Synthesis of 3-Phenyl-5-(trifluoromethyl)isoxazole and 5-Phenyl-3-(trifluoromethyl)isoxazole

James W. Pavlik*, Jennifer A. Lowell, and Vuthichai Ervithayasuporn

Department of Chemistry and Biochemistry
Worcester Polytechnic Institute, Worcester, MA 01609
Received May 23, 2005

Reaction of 4,4,4-trifluoro-1-phenyl-1,3-butanedione with hydroxylamine led to the formation of 5-hydroxy-3-phenyl-5-(trifluoromethyl)-4,5-dihydroisoxazole which was dehydrated to 3-phenyl-5-(trifluoromethyl)isoxazole. This isomer can also be synthesized by reaction of 4-chloro-4-phenyl-1,1,1-trifluoro-3-buten-2-one with sodium azide. The regioisomer, 5-phenyl-3-(trifluoromethyl)isoxazole was synthesized by reaction of 1,1,1-trifluoro-4-phenylbut-3-yn-2-one with hydroxylamine and by the reaction of 3-chloro-1-phenyl-4,4,4-trifluorobut-2-en-1-one with sodium azide. Both isomers were characterized by mass and NMR spectroscopy.

J. Heterocyclic Chem., **42**, 1253 (2005).

As part of our interest in the photochemistry of substituted isoxazoles [1] we were interested in obtaining samples of 3-phenyl-5-(trifluoromethyl)isoxazole (**1**) and 5-phenyl-3-(trifluoromethyl)isoxazole (**2**). The synthesis of **2** was originally reported by Carr, Durham, and Hass

Figure 1

[2]. Their synthesis started by allowing 4,4,4,-trifluoro-1-phenyl-1,3-butanedione (**3**) to react with hydroxylamine. According to these authors this reaction led to

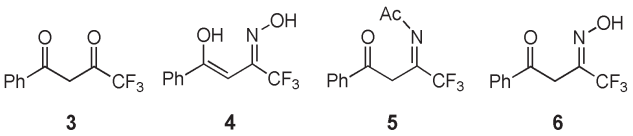

Figure 2

the formation of the (*Z*)-oxime **4**. Reid and Calvin [3] had previously carried out this reaction and reported the formation of a compound with a melting range of 143.1-144.1 that gave elemental analysis consistent with oxime **4**. Carr, Durham, and Hass reported the reaction of **4** in refluxing acetyl chloride led to the formation of 5-phenyl-3-(trifluoromethyl)isoxazole (**2**) in 67% and to the N-acetylated oxime **5** in 30%. They claimed that the latter is formed by acid catalyzed isomerization of the (*Z*)-oxime to the (*E*)-isomer. This stereoisomer is unable to cyclize to the isoxazole and therefore undergoes acetylation.

In our laboratory **3** was allowed to react with hydroxylamine hydrochloride in the presence of 0.5 *N* HCl and ethanol according to the published procedures [2,3]. This led to the formation of a white crystalline compound in 87% yield that exhibited a melting range of 144.0-144.2 ºC, identical to that reported [3].

The mass spectrum of this compound exhibited a molecular ion at m/z = 231, consistent with $C_{10}H_8F_3NO_2$, the molecular formula of **4**.

The ^{1}H-NMR of this compound exhibited a 5H multiplet at δ 7.36-7.66, consistent with the protons of the phenyl group, a 1H singlet at δ 2.99 (D_2O exchangeable), indicating an O-H proton, and an AB quartet at δ 3.61 (J_{AB} = 17.9 Hz). This spectrum is puzzling because the (*Z*)-oxime structure **4** assigned to this material would be expected to exhibit a 1H singlet in the vinyl region, not a 2H AB quartet at this chemical shift. Although a 2H signal might suggest that the oxime is in the keto form **6**, the two protons in this structure should appear as a singlet. Furthermore, the IR spectrum of the isolated compound shows O-H absorption at 3158 cm^{-1}, but no signal in the carbonyl range. Thus, this material cannot be the keto-oxime **6**.

