Synthesis and thermolysis of a spiro-fused oxadiazoline — Evidence for sequential formation of carbene and oxirane intermediates, and for oxirane dimerization

Arkadiusz Klys, Wojciech Czardybon, John Warkentin, and Nick Henry Werstiuk

Abstract: The spiro-fused oxadiazoline, 3,4-diaza-2,2-dimethyl-1,6,10-trioxaspiro[4.5]dec-3-ene, when thermolysed in a sealed tube in benzene-d_6 at 110 °C, afforded acetone and an apparent oxirane intermediate (2,2-dimethyl-1,4,8-trioxaspiro[2.5]octane) that could not be isolated. Attempts to isolate the oxirane gave a dimer (8,8,11,11-tetramethyl-1,5,7,10,12,16-hexaoxadispiro[5.2.5.2]hexadecane) as the major product. The oxirane is thermally stable at 110 °C but it is very sensitive to water, as indicated by its gradual disappearance after the tube was opened. The dimer of the oxirane is believed to form from a cation arising from the ring-opening of the oxirane when it reacts with moisture. This cation then reacts with the oxirane itself to regenerate water, which is effectively a catalyst for conversion of the oxirane to the dimer.

Key words: carbene, dioxacarbene, dialkoxyoxirane, oxadiazoline, 2,5-dihydrooxadiazole.

Résumé : Opérant dans un tube scellé, en solution dans du benzène-d_6 et à une température de 110 °C, on a réalisé la thermolyse de l'oxadiazoline à fusion spiro, 3,4-diaza-2,2-diméthyl-1,6,10-trioxaspiro[4.5]déc-3-ène, qui conduit à la formation d'acétone et d'un intermédiaire qui n'a pas été isolé et qui serait le 2,2-diméthyl-1,4,8-trioxaspiro[2.5]octane. Des essais en vue d'isoler l'oxirane ont conduit à la formation, comme produit majeur, du dimère 8,8,11,11-tétraméthyl-1,5,7,10,12,16-hexaoxadispiro[5.2.5.2]hexadécane. L'oxirane est thermiquement stable à 110 °C, mais il est très sensible à l'eau, comme on peut en déduire de sa disparition graduelle une fois que le tube est ouvert. On croit que le dimère de l'oxirane se forme à partir d'un cation qui se formerait à partir d'une ouverture de cycle de l'oxirane par réaction avec de l'eau. Ce cation pourrait alors réagir avec l'oxirane lui-même pour régénérer l'eau qui ne serait de fait qu'un catalyseur dans la conversion de l'oxirane en dimère.

Mots clés : carbène, dioxacarbène, dialkoxyoxirane, oxadiazoline, 2,5-dihydrooxadiazole.

[Traduit par la Rédaction]

Introduction

Many 2,2-dialkoxy-5,5-dialkyl-Δ^3-1,3,4-oxadiazolines (**1**), also known as 2,5-dihydro-2,2-dialkoxy-5,5-dialkyl-1,3,4-oxadiazoles, have been prepared and thermolyzed in benzene solution at temperatures near 110 °C (1). Their thermolysis is generally formulated as involving a 1,3-dipolar cycloreversion, by loss of N_2, to form a carbonyl ylide intermediate (**2**). Experimental evidence for a possible carbonyl ylide intermediate has been presented in only a few instances (2), suggesting that they are short-lived, if they bear two alkoxy groups, or that they are not real. Recent computational results[2] suggest that whether or not an ylide is a real intermediate in thermolysis of some oxadiazolines depends on the level of theory employed. In any case the ultimate products of oxadiazoline fragmentation are N_2, a ketone, and a dialkoxycarbene (**3**). An ylide intermediate, if real, fragments rapidly to the latter two products, Scheme 1. The carbene, a nucleophile, could then add to the ketone carbonyl group, either in a stepwise process via intermediate **4** or in a concerted reaction leading directly to oxirane **5**.

