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Diastereoselective reactions of 1,1,1-trichloro(trifluoro)-3-nitrobut-2-enes with 2-morpholinoalk-1-enes

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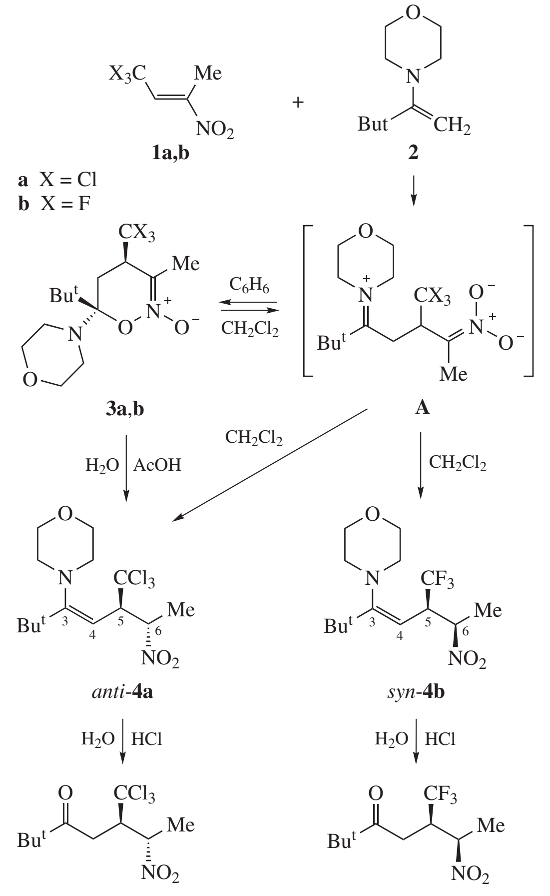
Reactions of (*E*)-1,1,1-trichloro(trifluoro)-3-nitrobut-2-enes with 3,3-dimethyl-2-morpholinobutene in benzene give (4*R**,6*R**)-6-*tert*-butyl-3-methyl-6-morpholino-4-trihalomethyl-5,6-dihydro-4*H*-1,2-oxazine 2-oxides. In a dichloromethane solution, these cyclic nitronates undergo diastereoselective ring opening to produce nitroalkylated *anti*-CCl_3- and *syn*-CF_3-enamines, which are hydrolysed with dilute HCl to afford the respective *anti*-CCl_3- and *syn*-CF_3-γ-nitroketones.

Nucleophilic addition of enolates and enamines to conjugated nitroalkenes is an efficient method for preparation of γ-nitroketones[1] that, in turn, are widely used in organic synthesis.[1,2] In the case of enamines, the dipolar intermediate formed at the 1,4-addition stage undergoes proton transfer and is usually converted into a nitroalkylated enamine or a γ-nitroketone.[3] However, depending on the nature of the reactants and reaction conditions, it can also afford other products: intramolecular attack of the ambident nitronate anion on the iminium carbon atom results either in [2+2]-carbocyclisation to give cyclobutanes[4] or [4+2]-heterocyclisation to give 1,2-oxazine *N*-oxides.[5] These reactions have been studied most thoroughly for 1(2)-nitropropenes, α(β)-nitrostyrenes and cycloalkanone enamines.[3–5] Especially useful are those reagents and conditions that allow isolation or *in situ* trapping of 1,2-oxazine *N*-oxides to be fulfilled. The latter are highly reactive 1,3-dipoles capable of adding to multiple bonds and reacting both with electrophiles and nucleophiles.[6]

Reactions of polyhaloalkylated nitroolefins with enamines are studied scarcely. To this, (*E*)-1-nitro-3,3,3-trifluoropropene reacts with ethyl 3-morpholinocrotonate to yield a [2+2]-carbocyclization cyclobutane derivative,[7] whereas polyfluoroalkylated nitroalkenes react with cycloalkanone enamines and acetophenone enamines to furnish β-polyfluoroalkyl-γ-nitroketones.[8] We have recently shown[9] that reactions of (*E*)-1-nitro-3,3,3-trichloro(trifluoro)propenes with morpholine-derived enamines of pinacoline and acetophenone lead to the respective nitroalkylated *Z*-enamines and β-trihalomethyl-γ-nitroketones.