At this point it became clear that the product from the reaction of 4,4,4-trifluoro-1-phenyl-1,3-butanedione (**3**) and hydroxylamine is not an oxime but is a compound isomeric with it. We suggest that it is a 5-hydroxy-4,5-dihydroisoxazole, either 3-trifluoromethyl-5-phenyl (**7**) or the 5-(trifluoromethyl)-3-phenyl isomer (**8**). Since this material was claimed to be the precursor of 3-(trifluoromethyl)-5-phenylisoxazole (**2**), the structure was originally assumed to be **7**. This conclusion is not supported by the ^{13}C-NMR

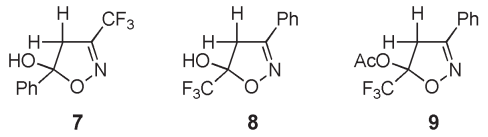

Figure 3

spectrum. Thus, in addition to signals for the carbons of the benzene ring, the ^{13}C-NMR spectrum exhibited a CH_2 signal (negative DEPT-135 signal) at δ 43.1 for the C-4 carbon and signals at δ 157.6 and 106.5 for two quaternary carbons. These were unambiguously assigned to C3 and C5 respectively, since the sp^2 hybridized imine C3 carbon is certainly expected to appear downfield from the sp^3 hybridized C5 carbon. Interestingly, it is this C5 carbon that appears as a quartet showing long-range coupling (J = 33.1 Hz) with the fluorine nuclei of the trifluoromethyl group while the signal for the C3 carbon shows no such coupling. This demands that the CF_3 group is bonded to C5. The phenyl group is then at C3. This leads to the conclusion that the compound is 5-hydroxy-3-phenyl-5-(trifluoromethyl)-4,5-dihydroisoxazole (**8**).

This structural conclusion has additional implications regarding the synthetic work of Carr, Durham, and Hass [2]. They reported that reaction of this compound, which they thought was the (*Z*)-oxime **4**, resulted in the formation of a mixture of 5-phenyl-3-(trifluoromethyl)isoxazole (**2**) and the acetylated oxime **5**. Neither of these structural assignments can be correct.

In our hands, reaction of 5-hydroxy-3-phenyl-5-(trifluoromethyl)-4,5-dihydroxyisoxazole (**8**) with acetyl chloride led to a single white crystalline compound with a melting point of 115.2-116.0 ºC, very close to the melting point reported by Carr, Durham, and Hass [2] for the (*E*)-O-acetylated oxime **5**. The mass spectrum of this compound exhibited a molecular ion at m/z = 273, consistent with the addition of an acetyl group to the compound. The ^{1}H-NMR spectrum revealed signals for the phenyl protons and the 2H AB quartet as was observed for the reactant. In addition, however, a 3H singlet was also present at δ 2.2, consistent with the methyl group of an acetyl group. It is now clear that this compound is not the (*E*)-acetylated oxime **5** but is the O-acetylated dihydroisoxazole **9**.

In contrast to these results, refluxing dihydroisoxazole **8** in benzene containing *p*-toluenesulfonic acid led to the formation of a crystalline product, mp 78.0-79.5 ºC, which exhibited a molecular ion in its mass spectrum at m/z 213, 18 mass units less than the reactant. This indicates that the reactant has undergone dehydration to yield $C_{10}H_6F_3NO$, the molecular formula for 3-phenyl-5-(trifluoromethyl)-isoxazole (**1**). The mass spectrum also exhibited an intense signal at m/z 144 indicating that the major fragmentation pathway involves cleavage of a trifluoromethyl group.

The NMR spectra of this compound is consistent with this structural assignment. Thus, dehydration is accompanied by replacement of the AB quartet in the ^{1}H-NMR spectrum due to the two non-equivalent C4 protons in **8**, with a 1H singlet at δ 7.01 due to the C4 proton of **1** and 2H and 3H multiplets at δ 7.83-7.80 and 7.50-7.26 respectively for the five phenyl protons. The ^{13}C-NMR spectrum exhibited four signals from δ 127-131 for the carbons of the phenyl group, a quartet (J = 270.2 Hz) at δ 117.9 for the carbon of the trifluoromethyl group, and signals at δ 162.6, 159.2, and 103.5 for the carbon atoms at ring positions 3, 5 and 4 of the isoxazole ring respectively. Significantly, although the signals for the C3 and C4 carbon atoms appeared as sharp singlets, the signal for the C5 carbon at δ 159.2 appeared as a quartet (J = 42.6 Hz) due to the long range coupling with the fluorine of the trifluoromethyl group. This confirms that the trifluoromethyl group is bonded to the C5 carbon of the isoxazole ring and that the product is 3-phenyl-5-(trifluoromethyl)isoxazole (**1**).

Laurent and colleagues have reported [4] that 3-phenyl-5-(trifluoromethyl)-isoxazole (**1**) can also be synthesized by reaction of 4-chloro-4-phenyl-1,1,1-trifluorobut-3-en-2-one (**10**) [5] with sodium azide in acetic acid. We have repeated this reaction and found that the isoxazole formed

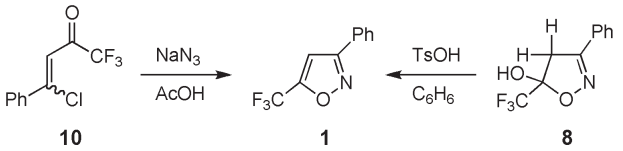

Figure 4

from **10** is chromatographically and spectroscopically identical to the product obtained from **8**. We conclude, therefore, that both compounds are 3-phenyl-5-(trifluoromethyl)isoxazole (**1**).