The existence of a ylide intermediate in oxadiazoline thermolysis has been questioned, on the basis of results of computation at a low level of theory. Smith (3) proposed a concerted reaction to afford a dialkoxycarbene without the intermediacy of a carbonyl ylide. If that were the case, products from apparent ylide intermediates could still arise via **4** or **5**, from attack of the carbene on the ketone, if **5** were to open to **2**.

We now present evidence for the formation of carbene **8** and oxirane **9** intermediates in the thermolysis of the spiro-fused oxadiazoline **6**, Scheme 2. Although a carbonyl ylide

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[2]W. Czardybon, J. Warkentin, and N.H. Werstiuk. Unpublished computations.

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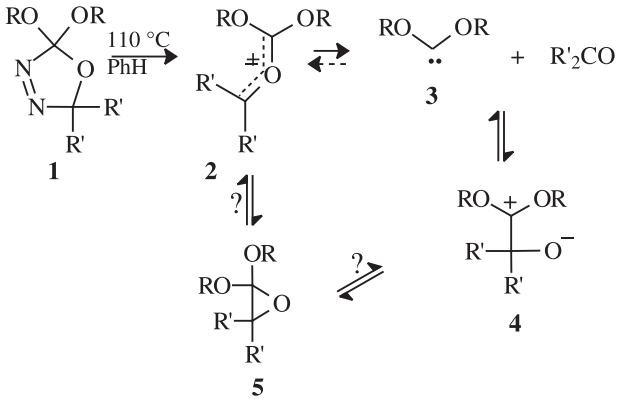
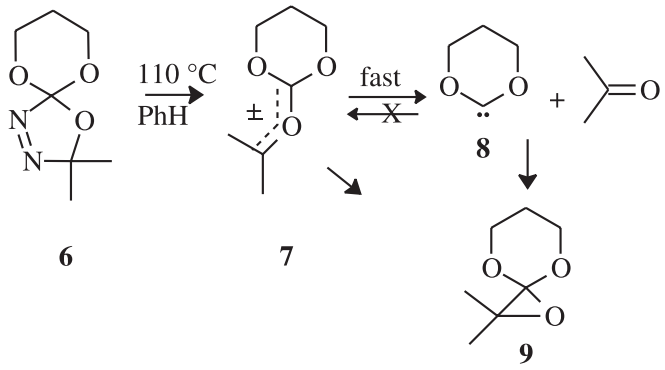
Scheme 1.



Scheme 2.



intermediate **7** is possible from a mechanistic point of view, there is not any experimental evidence for it in this case.

Results and discussion

Oxadiazoline **6** was prepared by hydrazinolysis of carbonate **10**, conversion of the product (**11**) to the isopropylidene hydrazone **12**, oxidative cyclization of **12** to **13** with $Pb(OAc)_4$ in dichloromethane (2*b*), and acid catalysed cyclization of **13** to **6**, Scheme 3. Heating of a benzene solution of **6** (72 h) at 110 °C in a sealed tube gave a major product (ca. 60% by GC) and several minor products, one of which had a longer GC retention time. The initial major product was transformed, at room temperature, into the latter minor product after the tube was opened. Sometimes this process took a few hours and sometimes about one day. It is probably related to the rate at which the solution absorbed water from the atmosphere after the reaction tube was opened. Chromatography of the initial reaction mixture caused the same transformation.

We suggest the following interpretation of these results, Scheme 4. Thermolysis of **6** leads to loss of N_2 to form carbonyl ylide **7**. Fragmentation of **7** to **8** is probably slowed, relative to the rate of fragmentation of analogous ylides that lead to an acyclic dialkoxycarbene, because carbene **8** is U-shaped. The U-conformation of allyloxymethoxycarbene lies about 11 kcal mol^{-1} higher in energy than the W-conformation (4). That energy difference could mean that the transition state for formation of a U-shaped dialkoxycarbene from a carbonyl ylide is higher in energy than an analogous transition state for fragmentation to a W-shaped dialkoxycarbene. Nevertheless, a large fraction of the ylide fragments to the carbene (**8**) and acetone, as discussed below.

