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# ELECTROCHEMICAL SYNTHESIS OF CIS–3,4–BIS(2,2,2–TRIFLUOROETHYL)PYRROLIDINE

Norbert Muller

Department of Chemistry, Purdue University
West Lafayette, Indiana 47906

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Abstract: Electrolysis of partially neutralized trifluoroacetic acid in the presence of diallylamine provided an 8% yield of the crystalline hydrochloride of the title compound. That the material has the cis configuration was deduced from the nmr spectra of its N–butyl derivative in acidic solutions.

Organic compounds with trifluoromethyl substituents often have physical, biological, or pharmacological properties rather similar to those of analogous methyl derivatives, but they also produce simple, strong $^{19}F$ nuclear magnetic resonance (nmr) signals with markedly solvent–dependent chemical shifts. Hence they may conveniently be used to study such phenomena as preferential solvation, micelle formation, or protein–ligand binding.[1] For a number of such compounds the most convenient method of preparation begins with the reaction between a suitable olefin and trifluoromethyl radicals generated by oxidation of trifluoroacetate ions at a smooth platinum anode. This paper describes a new application of this approach, where the olefin is diallylamine and the principal product is cis–3,4–bis(2,2,2–trifluoroethyl)pyrrolidine, isolated as its crystalline hydrochloride (1).

A problem always encountered in using anodic trifluoromethylation for preparative purposes is that the initial reaction, for example

$$CF_3\cdot + CH_2{=}CXY \rightarrow CF_3CH_2CXY\cdot \qquad (1)$$

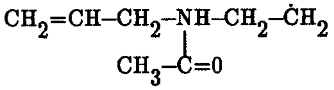
generates a new radical which may be transformed to stable products by one or more of the following processes:[2,3] Addition of a second trifluoromethyl radical to give $CF_3CH_2C(CF_3)XY$; combination with another $CF_3CH_2CXY\cdot$ radical to give the dimer; hydrogen atom abstraction to form $CF_3CH_2CHXY$; oxidation by transfer of an electron to the anode and subsequent loss of a proton to a base giving $CF_3CH{=}CXY$; attack on a second molecule of the olefin eventually leading to products derived from $CF_3CH_2CXYCH_2CXY\cdot$ or larger oligomers. In most instances, the electrolysis mixture then contains a collection of products resulting from simultaneous operation of several of these reactions. These are readily detected, but not so readily identified, in the $^{19}F$ nmr spectrum, even without workup. This makes it easy to find whether the nature of the product distribution is sensitive to changes in such reaction variables as current density, temperature, concentration, or solvent composition. Often this is not the case, so that manipulation of these factors provides only a very limited ability to maximize the yield of a desired material.

Because of these circumstances it has been necessary to use a rather Edisonian approach to discover situations where useful amounts of one or more products can readily be obtained in pure form. Sometimes one of the competing reactions listed above is strongly favored over the rest, as was found when allyl alcohol was the substrate and 4,4,4–trifluorobutanal the eventual product.[4a] Sometimes the chemical or physical properties of one of the products make it easy to isolate it or to convert it to another easily purifiable material, as in the production of trifluoroethylmalonic acid from acrylic acid.[4b] Even when the yield is low, the procedure may be more attractive than alternative methods because the starting materials are cheap and the reactions involve few steps and are easy to perform.[3–5]

The use of dienes as substrates for anodic trifluoromethylations with formation of cyclic products has not been extensively explored, although Renaud and coworkers reported reactions with some activated dienes, $ROOCCH{=}CH(CH_2)_nCH{=}CHCOOR$, giving bis(trifluoromethyl)alicyclic componds.[6] The substrate used in the present study, diallylamine, was expected to cyclize in a somewhat different manner. The first–formed radical, 2

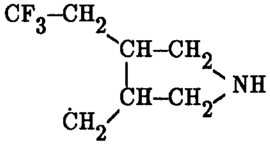
$$CH_2{=}CH{-}CH_2{-}NH{-}CH_2{-}\dot{C}H{-}CH_2{-}CF_3$$

is similar to those apparently formed[7] during Kolbe electrolysis of *β*–allylamino alkanoates, e.g.