In this work we have studied reactions of little-known (*E*)-1,1,1-trichloro(trifluoro)-3-nitrobut-2-enes **1a**,**b** with morpholine-derived enamines of pinacoline, cyclohexanone and acetophenone and have shown that moving from nitropropenes[9] to nitrobutenes allows one to obtain sufficiently stable 4-CX_3-1,2-oxazine *N*-oxides. The latter under mild conditions can undergo ring opening to result in nitroalkylated enamines or hydrolysis to give CCl_3- and CF_3-containing γ-nitroketones or γ-diketones with high stereoselectivity.

We have found that the reaction of nitroalkenes **1a**,**b** with 3,3-dimethyl-2-morpholinobutene **2** (obtained from pinacoline and morpholine) under kinetic control conditions (benzene, ~25 °C, 3 h) *via* dipolar intermediate **A** gives 1,2-oxazine *N*-oxides **3a**,**b** in 60 and 56% yields, respectively, which were sufficiently stable compounds and were characterised comprehensively (Scheme 1). The bulky trihalomethyl group in these compounds occupies an equatorial *cis* position with respect to the equatorial *tert*-butyl group, as indicated by high coupling constants of CH_2 group protons with the H(4) atom located in an axial position (^3J 9.2–10.7 and 8.4 Hz in $CDCl_3$). Additionally, piperidine-derived analogue **7a** (see below) was prepared and subjected to 2D NOESY experiment, whose spectrum did not contain a cross-peak between the Bu^t group and the H(4) proton [considering compound **7a** instead of **3a** was necessary since in the spectrum of **3a** H(4) proton is overlapped with signal from CH_2OCH_2 moiety].



Scheme 1

The reaction of compounds **1a**,**b** with **2** carried out in dichloromethane at ~20 °C (3 days for **1a** or 1 day for **1b**) leads to nitroalkylated enamines **4a**,**b** in 98 and 73% yields, respectively. Note that the same products were also obtained from oxazines **3a**,**b** upon keeping them in a chloroform solution for one week (for **4a**) or for two days (for **4b**). Opening of the oxazine ring in compounds **4a**,**b** occurs *via* betaine **A**; in the case of **3a** it can be accelerated by stirring in water in the presence of a catalytic amount of AcOH (~20 °C, 24 h, yield 64%), whereas compound **3b**, which is less stable, is hydrolyzed into γ-nitroketone **5b** within only 4 h. Irrespective of the preparation method, enamines **4a**,**b** were always formed as one diastereomer, which is not surprising because protonation of the nitronate carbon atom in betaine intermediate **A** usually occurs with high diastereoselectivity, as repeatedly reported previously.[10] Unexpected there was that the reaction of CCl_3-nitrobutene **1a** gave (*Z*)-*anti*-**4a**, whereas the reaction of CF_3-nitrobutene **1b** gave (*Z*)-*syn*-**4b**. The stereochemistry of both compounds was strictly proved by their X-ray diffraction study (Figures 1 and 2).† This result suggests that conversion of intermediate **A** to enamines **4** is mostly controlled by the size of the trihalomethyl group. Acid hydrolysis of compounds *anti*-**4a** and *syn*-**4b** under non-epimerizing conditions (dilute HCl, ethanol, 50 °C, 4 h) affords γ-nitroketones *anti*-**5a** (86%) and *syn*-**5b** (68%), respectively.‡ Unfortunately, all our attempts to transform them into the corresponding γ-diketones by the Nef reaction failed.