The longer lifetime of **7** could lead to some closure to oxirane **9**, which was a major initial product, but **9** must also come from attack of the carbene on acetone, as indicated by the results of inclusion of 1,1,1-trifluoroacetone, at two different concentrations, during the thermolysis. With a 5-fold excess of trifluoroacetone (0.5 mol/L), oxiranes **9** (3 parts) and **14** (7 parts) as well as diol **18** (4 parts) were the major products obtained before workup. With a 10-fold excess of trifluoroacetone (1.0 mol/L), oxirane **9** was not detected but **14** and **18** were observed in approximately a 4:3 ratio. Workup led to the conversion of **14** to a single diastereomer of **15** and to the loss of **18**. Products from **18** were not identified. The fact that formation of **9** was suppressed at the higher concentration of trifluoroacetone must mean that most of the **9** observed when trifluoroacetone was absent, or present at a low concentration, arose from addition of the free carbene (**8**) to acetone. Thus, fragmentation of presumed ylide **7**, although slowed because of the conformation imposed on carbene **8**, must still be fast relative to electrocyclic ring closure of **7** to **9**. Oxirane **9** must be formed primarily by reaction of carbene **8** with acetone. Trifluoroacetone, when present at a relatively high concentration, is expected to trap essentially all of the free carbene to form **14**. How **14** reacts to afford **15** is not known.

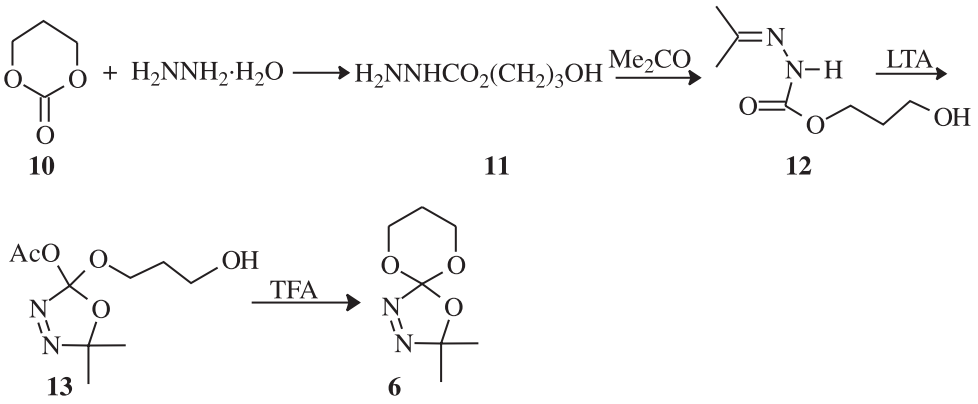
We did not find any **17**, which should have been present if **9** were in equilibrium with **16**, nor was any **20** detected. Compound **20** would be an expected product from the alternative ring opening of **9** to ylide **7**.

The finding of **9** and **14** is supported by precedent. One cyclic dialkoxyoxirane model (**24**) for **9** is known (5), and one 2,2-dimethoxyoxirane **25** has been reported (1*g*). In the absence of water, **9** must be relatively stable, since it can survive heating of **6** at 110 °C in benzene for 72 h. Oxirane **9** cannot undergo reversible ring opening rapidly, either to the carbonyl ylide **7** or to the isomeric zwitterion **16**, because those intermediates would react with trifluoroacetone.

