of **1a** occurs regioselectively such that the oxygen atom of dienophile is located at the 7a-position and from an endo transition state, which would account for the *cis*-*cis* stereochemistry observed between the H-4, H-4a, and H-7a atoms in the newly formed ring. The regioselectivity of 1,3-dipolar cycloaddition is usually highly substrate dependent, and it is controlled by both electronic and steric factors.[11] In our case, the NO_2 group is located at the 3-position and the relative configurations of the H-2, H-3, and H-3a atoms could be interpreted by assuming an *exo* transition state and *anti* selectivity with respect to the 4-CCl_3 group (for X-ray diffraction data, see below).

Similarly, reaction of **1b** with 2,3-dihydrofuran at ~20 °C for 3 h gave a 3:1 mixture of two regioisomeric cycloadducts **2b** and **3** in 41% total yield.‡ The lower regioselectivity was observed in this case, owing to the competition of two electron-withdrawing substituents at the double bond, in agreement with the reported behaviour of CF_3-containing alkenes in the reactions with nitrones and nitrile oxides.[12] No attempt was made to separate **2b** and **3**. Reactions of **1a**,**b** with ethyl vinyl ether and 3,4-dihydro-2*H*-pyran did not give the corresponding 2:1 cycloadducts even at higher temperatures.

All the signals in the ^{1}H and ^{13}C NMR spectra of compounds **2a**,**b** were assigned on the basis of 2D COSY, HSQC and HMBC experiments. The significant ^{1}H NMR chemical shifts and coupling constants compiled in Table 1 suggest differences in the regiochemistry at the C-2 and C-3 atoms of **2b** and **3**.

However, there is some equivocality in the stereochemical determination because of the flexibility of the five-membered rings.[13] To determine the relative configuration of the ring carbon atoms for **2a**,**b**, an X-ray diffraction study was carried out after the isolation of **2a** as a single crystal from the reaction mixture.§ This study proved the *endo*-[4 + 2], *exo-anti*-[3 + 2] structure of **2a**,**b** with the 2,3-*trans* and 3,4-*trans* arrangement of the substituents (Figure 1). The stereochemistry of regioisomer **3** as the *endo*-[4 + 2], *endo-anti*-[3 + 2] structure was tentatively assigned based on the presence of two characteristic doublets of quartets of the 4-CF_3 and 3-CF_3 groups at 94.9 and 101.4 ppm with $J_{F,H4}$ 8.3 Hz, $J_{F,H3}$ 10.0 Hz and $J_{F,F}$ 4.1 Hz, indicating that these groups were spatially close to each other. This means that the relative stereochemistry of the trifluoromethyl groups is *cis* and, consequently, the formation of **3** proceeded with *endo-anti*-[3 + 2] selectivity (*anti* with respect to the 4-CF_3 group).

In conclusion, the preparation of CX_3-containing tricyclic nitroso acetals from 3,3,3-trichloro(trifluoro)-1-nitropropenes and 2,3-dihydrofuran is the first example of tandem [4 + 2]/[3 + 2] cycloaddition in which a trihalomethylated nitroolefin acts as the heterodiene and dipolarophile.

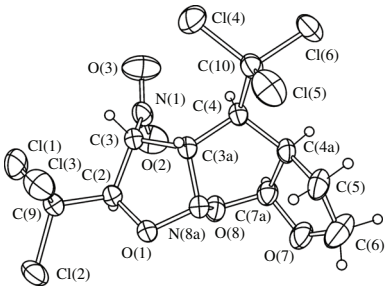


Figure 1 Molecular structure of nitroso acetal **2a** (thermal ellipsoids at 50% probability level).

