from hexane to give 7.2 g. (74% yield) of material melting at 81–82°.[3] Fehling solution was reduced by the ketol.

Anal.[4] Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.23; H, 4.88.

2-Furoyloxyacetylfuran.—Eleven grams (0.081 mole) of diazoacetylfuran was refluxed for four hours with 11 g. (0.099 mole) of furoic acid in 40 ml. of anhydrous, thiophene-free benzene. The solvent was removed under reduced pressure, and the crystalline residue was triturated with saturated sodium bicarbonate solution, and then with water, and finally recrystallized from aqueous methanol (Darco) and then from much hexane to give 8.1 g. (50% yield) of a product melting at 95°.

Anal. Calcd. for $C_{11}H_8O_5$: C, 59.73; H, 3.85. Found: C, 60.00; H, 3.66.

Summary

2-Hydroxyacetylfuran and 2-furoyloxyacetylfuran have been prepared by the interaction of 2-diazoacetylfuran with dilute sulfuric acid and furoic acid, respectively.

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[3] Melting points taken with Fisher–Johns apparatus.

[4] Analyses by Oakwold Laboratories, Alexandria, Virginia.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Aliphatic Ketones and Amines Containing the Trifluoromethyl Group

BY REUBEN G. JONES

It is well known that the introduction of fluorine atoms into aliphatic molecules has a profound effect upon the physical and chemical properties. In order to ascertain the effect of fluorine on the pharmacological properties of typical aliphatic compounds, it was of particular interest to prepare some ketones, amines, and alcohols containing the trifluoromethyl group. The compounds reported at this time were derived from trifluoroacetic acid.

Two methods were examined for the preparation of trifluoromethyl benzyl ketone. Trifluoroacetonitrile was allowed to react with benzylmagnesium chloride to produce the desired ketone in 38% yield.

$$CF_3CN + C_6H_5CH_2MgCl \xrightarrow{H_2O} CF_3COCH_2C_6H_5$$

The more convenient reaction of trifluoroacetyl chloride with benzyl zinc chloride gave a 54% yield of the ketone.

$$CF_3COCl + C_6H_5CH_2ZnCl \longrightarrow CF_3COCH_2C_6H_5$$

Both methods would appear to be quite generally applicable to the preparation of trifluoromethyl ketones. Trifluoromethyl phenyl ketone (trifluoroacetophenone[1]) was obtained readily in a yield of 61% by the reaction of trifluoroacetyl chloride with diphenylcadmium.

The pharmacology of these trifluoromethyl compounds will be reported elsewhere. However, it is of interest to note at this time that the acute toxicities were relatively low.

Experimental

Trifluoromethyl Benzyl Ketone.—A. Trifluoroacetonitrile was prepared from 56 g. (0.5 mole) of trifluoroacetamide by the method of Gilman and Jones.[2] The gaseous nitrile was led from the generating flask through glass tubing and introduced below the surface of a stirred solution of benzylmagnesium chloride prepared from 80 g. (0.63 mole) of benzyl chloride and 17 g. of magnesium in a total of 300 ml. of dry ether. When the reaction was complete, the brown ether solution was poured into a mixture of 150 g. of ice and 100 ml. of concentrated hydrochloric acid. The ether layer was separated, washed with water and dilute sodium bicarbonate solution and dried over magnesium sulfate. After evaporation of the ether the residual liquid was distilled through an eighteen-inch packed column under reduced pressure, and 36 g. (38.4% yield) of trifluoromethyl benzyl ketone was obtained as a colorless liquid; b. p. 73–73.5° (20 mm.), 163–163.5° (741 mm.): $n^{25}D$ 1.4625.

Anal. Calcd. for $C_9H_7F_3O$: C, 57.45; H, 3.75. Found: C, 57.05; H, 3.92.

B. Trifluoroacetyl chloride was prepared by the method of Tinker[3] from 57 g. (0.5 mole) of trifluoroacetic acid and 200 ml. of benzoyl chloride. The gaseous trifluoroacetyl chloride was led through a glass tube into a reaction flask containing benzylzinc chloride which was made by adding slowly, with the exclusion of air, 800 ml. of ether solution containing 1.0 mole of benzylmagnesium chloride to 136 g. (1.0 mole) of freshly fused, powdered zinc chloride. The reaction flask was provided with a Dry Ice condenser and the mixture was rapidly stirred. After several hours, the mixture was decomposed with ice and dilute hydrochloric acid. The ether layer was separated, the aqueous layer was washed with three 100-ml. portions of ether, and the combined ether solution was dried over magnesium sulfate. The ether was removed by distillation through a small packed column. From the mid fractions, distilling between 36 and 105°, was obtained 8 g. (14%) of trifluoroacetic acid (isolated as the ammonium salt), and 51 g. (54.3% yield) of trifluoromethyl benzyl ketone was collected at 160–165° (740 mm.); $n^{25}D$ 1.4621.