The reaction of nitroolefins **1a**,**b** with enamine **2** without a solvent (~30 °C, 0.5 h, kinetic control) produced mixtures with compositions **3a** : *anti*-**4a** = 80 : 20 and **3b** : *syn*-**4b** : *anti*-**4b** = = 78 : 14 : 8 (^{1}H and ^{19}F NMR data). An attempt at epimerization of *syn*-**4b** to *anti*-**4b** in a chloroform solution for one week gave only a small amount of the latter (8%). However, under thermodynamic control conditions (water, 2 days), enamine *anti*-**4b** was formed from oxazine **3b** as the major product [68%, δ_{CF_3} 96.2 (d, *J* 8.6 Hz)] in an equilibrium mixture with 32% of *syn*-**4b** [δ_{CF_3} 93.4 (d, *J* 8.5 Hz)]. A similar reaction (5 days) followed by

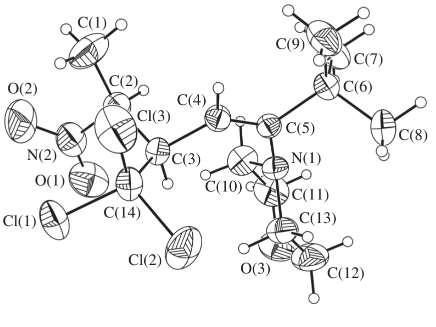


Figure 1 Molecular structure of enamine *anti*-**4a** (thermal ellipsoids at 50% probability level).

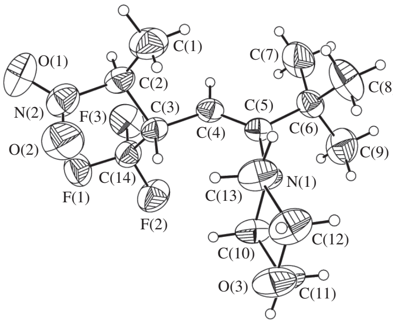


Figure 2 Molecular structure of enamine *syn*-**4b** (thermal ellipsoids at 50% probability level).

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† At 295 K crystals of *anti*-**4a** ($C_{14}H_{23}Cl_3N_2O_3$) are monoclinic, space group *C*2/*c*, $a = 27.173(3)$, $b = 7.8680(8)$ and $c = 18.6491(18)$ Å, $\beta = 114.931(10)°$, $V = 3615.6(6)$ Å^3, $Z = 8$, $d_{calc} = 1.373$ g cm^{-3}, $\mu = 0.519$ mm^{-1}, $F(000) = 1568$.

At 295 K crystals of *syn*-**4b** ($C_{14}H_{23}F_3N_2O_3$) are orthorhombic, space group *Pbca*, $a = 8.5638(9)$, $b = 15.4514(10)$ and $c = 25.1917(13)$ Å, $V = 3333.4(4)$ Å^3, $Z = 8$, $d_{calc} = 1.293$ g cm^{-3}, $\mu = 0.112$ mm^{-1}, $F(000) = 1376$.

At 150 K crystals of **8a** ($C_{14}H_{21}Cl_3N_2O_3$) are triclinic, space group $P\bar{1}$, $a = 7.6736(7)$, $b = 8.9452(8)$, and $c = 13.5436(6)$ Å, $\alpha = 74.587(7)°$, $\beta = 79.262(7)°$, $\gamma = 66.959(9)°$, $V = 821.17(11)$ Å^3, $Z = 2$, $d_{calc} = 1.503$ g cm^{-3}, $\mu = 0.571$ mm^{-1}, $F(000) = 388$.

Diffraction data were collected on an Xcalibur 3 automatic single-crystal diffractometer (graphite-monochromated MoKα radiation, ω-scans). The structures were solved by direct methods and refined by the full-matrix least-squares method using the SHELX-97 program package.[12] The H atoms were located geometrically using the riding model.

CCDC 788796–788798 contain 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, 2011.