‡ *2,3*-trans-*3,3a*-cis-*3a,4*-trans-*4,4a*-cis-*4a,7a*-cis-*3-Nitro-2,4-bis(trifluoromethyl)octahydrofuro[3,2*-e*]isoxazolo[2,3*-b*][1,2]oxazine* **2b** and *2,3*-trans-*3,3a*-trans-*3a,4*-trans-*4,4a*-cis-*4a,7a*-cis-*2*-nitro-*3,4-bis(trifluoromethyl)-octahydrofuro[3,2*-e*]isoxazolo[2,3*-b*][1,2]oxazine* **3**. A mixture of 3,3,3-trifluoro-1-nitropropene **1b** (0.56 g, 4.0 mmol) and 2,3-dihydrofuran (0.14 g, 2.0 mmol) was kept for 3 h at ~20 °C (TLC). After that, the mixture was concentrated under reduced pressure and the solid formed was recrystallized from CH_2Cl_2–hexane (1:2). Yield 0.29 g (41%), colourless powder, mp 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: (**2b**, 78%) 2.06–2.28 (m, 2H, 5-CH_2), 2.82 (tdd, 1H, H-4a, *J* 10.0, 6.9, 4.5 Hz), 2.99 (quint. d, 1H, H-4, *J* 8.2, 4.5 Hz), 3.93 (q, 1H, H-6, *J* 8.1 Hz), 4.11 (t, 1H, H-3a, *J* 8.0 Hz), 4.37 (td, 1H, H-6′, *J* 8.8, 3.3 Hz), 5.37 (d, 1H, H-7a, *J* 6.9 Hz), 5.40 (dd, 1H, H-3, *J* 8.5, 4.1 Hz), 5.89 (qd, 1H, H-2, *J* 6.4, 4.1 Hz); (**3**, 22%) 1.80–2.05 (m, 2H, 5-CH_2), 2.80–2.90 (m, 1H, H-4a), 3.12 (quint. d, 1H, H-4, *J* 8.2, 4.2 Hz), 3.85 (q, 1H, H-6, *J* 8.5 Hz), 3.94 (m, 1H, H-6′), 4.23 (t, 1H, H-3a, *J* 8.9 Hz), 4.40 (m, 1H, H-3), 5.44 (d, 1H, H-7a, *J* 7.0 Hz), 6.33 (d, 1H, H-2, *J* 2.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: (**2b**, 78%) 86.68 (d, 2-CF_3, $J_{F,2}$ 6.4 Hz), 92.76 (d, 4-CF_3, $J_{F,4}$ 8.3 Hz); (**3**, 22%) 92.57 (dq, 4-CF_3, $J_{F,4}$ 8.3 Hz, $J_{F,F}$ 4.0 Hz), 99.96 (dq, 3-CF_3, $J_{F,3}$ 8.8 Hz, $J_{F,F}$ 4.0 Hz). ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: (**2b**, 75%) 1.90–2.13 (m, 2H, 5-CH_2), 2.86 (tdd, 1H, H-4a, *J* 10.2, 6.8, 4.2 Hz), 3.14 (qdd, 1H, H-4, *J* 8.9, 8.3, 4.2 Hz), 3.78 (q, 1H, H-6, *J* 8.1 Hz), 4.15 (ddd, 1H, H-6′, *J* 9.1, 8.2, 3.2 Hz), 4.42 (t, 1H, H-3a, *J* 8.3 Hz), 5.36 (d, 1H, H-7a, *J* 6.8 Hz), 6.22 (qd, 1H, H-2, $J_{2,F}$ 6.8 Hz, $J_{2,3}$ 4.1 Hz), 6.36 (dd, 1H, H-3, $J_{3,3a}$ 8.3 Hz, $J_{3,2}$ 4.1 Hz); (**3**, 25%) 1.90–2.13 (m, 2H, 5-CH_2), 2.85–2.93 (m, 1H, H-4a), 3.23 (quint. d, 1H, H-4, *J* 8.8, 4.0 Hz), 3.78 (q, 1H, H-6, *J* 8.1 Hz), 4.19 (td, 1H, H-6′, *J* 8.4, 3.0 Hz), 4.37 (t, 1H, H-3a, *J* 9.0 Hz), 4.64 (quint. d, 1H, H-3, *J* 10.0, 2.0 Hz), 5.41 (d, 1H, H-7a, *J* 7.0 Hz), 7.06 (d, 1H, H-2, *J* 2.0 Hz). ^{19}F NMR (376 MHz, [$^2H_6$]DMSO) δ: (**2b**, 75%) 89.06 (d, 2-CF_3, $J_{F,2}$ 6.8 Hz), 95.26 (d, 4-CF_3, $J_{F,4}$ 8.9 Hz); (**3**, 25%) 94.90 (dq, 4-CF_3, $J_{F,4}$ 8.3 Hz, $J_{F,F}$ 4.1 Hz), 101.45 (dq, 3-CF_3, $J_{F,3}$ 10.0 Hz, $J_{F,F}$ 4.1 Hz). ^{13}C NMR (100 MHz, [$^2H_6$]DMSO) δ: (**2b**) 24.94 (C-5), 37.38 (C-4a), 37.44 (q, C-4, $^2J_{C,F}$ 28.2 Hz), 67.80 (C-3a), 68.82 (C-6), 82.80 (q, C-2, $^2J_{C,F}$ 32.5 Hz), 85.55 (C-3), 102.96 (C-7a), 122.35 (q, 2-CF_3, $^1J_{C,F}$ 280.1 Hz), 125.66 (q, 4-CF_3, $^1J_{C,F}$ 279.4 Hz). IR (KBr, ν/cm^{-1}): 1574, 1486, 1458, 1395. Found (%): C, 34.27; H, 2.78; N, 7.87. Calc. for $C_{10}H_{10}F_6N_2O_5$ (%): C, 34.10; H, 2.86; N, 7.95.