Trifluoromethylbenzylcarbinol.—A solution of 23.5 g. (0.125 mole) of trifluoromethyl benzyl ketone in 50 ml. of anhydrous ether with 5 g. of 5% palladium–charcoal catalyst was hydrogenated under 60 lb. pressure. The theoretical quantity of hydrogen was taken up in about twenty minutes with evolution of heat. The solution was filtered and distilled to yield 23.0 g. (98%) of trifluoromethylbenzylcarbinol; b. p. 204–204.5° (740 mm.); $n^{25}D$ 1.4678.

Anal. Calcd. for $C_9H_9F_3O$: C, 56.84; H, 4.75. Found: C, 56.74; H, 4.76.

Trifluoromethyl Benzyl Ketoxime.—A solution of 23.5 g. (0.125 mole) of trifluoromethyl benzyl ketone in 100 ml. of methanol was treated with 28 g. (0.4 mole) of powdered hydroxylamine hydrochloride followed by 30

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[1] Simons and Ramler, THIS JOURNAL, **65**, 389 (1943).

[2] Gilman and Jones, *ibid.*, **65**, 1458 (1943); Swarts, *Bull. sci. acad. roy. Belg.*, **8**, 343 (1922) [*C. A.*, **17**, 769 (1923)].

[3] Tinker, U. S. Patent 2,257,868, Oct. 7, 1941; [*C. A.*, **36**, 495 (1942)].

ml. of 12 *N* sodium hydroxide solution. The mixture was refluxed for sixteen hours and then most of the methanol was removed by distillation. To the residue was added 100 ml. of water, and the mixture was extracted with three 50-ml. portions of ether. The ether solution was dried over magnesium sulfate, the ether was removed, and the oxime was distilled in vacuum to yield 25.0 g. (98%) of product, b. p. 118–119° (20 mm.).

Anal. Calcd. for $C_9H_8F_3NO$: C, 53.20; H, 3.97; N, 6.89. Found: C, 53.87; H, 4.40; N, 6.44.

1,1,1-Trifluoro-2-amino-3-phenylpropane.—A solution of 41 g. (0.20 mole) of trifluoromethyl benzyl ketoxime in 150 ml. of anhydrous ether with 8 g. of 5% palladium-charcoal catalyst was placed in a steel hydrogenation bomb under a pressure of 1450 lb./sq. in. of hydrogen, heated to 150° and agitated. The theoretical quantity of hydrogen was taken up in one hour. The bomb was cooled and opened and the ether solution, after filtration, was extracted with cold dilute hydrochloric acid solution. The aqueous layer was separated, made basic with sodium hydroxide and extracted with ether. After the ether extract had been dried over magnesium sulfate, the ether was evaporated and the amine was distilled at atmospheric pressure; b. p. 189–191° (739 mm.). The yield of clear colorless liquid was 33 g. (87%); $n^{25}\text{D}$ 1.4470.

Anal. Calcd. for $C_9H_{10}F_3N$: N, 7.40. Found: N, 7.56.

The amine hydrochloride, prepared by passing dry hydrogen chloride into a solution of the amine in anhydrous ether, melted at 231–233°.

Anal. Calcd. for $C_9H_{10}F_3N \cdot HCl$: C, 47.95; H, 4.92. Found: C, 47.47; H, 4.89.

Ethyl 3-Hydroxy-4,4,4-trifluorobutyrate.—Ethyl trifluoroacetoacetate was prepared in 83.5% yield from ethyl acetate and ethyl trifluoroacetate according to the directions of Swarts.[4]

To a solution of 27.6 g. (0.15 mole) of ethyl trifluoroacetoacetate in 50 ml. of anhydrous ether was added 0.15 g. of platinum oxide catalyst and the mixture was shaken under an initial hydrogen pressure of 60 lb. Hydrogenation was complete in seven hours. The solution was filtered and distilled, and, after the forerun of ether, the ethyl 3-hydroxy-4,4,4-trifluorobutyrate, 24.8 g. (90% yield), boiled at 177–178° (750 mm.). When 55.2 g. (0.30 mole) of ethyl trifluoroacetoacetate was shaken under 60 lb. hydrogen pressure using 2 g. of 5% palladium-charcoal catalyst, the theoretical quantity of hydrogen was absorbed in three hours. Under high pressure (1200 lb.), 50 g. (0.27 mole) of ethyl trifluoroacetoacetate in 100 cc. of anhydrous ether with 15 g. of 5% palladium-charcoal catalyst absorbed the theoretical quantity of hydrogen in two to three minutes, and no more hydrogen was taken up even when the bomb was heated to 100° and agitated for five hours.

The ester isolated directly from the hydrogenation reaction could not be obtained analytically pure even after several distillations. A pure sample of ethyl 3-hydroxy-4,4,4-trifluorobutyrate was prepared in 90% yield by esterification of 3-hydroxy-4,4,4-trifluorobutyric acid (see below) with ethanol and hydrogen chloride. It has the following properties: b. p. 180–180.2° (748 mm.); m. p. 26.9–27.0°; $n^{30}\text{D}$ 1.3707; d^{30}_{30} 1.275.