‡ NMR spectra were recorded for $CDCl_3$ solutions of compounds at 400 MHz for ^{1}H and 100 MHz for ^{13}C.

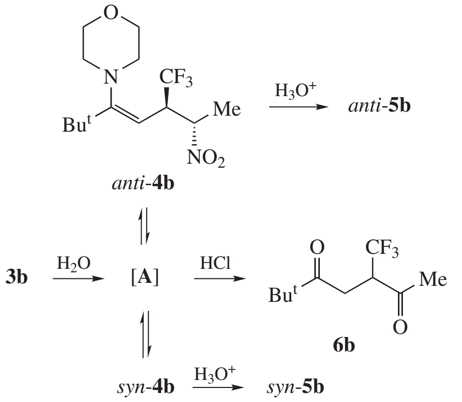
*(4*R**,6*R**)-6-*tert*-Butyl-3-methyl-6-morpholino-4-trichloromethyl-5,6-dihydro-4*H*-1,2-oxazine-2-oxide* **3a**. A solution of nitrobutene **1a** (2.04 g, 10.0 mmol) in dry benzene (10 ml) was added dropwise to the enamine **2** (1.69 g, 10.0 mmol) in 5 ml of dry benzene for 15 min with stirring. Then, the reaction mixture was stirred for 3 h at ~20 °C, the solvent was evaporated to half of its initial volume and 10 ml of hexane was added. The solid formed was filtered off and washed with hexane. Yield 2.24 g (60%), mp 151–152 °C, colourless powder. ^{1}H NMR, δ: 1.12 (s, 9H, CMe_3), 2.39 (d, 3H, Me, *J* 0.9 Hz), 2.57 (dd, 1H, H-5a, *J* 15.2, 8.4 Hz), 2.68 (dd, 1H, H-5b, *J* 15.2, 9.2 Hz), 2.99 [dt, 2H, N(C*H*H)$_2$, *J* 12.3, 4.2 Hz], 3.12 [dt, 2H, N(CH*H*)$_2$, *J* 12.3, 4.2 Hz], 3.50–3.57 [m, 5H, O(CH_2)$_2$, H-4]. ^{1}H NMR (C_6D_6), δ: 0.87 (s, 9H, CMe_3), 2.14 (d, 3H, Me, *J* 0.8 Hz), 2.16 (dd, 1H, H-5a, *J* 15.1, 9.5 Hz), 2.42 (dd, 1H, H-5b, *J* 15.1, 7.8 Hz), 2.55 [br. s, 2H, N(C*H*H)$_2$], 2.80 [br. s, 2H, N(CH*H*)$_2$], 3.06 (t, 1H, H-4, *J* 8.8 Hz), 3.24–3.36 [m, 4H, O(CH_2)$_2$]. ^{13}C NMR, δ: 21.0 (qd, 3-Me, *J* 131.6, 2.1 Hz), 26.8 (q. sept, *Me*$_3$C, *J* 126.3, 4.7 Hz), 30.2 (td, C-5, *J* 132.1, 4.8 Hz), 42.8 (m, Me$_3$*C*), 48.6 (tm, NCH_2, *J* 134.2 Hz), 56.7 (dddq, C-4, *J* 136.9, 5.6, 2.8 Hz), 68.3 (tm, OCH_2, *J* 142.8 Hz), 101.2 (tm, CCl_3, *J* 8.6 Hz), 101.7 (m, C-6), 118.9 (d. quint, C-3, *J* 11.1, 3.8 Hz). IR (KBr, ν/cm^{-1}): 1604, 1359. Found (%): C, 45.01; H, 6.20; N, 7.37. Calc. for $C_{14}H_{23}Cl_3N_2O_3$ (%): C, 45.00; H, 6.20; N, 7.50.