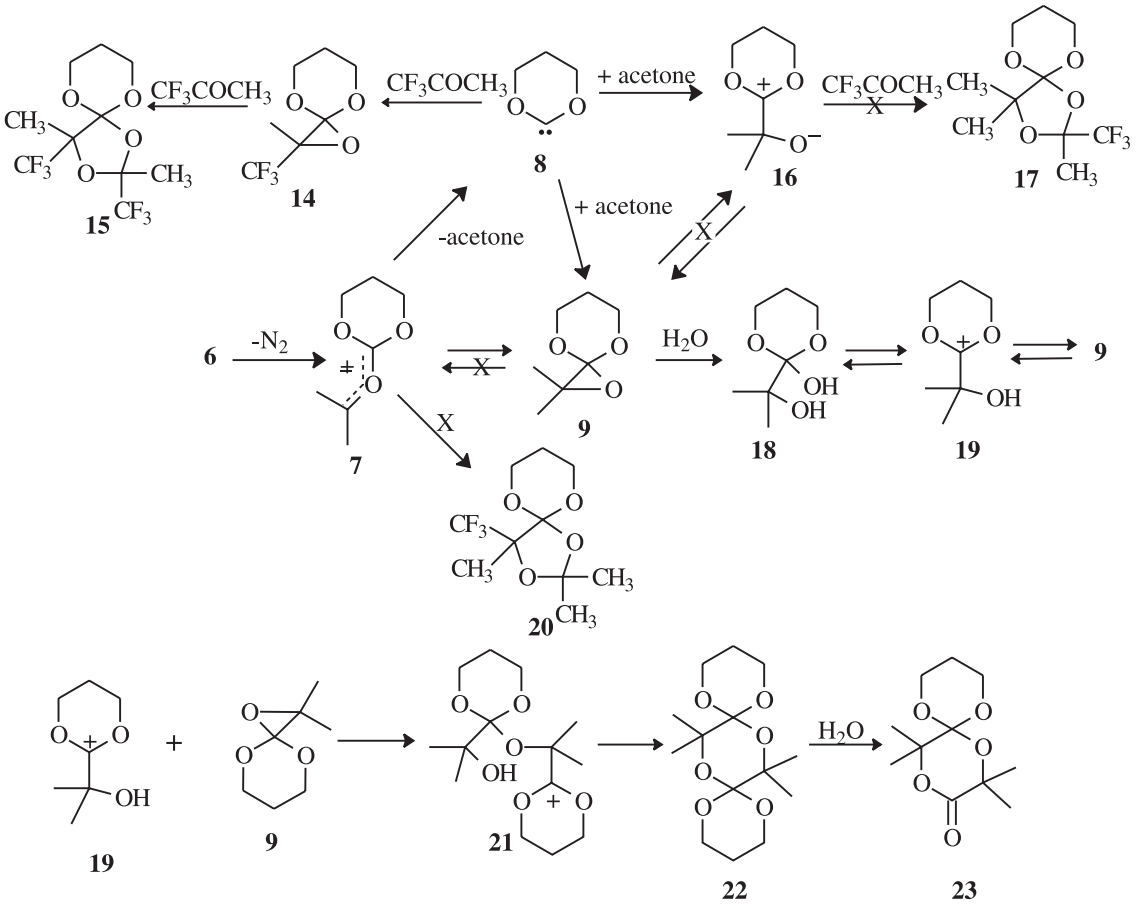
In the presence of moisture, which enters slowly from the atmosphere once the sealed tube has been opened, oxirane **9** undergoes ring opening to the dihydroxy compound **18**, which must itself be in equilibrium with oxirane **9**, via cationic intermediate **19**, Scheme 4. Cation **19** reacts with oxirane **9** to afford 8,8,11,11-tetramethyl-1,5,7,10,12,16-hexaoxadispiro[5.2.5.2]hexadecane (**22**) the structure of which was secured by means of single crystal X-ray diffraction. Presumably the mechanism of formation of **22** involves intermediate **21**. Such a reaction would be unlikely in the presence of excess water, because there would not be any oxirane available, but it is likely when the available water is that absorbed from the atmosphere. Water is probably catalytic at very low concentrations, promoting the conversion of **9** to **22** without being consumed significantly. Lactone **23** is presumably the result of partial hydrolysis of **22** during the workup.