$$CH_2{=}CH{-}CH_2{-}\underset{\underset{CH_3-C=0}{|}}{N}H{-}CH_2{-}\dot{C}H_2$$

The latter gives rise to substituted pyrrolidines, suggesting that 2 would lead to products derived from its cyclic isomer,



Indeed, when the reaction is carried out as described below the predominant product appears to arise from the combination of this species with a second trifluoromethyl radical. The nmr spectrum shows this together with lesser amounts of several unidentified byproducts, giving badly overlapped $^{19}F$ triplets. To date the only pure material obtained by working up such mixtures is compound 1.

The physical properties and nmr spectra of 1 do not provide conclusive evidence to show that it is the cis isomer. To do this, the material was converted to the free base, which was then treated with bromobutane and sodium carbonate[8] to form 1–butyl–cis–3,4–bis(2,2,2–trifluoroethyl)pyrrolidine, isolated and purified as its crystalline hydrobromide 3.

The nmr spectra of 3 are quite pH dependent, because addition of acid reduces the rate of inversion at the nitrogen atom. In water–$d_2$ containing 20% deuterium chloride, they clearly indicate that it is a mixture of two isomers having the butyl group either cis or trans to the two trifluoroethyl groups, with a concentration ratio of about 1:5. (When the solvent is a mixture of water–$d_2$ and trifluoroacetic acid, the relative concentrations become very nearly equal.) This is particularly evident on examining the signals from the ring methylene protons adjacent to the nitrogen atom. Each methylene group comprises two nonequivalent protons, each of which gives rise to a doublet of doublets, so that the mixture produces a total of four such quartets, two strong and two weak. When the spectra are taken in water–$d_2$ without added deuterium chloride, the rate of inversion is increased just enough to cause all of these signals to be replaced by a single unresolved line with a width near 0.9 ppm.

Similarly, the ring hydrogen atoms on carbons 3 and 4 produce separate signals of unequal intensity at low pH which coalesce as the pH increases. Again, the $^{19}F$ signal of the trifluoroethyl groups consists of a pair of triplets in acid solution and just one triplet at higher pH.

If the trifluoroethyl groups of 1 were on opposite sides of the ring, this should be true also of 3. Then in the limit of slow inversion one would still expect that many of the nmr signals, such as the $^{19}F$ triplets, would be doubled owing to nonequivalence, but the relative intensities would have to be 1:1.

Somewhat surprisingly, neither 1 nor 3 was found to be hygroscopic.

## Experimental Procedures

$^{19}F$ nmr spectra were obtained at 34 °C with a Perkin–Elmer R32 spectrometer at 84.669 MHz using 1,1,2–trichlorotrifluoropropene as an external reference. Negative values indicate upfield shifts and were converted to the $\phi^*$ scale by adding –62.8 ppm. The reader is reminded that these shifts are markedly affected by small changes in sample composition or temperature. Proton shifts, from spectra taken with a Varian VXR–500S spectrometer at 499.843 MHz, were measured using the signal from water–$d_1$ as an internal reference and converted to the $\delta$ scale by adding 4.68 ppm.

Electrolyses were carried out with stirring in an undivided cell consisting of a 500 mL hydrogenation bottle with electrodes made of No. 20 platinum wire wound into spirals of 6mm and

18 mm diameter, mounted concentrically. Current from an unregulated DC supply was kept roughly constant at 1.2 amp by adjusting the voltage from time to time as the internal resistance increased owing to the decreasing concentration of trifluoroacetic acid. A water bath was used to keep the temperature from rising above 45 °C. Changes in current density or temperature had very little effect on the course of the reaction.