5-Phenyl-3-(trifluoromethyl)isoxazole **2** was first reported by Tanaka and colleagues [6] to result from the cycloaddition of trifluoromethylacetonitrile oxide (**12**),

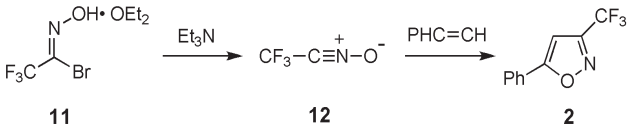

Figure 5

generated from the trifluoroacetoxyhydroximoyl bromide (**11**) with phenylacetylene. Laurent and workers [4] have also reported that **2** can be synthesized by reaction of 3-chloro-1-phenyl-4,4,4-trifluoro-but-2-en-1-one (**13**) with sodium azide. We have also synthesized **2** by the reaction

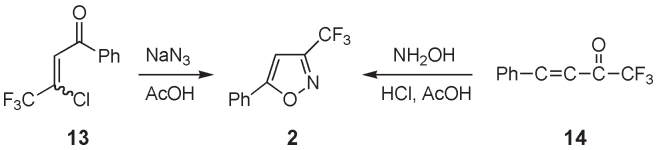

Figure 6

of 1,1,1-trifluro-4-phenylbut-3-yn-2-one (**14**) [7] with hydroxylamine according to a modification of a procedure developed by Linderman [8] for the synthesis of 5-octyl-3-(trifluromethyl)isoxazole.

The products obtained in our laboratory from **13** and **14** were identical and exhibited a melting range of 40-42 ºC, similar to the value reported by Tanaka [6] but quite different from the melting range of the regiosiomer **1**. The mass spectrum of this material also exhibited a molecular ion at m/z = 213. Unlike the mass spectrum of **1**, however, the major fragmentation pathway for **2** does not result from cleavage of the trifluoromethyl group but leads to a signal at m/z 105, most likely due to loss of a benzoyl group (PhC=O).

The ^{1}H-NMR spectrum of **2** exhibited a 1H singlet at δ 6.73 due to the H4 proton and 3H and 2H multiplets centered at δ 7.50 and 7.79 due to protons of the phenyl rings. The ^{13}C-NMR spectrum of **2** exhibited signals at δ 126.4, 129.7, and 131.7 for the carbons of the phenyl group, a quartet at 120.0 (J = 271.0 Hz) for the carbon of the trifluoromethyl group, and signals at δ 172.8, 156.4 and 97.2 for the carbons of the isoxazole ring. Surprisingly, the signal at δ 156.4 appeared as a quartet (J = 38.0 Hz), indicating long-range coupling with the fluorine nuclei of the trifluoromethyl group. Accordingly, in contrast to isomer **1**, in this compound the C5 carbon absorbs furthest downfield in the ^{13}C-NMR spectrum and the absorption due to the C3 carbon appears slightly upfield at δ 156.4 between the signals for the C5 and C4 carbons.

EXPERIMENTAL

^{1}H- and ^{13}C spectra were recorded at 400.1 and 100.6 MHz in deuteriochloroform on a Bruker FT-NMR system. ^{1}H and ^{13}C chemical shifts were measured relative to internal tetramethylsilane and chloroform respectively. Mass spectra were recorded with an HP 5970 B mass selective detector interfaced to an HP588 capillary column gas chromatograph.

Reactant (**3**) is commercially available. Compounds (**10**) and (**13**) were synthesized by methods described in [5]. Compound (**14**) was prepared by the procedure given in [7].

5-Hydroxy-3-Phenyl-5-(trifluoromethyl)-4,5-dihydroisoxazole (**8**).

A solution of hydroxylamine hydrochloride (3.8 g, 54.7 mmol) in water (14.0 ml) was added to a solution of 4,4,4-trifluoro-1-phenyl-1,3-butanedione (**3**) (5.6 g, 25.9 mmol) dissolved in a mixture of 0.5 *M* hydrochloric acid (50 ml) and ethanol (210 ml). The solution was stored in a refrigerator for 48 hours and concentrated to a volume of 50 ml. Further storage in the refrigerator overnight gave **8** as white crystals (3.6 g, 15.6 mmol, 60%) mp 140.5-142.0 ºC, lit [3], mp 143.3-144.1 ºC; ^{1}H-NMR (deuteriochloroform): δ 3.61 (AB quartet, 2H, J_{AB} = 17.9 Hz), 3.78 (s, 1H), 7.42-7.46 (m, 3H), 7.63-7.65 (m, 2H); ^{13}C-NMR (deuteriochloroform): δ (DEPT-135) 43.0 (-), 103.5 (q, J= 34.5 Hz) (0), 121.q (q, J= 283.9 Hz)(0), 127.0(+), 127.7(0), 129.0(+), 131.2(+), 157.0(0); MS m/z (%) 231(57), 162(52), 144(16), 120(36), 119(24), 103(33), 91 (33), 77 (100).