*(3Z,5*R**,6*R**)-2,2-Dimethyl-3-morpholino-6-nitro-5-(trichloromethyl)-hept-3-ene* **4a**. A solution of nitrobutene **1a** (2.04 g, 10.0 mmol) in 10 ml of dichloromethane was added dropwise to enamine **2** (1.69 g, 10.0 mmol) in 5 ml of dichloromethane for 15 min with stirring. Then, the reaction mixture was stirred for 3 days at ~20 °C, the solvent was evaporated to half of its initial volume and 10 ml of hexane was added. The solid formed was filtered off and recrystallized from hexane. Yield 3.66 g (98%), mp 105–106 °C. ^{1}H NMR, δ: 1.16 (s, 9H, CMe_3), 1.80 (d, 3H, Me, *J* 6.8 Hz), 2.96–3.06 [m, 2H, N(C*H*H)$_2$], 3.07–3.16 [m, 2H, N(CH*H*)$_2$], 3.72 [t, 4H, O(CH_2)$_2$, *J* 4.5 Hz], 4.39 (dd, 1H, H-5, *J* 10.0, 4.7 Hz), 5.14 (qd, 1H, H-6, *J* 6.8, 4.7 Hz), 5.42 (d, 1H, H-4, *J* 10.0 Hz). ^{13}C NMR, δ: 19.9 (qdd, C-7, *J* 130.6, 4.4, 2.9 Hz), 30.3 (q. sept, C-1, *J* 126.1, 4.9 Hz), 40.3 (undec., C-2, *J* 3.6 Hz), 52.5 (tt, NCH_2, *J* 134.7, 4.0 Hz), 60.4 (d. quint, C-5, *J* 138.1, 4.4 Hz), 67.8 (tm, OCH_2, *J* 142.6 Hz), 84.5 (d. quint. d, C-6, *J* 150.0, 4.3, 1.6 Hz), 100.6 (ddd, CCl_3, *J* 6.2, 4.4, 3.8 Hz), 116.2 (ddd, C-4, *J* 158.2, 6.0, 2.1 Hz), 163.5 (m, C-3). IR (KBr, ν/cm^{-1}): 1642, 1555, 1390, 1364, 1352. Found (%): C, 45.03; H, 6.28; N, 7.49. Calc. for $C_{14}H_{23}Cl_3N_2O_3$ (%): C, 45.00; H, 6.20; N, 7.50.

*(5*R**,6*R**)-2,2-Dimethyl-6-nitro-5-(trichloromethyl)heptan-3-one* **5a**. A mixture of enamine **4a** (0.37 g, 1.0 mmol), 2 ml of 0.1 M HCl solution and 2 ml of ethanol was stirred for 4 h at 50 °C. After cooling, the resulting solid was filtered off, washed with water, dried, and recrystallized from pentane. Yield 0.28 g (86%), mp 86–87 °C. ^{1}H NMR, δ: 1.25 (s, 9H, CMe_3), 1.58 (d, 3H, Me, *J* 6.9 Hz), 3.20 (dd, 1H, H-4a, *J* 19.6, 3.4 Hz), 3.48 (dd, 1H, H-4b, *J* 19.6, 5.5 Hz), 3.82 (dt, 1H, H-5, *J* 5.5, 3.0 Hz), 5.46 (qd, 1H, H-6, *J* 6.9, 2.6 Hz). IR (KBr, ν/cm^{-1}): 1708, 1552, 1362. Found (%): C, 39.70; H, 5.29; N, 4.61. Calc. for $C_{10}H_{16}Cl_3NO_3$ (%): C, 39.43; H, 5.29; N, 4.60.

For characteristics of compounds **3b**, **4b**, *syn*-**5b**, *anti*-**5b**, **7a**, **8a**,**b** and **9a**,**b**, see Online Supplementary Materials.