Preparation of 1. For a typical run the cell was charged with 18 mL (0.146 mol) diallylamine, 32 mL (0.416 mol) trifluoroacetic acid, 160 mL acetone, 40 mL water, and 0.8 g (0.02 mol) sodium hydroxide. After passing 0.36 Faradays (8 h) acetone was removed by evaporation at reduced pressure, 350 mL of 0.65 M aqueous sodium hydroxide was added, and the resulting mixture distilled, with further addition of 200 mL of water, until about 350 mL of material had been collected. This consisted of a large aqueous layer and about 15 mL of dense oil, which dissolved on adding 15 mL of concentrated hydrochloric acid. This solution was washed with 50 mL of ether or dichloromethane, concentrated by evaporation at reduced pressure, and combined with similar material from two other identical runs. Crystals obtained on further evaporation were recrystallized from acetone/ether to yield 9.5 g (0.035 mol, 8% based on diallylamine) of nearly pure 1. The analytical sample was further recrystallized from acetone/hexane, m.p. 235.5–237 °C, uncorrected. Analysis:
Found: C, 35.14; H, 4.63%. $C_8H_{12}F_6NCl$ requires C, 35.37; H, 4.45%. NMR (30 mg/mL, water–$d_2$): $^{19}F$: $\phi^*$ –65.2 (t, J = 10.8 Hz). $^1H$: $\delta$ 3.40 (2H, doublet of doublets, J = 12.2 Hz, 6.8 Hz), 3.14 (2H, doublet of doublets, J = 12.0 Hz, 6.5 Hz), 2.68 to 2.75 (2H, irreg. oct.), 2.31 to 2.41 (2H, c.m.), 2.09 to 2.19 (2H, c.m.).

Preparation of 3. A sample of 1 (13 g, 0.048 mol) was treated with 2.5 g (0.063 mol) sodium hydroxide in 100 mL water, and the colorless oil isolated and dried. This was mixed with 4.9 g (0.046 mol) dried, powdered sodium carbonate, 6.3 g (0.046 mol) bromobutane, and 3 mL ethylene glycol, and heated barely to boiling under reflux with stirring for 44 h. The cooled mixture was treated with 25 mL water and 80 mL ether, the aqueous layer being discarded. The residue remaining after the ether layer was washed with water and then evaporated was heated with 6.5 mL of 48% hydrobromic acid in 150 mL water. The aqueous solution was filtered and evaporated to dryness, leaving crude solid 3, recrystallized from 20 mL propanol and 45 mL hexane to give two crops totalling 11.9 g (0.032 mol, 67%) of nearly pure product. This was further purified by recrystallization from propanol/hexane and then from water, m.p. 119.5–123 °C, uncorrected. Analysis: Found: C, 38.68; H, 5.52%. $C_{12}H_{20}F_6NBr$ requires C, 38.72; H, 5.42%. NMR (50 mg/mL, water–$d_2$): $^{19}F$: $\phi^*$ – 65.2 (t, J = 10.8 Hz). $^1H$: $\delta$ 3.0 to 3.9 (4H, broad line), 3.14 to 3.18 (2H, c.m.), 2.8 to 2.9 (2H, bread s.), 2.4 to 2.5 (2H, c.m.), 2.2 to 2.3 (2H, c.m.), 1.56 to 1.63 (2H, c.m.), 1.277 (2H, 6tet, J = 7.4 Hz), 0.818 (3H, t, J = 7.5 Hz). Additional NMR (50 mg/mL, 20% DCl in water–$d_2$): $^{19}F$: $\phi^*$ – 64.4 (rel. int. 4, t, J = 10.6 Hz), –64.5 (rel. int. 1, t, J = 10.6 Hz). $^1$H: $\delta$ 3.87 (0.34 H, doublet of doublet, J = 12 Hz, 7Hz), 3.56 (1.66H, doublet of doublets, J = 12.2 Hz, 5.7 Hz), 3.35 (1.66H, doublet of doublets, J = 12.2 Hz, 6.7 Hz), 3.18 to 3.21 (2H, c.m.), 3.05 (0.34H, doublet of doublets, J = 12 Hz, 9 Hz), 2.92 to 2.96 (1.66H, broad s.), 2.81 to 2.87 ( 0.34H, broad s.), 2.3 to 2.5 (4H, c.m.), 1.59 to 1.65 (2H, c.m.), 1.283 (2H, 6tet, J = 7.3 Hz), 0.818 (3H, t, J = 7.5 Hz).

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