Anal. Calcd. for $C_6H_9F_3O_3$: C, 38.71; H, 4.87. Found: C, 38.25; H, 5.09.

3-Hydroxy-4,4,4-trifluorobutyric Acid.—A solution of 35 g. (0.223 mole) of 3-hydroxy-4,4,4-trifluorobutyramide (see below) in 40 ml. of 12 *N* sodium hydroxide solution was heated on the steam-bath for fifteen minutes. The clear solution was cooled in an ice-bath and treated with 60 ml. of 12 *N* hydrochloric acid. The salt was collected on a filter, washed with ether, and the filtrate was extracted with three 100-ml. portions of ether. The combined ether solution was dried over magnesium sulfate and evaporated on the steam-bath. To the residual liquid was added 100 ml. of petroleum ether (b. p. 60–68°) whereupon crystallization quickly took place. The acid was collected and dried in vacuum over calcium chloride. The yield was 34.1 g. (97.2%); m. p. 69 5–70°.

Anal. Calcd. for $C_4H_5F_3O_3$: C, 30.39; H, 3.19. Found: C, 30.43; H, 3.28.

The pure acid was also readily obtained by saponification of the crude ester. It was sparingly soluble in petroleum ether, very soluble in ether, alcohol and water but apparently not hygroscopic.

3-Hydroxy-4,4,4-trifluorobutyramide.—A solution of 4.6 g. (0.025 mole) of crude ethyl 3-hydroxy-4,4,4-trifluorobutyrate in 25 ml. of methanol was saturated with dry ammonia and allowed to stand for three days. The methanol was evaporated, finally under vacuum leaving a mass of colorless prismatic crystals. The product was washed with 10 ml. of dry ether and air dried. It weighed 3.5 g. (90% yield) and melted at 124–125°.

Anal. Calcd. for $C_4H_6F_3NO_2$: N, 8.92. Found: N, 8.73.

The compound was soluble to the extent of about 1 g. per 100 ml. of dry ether, very sparingly soluble in petroleum ether, highly soluble in alcohol or water and not hygroscopic.

N-2′-Hydroxyethyl-3-hydroxy-4,4,4-trifluorobutyramide.—A mixture of 9.3 g. (0.05 mole) of ethyl 3-hydroxy-4,4,4-trifluorobutyrate and 3.5 g. (0.058 mole) of ethanolamine was heated at 140° for four hours. The mixture was distilled in vacuum and, after a small forerun, 9.5 g. (95% yield) of viscous colorless liquid distilled at 186–188° (2 mm.). It crystallized after standing; m. p. 59–61°.

Anal. Calcd. for $C_6H_{10}F_3NO_3$: N, 6.96. Found: N, 7.10.

2-Hydroxy-3,3,3-trifluoropropylamine Hydrochloride.—To a mixture of 150 g. of ice and potassium hypochlorite solution made by dissolving 11.0 g. (0.153 mole) of chlorine in a solution of 33.6 g. of potassium hydroxide in 90 ml. of ice water was added 23.6 (0.15 mole) of 3-hydroxy-4,4,4-trifluorobutyramide. The solution was kept at 0° for twenty minutes, then allowed to warm slowly to room temperature and finally heated on the steam-bath for thirty minutes. The solution was cooled and extracted with ten 100-ml. portions of ether. The ether solution was dried over magnesium sulfate, filtered and saturated with dry hydrogen chloride to yield 13.9 g. (56%) of white crystalline amine hydrochloride; m. p. 147–148°.

Anal. Calcd. for $C_3H_6F_3NO \cdot HCl$: C, 21.76; H, 4.26; N, 8.46. Found: C, 21.93; H, 4.31; N, 8.32.

To 3 ml. of 15% aqueous sodium hydroxide was added 0.5 g. of 2-hydroxy-3,3,3-trifluoropropylamine hydrochloride followed by 0.5 ml. of benzoyl chloride added dropwise with shaking. The resulting white, crystalline dibenzoyl compound, 0.9 g., was collected on a filter and recrystallized from petroleum ether containing a little ethyl acetate; m. p. 126.5–127.5°.

Anal. Calcd. for $C_{17}H_{14}F_3NO_3$: C, 60.53; H, 4.18. Found: C, 60.33; H, 4.11.

Summary

Two general methods for the synthesis of ketones have been applied successfully to the preparation of trifluoromethyl benzyl ketone.

1,1,1-Trifluoro-2-amino-3-phenylpropane has been obtained by hydrogenation of the ketoxime.

Trifluoromethyl benzyl ketone has been hydrogenated to yield trifluoromethylbenzylcarbinol.

3-Hydroxy-4,4,4-trifluorobutyric acid, its ethyl ester, amide, and N-2′-hydroxyethyl amide, and 2-hydroxy-3,3,3-trifluoropropylamine have been made starting from ethyl trifluoroacetoacetate.

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(4) Swarts, *Bull. sci. acad. roy. Belg.*, [5] **12**, 692 (1926); [*C. A.*, **21**, 2120 (1927)].