The present results may be surprising in view of the fact that oxadiazoline **26**, upon thermolysis in benzene, was reported (2*b*) to afford the carbene dimer **27** (ca. 20%), Scheme 5. An oxirane dimer, analogous to **22**, was not re-

Scheme 3.



Scheme 4.

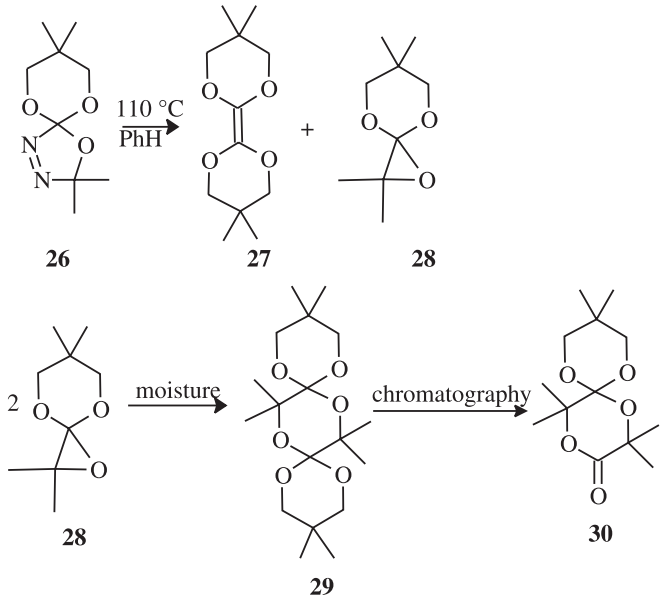


ported and in the present case, a carbene dimer was not isolated from thermolysis of **6**. Checking the NMR spectra and mass spectra again confirmed that the compound isolated from **26** was indeed **27**. However, **27** was obtained in only about 20% yield and only one additional, minor product (**30**) was identified. Compound **30**, analogous to **23**, is presumably derived from dimerization of oxirane **28** to **29** and partial hydrolysis of the latter, Scheme 6 (2*b*). The presumed intermediates, **28 and 29**, were not seen. Similarly, the thermolysis of **6** in the absence of trifluoroacetone gave many products that could have included the dimer of **8**.

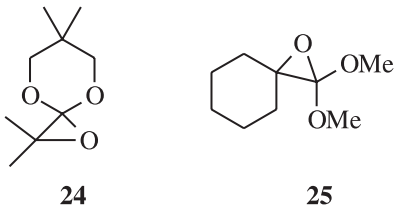
In conclusion, it is likely that **6** and **26** undergo thermolysis by analogous mechanisms, affording products from the appropriate carbenes and from reaction of those carbenes with acetone. Although not all of the products were isolated and identified by different workers, there is no conflict between the results from thermolysis of **6** and **26**, which are expected to be qualitatively the same. However, it appears that the products are very sensitive to the humidity and to the adsorbent used in chromatographic separations.

Catalysis of organic reactions by water is rare but not new. It is believed to occur, for example, during chlorination of olefins (6) and in the ketonization of enols (7). In the present case, water protonates and opens a highly reactive dialk-

Scheme 5.



Scheme 6.



oxyoxirane and the cationic intermediate attacks an oxirane molecule to afford an oxirane dimer.

Experimental

^{1}H NMR spectra run in benzene-d_6 are referenced to the signal for residual H in the solvent, set at 7.15 δ for benzene. ^{13}C NMR spectra were run in $CDCl_3$ and are referenced to the solvent signal at 77.16 δ for the center line.