3-Phenyl-5-(trifluoromethyl)isoxazole (**1**).

A solution of 5-hydroxy-3-phenyl-5-(trifluoromethyl)-4,5-dihydroxyisoxazole (**8**) (6.2 g, 16.9 mmol) and *p*-toluenesulfonic acid (0.60 g, 3.3mmol) in benzene (120 ml) was refluxed for 12 hr. Most of the benzene was removed by simple distillation and the gray solid was collected and dissolved in dichloromethane (180 ml). The solution was filtered, washed with saturated aqueous bicarbonate (3 x 50 ml), dried (sodium sulfate), and concentrated to dryness. The resulting white solid was recrystallized from 20% aqueous methanol to yield **1** as white crystals (2.7 g, 12.7 mmol, 47.2%) which was sublimed (40 ºC, 1.5 mm Hg) to give white crystals mp 78.0-79.5 ºC, lit [4], 80 ºC; ^{1}H-NMR (deuteriochloroform): δ 7.01 (s, 1H), 7.49-7.51 (m, 3H), 7.80-7.83 (m, 2H): ^{13}C-NMR (deuteriochloroform): δ (DEPT-135) 103.5(+), 117.9 (q, J + 270.2 Hz) (0), 126.9 (+), 127.2 (0), 129.2 (+), 131.0 (+), 159.2 (q, J = 42.6 Hz) (0), 162.6 (0); Ms m/z (%) 213 (45), 144(100), 116(27), 77 (61.5).

5-Phenyl-3-(trifluoromethyl)isoxazole (**2**).

4-Phenyl-1,1,1-trifluorobut-3-yn-2-one (**14**) [7] (0.31 g, 1.6 mmol) was dissolved in glacial acetic acid (2.0 ml). Aqueous hydrochloric acid (10%, 3 drops) and water (10 drops) were added. Hydroxylamine hydrochloride (0.11 g, 1.6 mmol) was added and the solution was stirred at room temperature for 24 hr. The solution was filtered and the filtrate was extracted with ether (5 x 10 ml). The combined ether extract was dried (sodium sulfate) and concentrated to dryness. The pale yellow residual oil solidified upon standing at room temperature to provide **2** as a pale yellow solid (0.32 g, 1.5 mmol, 94%) which was recrystallized from 20% aqueous methanol to give white crystals of **2** mp 41.0-41.8 ºC, lit [6] 44-45.5 ºC; ^{1}H-NMR (deuteriochloroform): δ 6.74 (s, 1H), 7.51 (m, 3H), 7.81 (m, 2H: ^{13}C-NMR (deuteriochloroform): δ (DEPT-135) 96.8 (+), 119.7 (q, J = 270.8 Hz), 126.0 (+), 129.3 (+), 131.3(+), 156.0 (q, J = 38.3 Hz) (0), 172.4 (0); MS m/z (%) 213 (100), 105 (57), 77 (41).

REFERENCES AND NOTES

[1] J. W. Pavlik, H. St. Martin, K. A. Lambert, J. A. Lowell, V. M. Tsefrikas, C. K. Eddins, and N. Kebede, *J. Heterocyclic Chem.*, **42**, 273 (2005).

[2] J. B. Carr, H. G. Durham, and D. K. Hass, *J. Med. Chem.*, **20**, 934 (1977).

[3] J. C. Reid and M. Calvin, *J. Am. Chem. Soc.*, **72**, 2948 (1950).

[4] J. Diab, A. Laurent, and I. LeDréan, *J. Fluorine Chem.*, **84**, 145 (1997).

[5] G. Alvernhe, D. Greif, B. Langlois, A. Laurent, I. LeDréan, M. Pulst, A. Selmi, and M. Weissenfels, *Bull. Soc. Chim. Fr.* **131**, 167 (1994).

[6] K. Tanaka. H. Masuda, and K. Mitsuhashi, *Bull Chem. Soc., Jpn.*, **57**, 2184 (1984).

[7] R. J. Linderman and M. S. Lonikar, *J. Org. Chem.*, **53**, 6013 (1988).

[8] R. J. Linderman and K. S. Kirollos, *Tetrahedron Lett.*, **30**, 2049 (1989).