§ *Crystal data for* **2a**: $C_{10}H_{10}Cl_6N_2O_5$, M = 450.92, monoclinic, space group $P2_1/c$, a = 12.961(1), b = 11.403(8) and c = 10.957(1) Å, β = 91.581(7)°, V = 1618.7(2) Å^3, Z = 4, d_{calc} = 1.850 g cm^{-3}, μ = 1.085 mm^{-1}. The intensities of 3514 independent reflections were measured on a Bruker P4 diffractometer [MoKα radiation, graphite monochromator, λ(MoKα) = = 0.71073, 296 K, $\theta/2\theta$ scan mode in the range $\theta < 27°$]. The structure was solved by a direct method with the use of the SHELXS-97 program package.[14]

CCDC 742730 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.

This study was supported by the Russian Foundation for Basic Research (grant no. 06-03-04004).

References

1 (*a*) F. Brower and H. Burkett, *J. Am. Chem. Soc*., 1953, **75**, 1082; (*b*) H. Burkett, G. Nelson and W. Wright, *J. Am. Chem. Soc*., 1958, **80**, 5812; (*c*) S. Iwata, Y. Ishiguro, M. Utsugi, K. Mitsuhashi and K. Tanaka, *Bull. Chem. Soc. Jpn*., 1993, **66**, 2432; (*d*) V. Yu. Korotaev, I. B. Kutyashev and V. Ya. Sosnovskikh, *Heteroat. Chem*., 2005, **16**, 492; (*e*) V. Yu. Korotaev, V. Ya. Sosnovskikh, I. B. Kutyashev, A. Yu. Barkov, E. G. Matochkina and M. I. Kodess, *Tetrahedron*, 2008, **64**, 5055.

2 A. Barański, *Pol. J. Chem.*, 1982, **56**, 257.

3 (*a*) K. Tanaka, T. Mori and K. Mitsuhashi, *Bull. Chem. Soc. Jpn*., 1993, **66**, 263; (*b*) K. Tanaka, T. Mori and K. Mitsuhashi, *Chem. Lett*., 1989, 1115; (*c*) R. Jasiński and A. Barański, *Pol. J. Chem*., 2006, **80**, 1493.

4 K. B. G. Torssell, *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, Weinheim, 1988.

5 (*a*) H. Burkett and W. Wright, *J. Org. Chem*., 1960, **25**, 276; (*b*) O. Klenz, R. Evers, R. Miethchen and M. Michalik, *J. Fluorine Chem*., 1997, **81**, 205.

6 (*a*) S. E. Denmark and A. Thorarensen, *Chem. Rev*., 1996, **96**, 137; (*b*) S. E. Denmark, R. Y. Baiazitov and S. T. Nguyen, *Tetrahedron*, 2009, **65**, 6535.

7 M. Avalos, R. Babiano, P. Cintas, F. J. Higes, J. L. Jiménez, J. C. Palacios and M. A. Silva, *J. Org. Chem*., 1996, **61**, 1880.

8 Y. Tohda, N. Yamawaki, H. Matsui, T. Kawashima, M. Ariga and Y. Mori, *Bull. Chem. Soc. Jpn*., 1988, **61**, 461.

9 R. M. Uittenbogaard, J.-P. G. Seerden and H. W. Scheeren, *Tetrahedron*, 1997, **53**, 11929.

10 G. J. T. Kuster, R. H. J. Steeghs and H. W. Scheeren, *Eur. J. Org. Chem*., 2001, 553.

11 *The Chemistry of Heterocyclic Compounds, V. 59: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, eds. A. Padwa and W. H. Pearson, Jonh Wiley & Sons, 2002.

12 P. Bravo, L. Bruché, A. Mele and G. Zecchi, *J. Chem. Res. (S)*, 1991, 81.

13 M. G. Constantino and G. V. J. da Silva, *Tetrahedron*, 1998, **54**, 11363.

14 G. M. Sheldrick, *SHELX-97, Programs for Crystal Structure Determination and Refinement*, University of Göttingen, Göttingen (Germany), 1997.

Received: 12th August 2009; Com. 09/3376