1,3-Dioxan-2-one

1,3-Propanediol (15.6 g, 0.20 mol) and diethyl carbonate (30 g, 0.25 mol) in a 100 mL round-bottom flask fitted with a distillation column, were treated with freshly prepared NaOMe made from Na (0.18 g) and MeOH (3 mL). The solution was slowly heated to 100 °C and alcohols (methanol and ethanol, 70–85 °C at the top of the column) were collected. The temperature in the flask was slowly increased to 170 °C over a 5 h period. During this time about 80% of the product distilled at 130–150 °C. After cooling, the column was removed, excess diethyl carbonate and a trace amount of ethanol were distilled out (oil pump) and the product was distilled at 130–160 °C. Some fractions crystallized spontaneously; those that did not were dissolved in ether and the solutions were cooled to –55 °C to cause crystallization. The total yield of white crystalline product (8) was 7.65 g (30%), mp 45–46 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.13 (quint, ^3J = 5.6 Hz, 2H) and 4.44 (t, ^3J = 5.6 Hz, 4H).

Synthesis of hydrazinecarboxylic acid, 3-hydroxypropyl ester (11)

To compound **10** (2.0 g, 20 mmol) in 10 mL of ethanol, in a round-bottom flask with an efficient condenser, was added hydrazine hydrate (98%, 20 mmol) during 20 min. After refluxing for 18 h the volatiles were evaporated leaving a colourless oil (2.7 g, 99%) that solidified in the freezer (9). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.75 (quint, ^3J = 6.3 Hz, 2H), 3.57 (t, ^3J = 6.3 Hz, 2H), and 4.08 (t, ^3J = 6.3 Hz, 2H).

Synthesis of 12

After acetone (15 mL) and **11** (1.0 g, 7.5 mmol) had formed a homogeneous solution (30–45 min), it was treated overnight with anhydrous Na_2SO_4. Decanting and evaporation of the acetone left **12** as a colourless oil (1.29 g, 99%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.83 and 1.91 (s and m, 5H), 2.05 (s, 3H), 3.72 (t, ^3J = 5.8 Hz, 2H), and 4.40 (t, ^3J = 5.8 Hz, 2H).

Synthesis of 6

To an ice-cooled heterogeneous mixture of $Pb(OAc)_4$ (LTA) (7.4 g, 16.5 mmol) in dry CH_2Cl_2 (15 mL) was added slowly, during 1h, a solution of **12** (2.5 g, 14.4 mmol) in 10 mL of CH_2Cl_2. Glacial acetic acid (two drops) was added and the yellow mixture was stirred for 4 h at 0 °C and for 16 h at room temperature. Filtration through Celite, washing with a $NaHCO_3$ solution (5%, 2 × 50 mL), drying over Na_2SO_4, and concentration gave a crude material **13** that was dissolved in CH_2Cl_2 (20 mL). Trifluoroacetic acid (3 drops) was added and, after stirring for 90 min, thin layer chromatography (TLC) analyses showed that conversion of **13** to **6** was complete. Concentration and column chromatography on silica gel (hexane/EtOAc = 4:1) gave **6** that could be crystallized from pentane at –55 °C to give 0.55 g (22%) of pure **6,** mp 63–64 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.53 (s, 6H), 1.88 (m, 1H), 2.17 (m, 1H), 4.20 (m, 2H), and 4.60 (m, 2H). The methyl groups of the oxadiazoline ring of a close analog of **6** absorb at δ = 1.52 (1*b*).

Thermolysis of 6 in benzene

A solution of **6** (344 mg, 2.0 mmol) in dry benzene was sealed into a glass tube and the tube was immersed in an oil bath at 110 °C for 72 h. One major product was detected by GC along with two minor products having longer retention times. A GC-MS gave a mass of 144 for the major product, which is consistent with oxirane **9**. The major product was transformed into one of the minor products as the feedstock aged. Isolation of the growing minor product and single crystal X-ray diffraction showed it to be **22**. The other material with a long retention time was identified as **23** on the basis of spectroscopy and analogy. A compound similar to **23**, except for a phenyl substituent, has been reported (2*b*). Chromatography (Chromatotron, SiO_2) afforded primarily the material with the longer GC retention time.