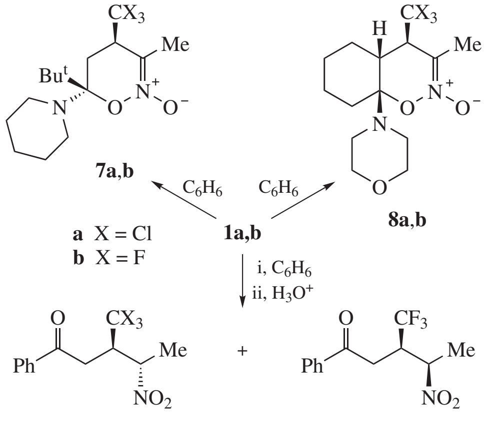
hydrolysis with dilute HCl in ethanol led to a mixture of diastereomeric γ-nitroketones *anti*-**5b** [28%, δ_{CF_3} 93.6 (d, *J* 9.2 Hz)] and *syn*-**5b** [33%, δ_{CF_3} 93.2 (d, *J* 9.2 Hz)] along with enamines *syn*-**4b** (37%) and *anti*-**4b** (2%). Apparently, in the case of CCl_3-nitrobutene **1a**, enamine *anti*-**4a** is both a kinetically and thermodynamically controlled product; as a result, *syn*-**4a** was not detected. Treatment of compound **3b** with concentrated HCl at ~15 °C for 0.5 h afforded γ-diketone **6b** in 72% yield (oxazine **3a** gave a complex mixture of products under these conditions) (Scheme 2).



Scheme 2

Note that [4+2]-heterocyclization leading to 1,2-oxazine *N*-oxides from 1,1,1-trihalo-3-nitrobut-2-enes **1a**,**b** is not limited to the use of the morpholine-derived pinacoline enamine **2**. Pyperidine-derived pinacoline enamine and 1-morpholinocyclohexene undergo a similar reaction to give oxazines **7a**,**b** and **8a**,**b** in high yields (Scheme 3); of these, trichloromethylated derivatives are more stable and can be stored at ~5 °C for a long time. The stereochemistry of compounds **8a**,**b** was reliably determined by X-ray diffraction analysis of crystalline specimens of compound **8a** (Figure 3);[†] it is in good agreement with literature data on related but non-halogenated analogues of compounds **8**.[10,11]

Unlike enamines of aliphatic ketones, we failed to isolate the respective 1,2-oxazine *N*-oxides and nitroalkylated enamines in the case of 1-morpholino-1-phenylethene (morpholine-derived acetophenone enamine) because these products readily underwent hydrolysis in the presence of atmospheric moisture. The same reaction performed in benzene followed by acid hydrolysis of the reaction mixture resulted in a CCl_3-γ-nitroketone (yield 86%) as one diastereomer *anti*-**9a** and a CF_3-γ-nitroketone (yield 75%) as a mixture of approximately equal amounts of *anti*-**9b** and *syn*-**9b** (^{1}H and ^{19}F NMR spectroscopic data) (Scheme 3).



Scheme 3

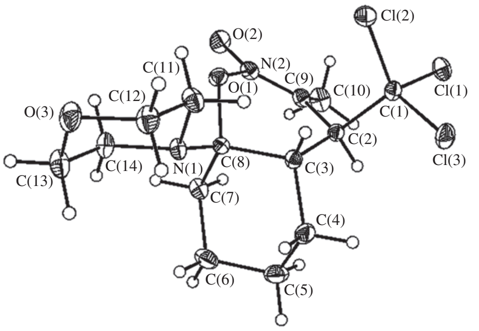


Figure 3 Molecular structure of 1,2-oxazine *N*-oxide **8a** (thermal ellipsoids at 50% probability level).

To conclude, depending on conditions, reactions of (*E*)-1,1,1-trihalo-3-nitrobut-2-enes with enamines represent a promising access to 1,2-oxazine *N*-oxides, nitroalkylated enamines, β-trihalomethyl-γ-nitroketones or γ-diketones, with the processes occurring diastereoselectively. The products described here are undoubtedly of interest for chemo- and stereoselective syntheses of polyfunctional CCl_3- and CF_3-containing compounds.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.03.020.

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