Compound 9

Compound **9** could not be isolated. In the ^{1}H NMR spectrum of the crude (200 MHz, C_6D_6) there was a strong singlet signal at 0.42 δ that disappeared slowly when the tube was opened. GC-MS *m/z*: 144 (M^+), 143 $(M-1)^+$,129 $(M-Me)^+$, 114 $(M-CH_2O)^+$, and 87 ($C_4H_7O_2^+$, 100%).

Compound 22

^{1}H NMR (500 MHz, C_6D_6) δ: 0.72 (d, J = 12 Hz, 2H), 1.68 (s, 12H), 1.73 (m, 2H), 3.44 (m, 4H), and 4.10 (t, J = 12 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.76, 24.86, 30.21, 59.47, 79.13, and 108.43. MS (CI, NH_3) m/z: 289 $(M + H)^+$ (100), 288 (M^+, 14), 145 $(M/2 + H)^+$ (37), and 128 (33). The molecular structure of **22** was secured by means of single crystal X-ray diffraction.

Compound 23

^{1}H NMR (200 MHz, C_6D_6) δ: 1.35 (m (br), 2H), 1.44 (s, 6H), 1.51 (s, 6H), 3.28 (m, 2H), and 3.78 (m, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 23.8, 24.3, 28.6, 29.8, 60.3, 84.9, 108.0, and 172.5. MS (EI) m/z: 231 (M + 1), 215, 200, 172, 164, 129, 103, and 70 (100%); MS (CI, NH_3) m/z: 231 $(M + H)^+$ (100), 173 (3), 145 (13), and 128 (34).

Thermolysis of 6 in benzene containing 1,1,1-trifluoroacetone in 5-fold excess

A solution of **6** (172 mg, 1.0 mmol) in benzene (10 mL) containing 1,1,1-trifluoroacetone (560 mg, 5.0 mmol) was heated as described above. Three products, with GC retention times (rt) of 5.2, 6.1, and 6.9 min were obtained. The fraction with rt = 6.9 min was collected and shown to be **15** (one diastereomer) by means of NMR spectroscopy (^{1}H, ^{19}F) and mass spectrometry. The mass spectra of the other fractions did not match the expectation for **17** which, like **15**, should have provided $(M + H)^+$ and $(M + NH_4)^+$ signals in the CI, NH_3 spectra.

Compound 15

^{1}H NMR (200 MHz, C_6D_6) δ: 1.38 (s, 3H), 1.43 (s, 3H), 1.52 (m, 2H), 3.34 (m, 2H), 3.74 (m, 2H). ^{19}F NMR (188.3 MHz, $CDCl_3$, ref. external $CFCl_3$ at –71.3 δ) δ: –78.82 (s), and –78.84 (s). MS (CI, NH_3) m/z: 328 $(M + NH_4)^+$ (12), 311 $(M + H)^+$ (100), 241(37), and 199 (15).

Compound 18

This material was not isolated in pure form. Structure **18** was assigned tentatively on the basis of its GC retention time, its mass spectrum (GC-MS) in which $(M\text{-}H_2O)^+$ was prominent at m/z = 144, and the ^{1}H NMR spectrum (200 MHz, C_6D_6) of a crude sample, that showed absorption at δ = 0.72, 1.74 (s, 5H), 3.41(m, 4H), 4.33 (s, 1H), and 5.95 (s, 1H). As expected for structure **18**, the compound was very unstable.

Thermolysis of 6 in benzene containing 1,1,1-trifluoroacetone in 10-fold excess

A solution of **6** (172 mg, 1.0 mmol) in benzene (10 mL) containing 1,1,1-trifluoroacetone (1.12 g, 10 mmol) was heated as described above. Two products were identified by GC as **15** and, tentatively, as the trifluoromethyl analogue of **18**.

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References

1. See, for example: (*a*) N. Merkley, D.L. Reid, and J. Warkentin. Tetrahedron Lett. **43**, 1927 (2002); (*b*) N. Merkley and J. Warkentin. http://www.Arkat-usa.org/ark/journal/Volume2/Part3/Tee/001/001_index.htm ARKIVOC [online], **2**, 12 (2001); (*c*) N. Merkley, P.C. Venneri, and J. Warkentin. Can. J. Chem. **79**, 312 (2001); (*d*) N. Merkley and J. Warkentin. Can. J. Chem. **78**, 942 (2000); (*e*) N. Merkley, M. El-Saidi, and J. Warkentin. Can. J. Chem. **78**, 356 (2000); (*f*) M. Dawid, G. Mloston, and J. Warkentin. J. Org. Lett. **3**, 2455 (2001); (*g*) M. Dawid, P.C. Venneri, and J. Warkentin. Can. J. Chem. **79**, 110 (2001); Addendum, **79**, 1294 (2001); (*h*) V. Nair, S. Bindu, and L. Balagopal. Tetrahedron Lett. **42**, 2043 (2001); (*i*) P.C. Venneri and J. Warkentin. Can. J. Chem. **78**, 1194 (2000); (*j*) J.A. Dunn, J.P. Pezacki, M.J. McGlinchey, and J. Warkentin. J. Org. Chem. **64**, 434 (1999); (*k*) J.H. Rigby, S. Laurent, A. Cavezza, and M.J. Heeg. J. Org. Chem. **63**, 5587 (1998); (*l*) H.M. Muchall, N.H. Werstiuk, B. Choudhury, J. Ma, J. Warkentin, and J.P. Pezacki. Can. J. Chem. **76**, 238 (1998); (*m*) J.H. Rigby, A. Cavezza, and M.J. Heeg. J. Am. Chem. Soc. **120**, 3664 (1998); (*n*) J.P. Ross, P. Couture, and J. Warkentin. Can. J. Chem. **75**, 1331 (1997); (*o*) P. Couture, D.L. Pole, and J. Warkentin. J. Chem. Soc., Perkin Trans. 2, 1565 (1997); (*p*) D.L. Pole and J. Warkentin. J. Org. Chem. **62**, 4065 (1997); (*q*) J.H. Rigby, A. Cavezza, and G. Ahmed. J. Am. Chem. Soc. **118**, 12848 (1996); (*r*) K. Kassam, D.L. Pole, M. El-Saidi, and J. Warkentin. J. Am. Chem. Soc. **116**, 1161 (1994); (*s*) M. El-Saidi, K. Kassam, D.L. Pole, T. Tadey, and J. Warkentin. J. Am. Chem. Soc. **14**, 8751 (1992).
2. (*a*) P. Couture, M. El-Saidi, and J. Warkentin. Can. J. Chem. **75**, 326 (1997); (*b*) N. Merkley and J. Warkentin. Can. J. Chem. **80**, 1187 (2002).
3. W.B. Smith. J. Org. Chem. **60**, 7456 (1995).
4. D.L. Reid and J. Warkentin. J. Chem. Soc., Perkin Trans. 2, 1980 (2000).
5. M.S. Newman and E. Kilbourn. J. Org. Chem. **35**, 3186 (1970).
6. V.A. Tikhomirov, V.V. Smirnov, and I.V. Rostov. Zh. Fiz. Khim. **70**, 183 (1996); Chem. Abstr. 124, 288 514 (1996).
7. O.N. Ventura, A. Lledos, R. Bonaccorsi, J. Bertran, and J. Tomasi. Theor. Chim. Acta, **72**, 175 (1987).
8. S. Sarel, J. Katzhendler, and L.A. Poles. J. Chem. Soc. B, 1847 (1971); S. Li and P. Deslongchamps. Tetrahedron Lett. **35**, 5641 (1994).
9. M. Yan, Z. Zhang, X. Lei, Y. Xi, and Y. Xu. Yaoxue Xuebao, **20**, 219 (1985); Chem. Abstr. 104, 109 566 (1986).