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# 5-TRIFLUOROMETHYLFURAN DERIVATIVES

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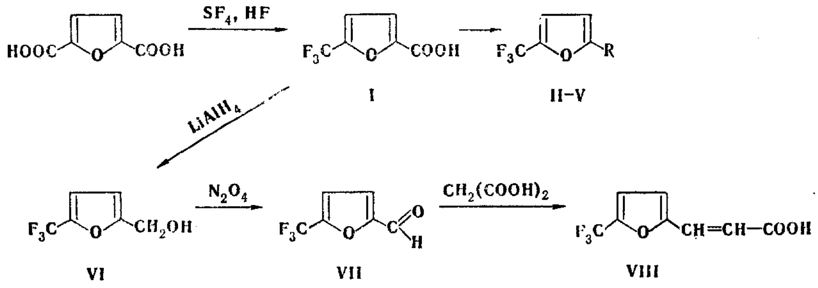
Methods for the preparation of 5-trifluoromethylfuran-2-carboxylic acid, 5-trifluoromethylfurfural, and 5-trifluoromethyl-2-aminofuran derivatives were developed.

Trifluoromethylfurans are valuable intermediates for the synthesis of physiologically active substances [1-3]. Derivatives of 5-trifluoromethylfuran, which was previously obtained by a multistep method [3], are of particular interest. 5-Trifluoromethylfuran-2-carboxylic acid, which we have previously obtained by fluorination of furan-2,5-dicarboxylic acid with sulfur tetrafluoride, could have been a convenient starting compound for the synthesis of various 5-trifluoromethylfuran derivatives. However, it was obtained in only 16% yield, and mainly 2,5-bis(trifluoromethyl)furan was obtained in the fluorination [1]. Fluorination was accomplished under severe conditions (at 185°C for 45 h). Under milder conditions the carboxyl groups were not converted to trifluoromethyl groups.

It was recently found that the fluorination of carboxylic acids with sulfur tetrafluoride in anhydrous hydrogen fluoride proceeds at a considerably lower temperature and gives the trifluoromethyl derivatives in higher yields [4]. It was found that one can realize partial fluorination of furan-2,5-dicarboxylic acid with sulfur tetrafluoride when the process is carried out in HF solution under mild conditions (at 40-50°C). 5-Trifluoromethylfuran-2-carboxylic acid (I) was obtained in 60-65% yield in this case. Thus acid I became a fully accessible compound, from which we synthesized a number of 5-trifluoromethylfuran derivatives. From acid I we obtained its methyl ester (II), acid chloride (III), amide, hydrazide (IV), and nitrile (V). Acid I and its ester II and chloride III are converted to 5-trifluoromethyl-2-hydroxymethylfuran (VI) by reduction with lithium aluminum hydride. 5-Trifluoromethylfurfural (VII) was obtained in good yield by oxidation of carbinol VI with nitrogen tetroxide.

β-(5-Trifluoromethyl-2-furyl)acrylic acid (VIII) was synthesized by condensation of aldehyde VII with malonic acid.



II $R=COOCH_3$; III $R=COCl$; IV $R=CONHNH_2$; V $R=CN$

5-Trifluoromethyl-2-nitrofuran (IX), which was previously obtained in 37% yield [2] by fluorination of 2-nitrofuran-5-carboxylic acid with sulfur tetrafluoride at 120°C, was necessary for the preparation of amino derivatives of 5-trifluoromethylfuran. When we carried

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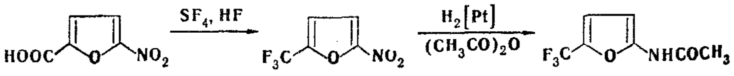
TABLE 1. 5-Trifluoromethylfurans II-XI

| Compound | bp, °C (mm) | mp, °C | $n_D^{20}$ | Found, % |  |  | Empirical formula | Calc., % |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | C | H | F |  | C | H | F |  |
| II | 170 | — | 1,4169 | 43,4 | 2,6 | 29,2 | $C_7H_5F_3O_3$ | 43,3 | 2,6 | 29,4 | 74 |
| III | 91 (80) | — | 1,4380 | — | — | — | $C_6H_2ClF_3O_2$ [a] | — | — | — | 93 |
| IV |  | 113 [b] | — | — | — | 29,4 | $C_6H_5F_3N_2O_2$ [c] | — | — | 29,4 | 84 |
| V | 138—139 | — | 1,4060 | 44,7 | 1,3 | 35,3 | $C_6H_2F_3NO$ | 44,7 | 1,2 | 35,4 | 88 |
| VI | 172 | — | 1,4074 | 43,5 | 3,2 | 34,1 | $C_6H_5F_3O_2$ | 43,4 | 3,0 | 34,3 | 65 |
| VII [d] | 143—144 | — | 1,4275 | — | — | 34,7 | $C_6H_3F_3O_2$ | — | — | 34,8 | 78 |
| VIII |  | 146—147 [b] |  | 46,7 | 2,3 | 27,7 | $C_8H_5F_3O_3$ | 46,6 | 2,4 | 27,7 | 74 |
| X [e] |  | 122—123 [f] |  | 43,7 | 3,2 | 29,6 | $C_7H_6F_3NO_2$ | 43,5 | 3,1 | 29,5 | 36 |
| XI [e] |  | 92—93 [b] |  | 43,2 | 3,7 | 25,5 | $C_8H_8F_3NO_3$ | 43,1 | 3,6 | 25,6 | 47 |

a) Analysis of this compound gave satisfactory results for chlorine. b) From benzene. c) Analysis of this compound gave satisfactory results for nitrogen. d) The 2,4-dinitrophenylhydrazone had mp 239°C (dec., from toluene). e) The compositions of III, IV, X, and IX were confirmed by determination of the Cl content for III and the nitrogen content for the remaining compounds. Found: Cl 17.9%. Calculated: Cl 17.7%. Found: N 14.3, 7.3, 6.2%. Calculated: N 14.4, 7.3, 6.3%. f) From benzene—hexane.

out the fluorination in HF solution at 40-50°C, we were able to raise the yield of nitro compound IX to 81%. Reduction of the latter in ethyl acetate on a platinum catalyst was unsuccessful — resinous products are formed. 5-Trifluoromethyl-2-acetamidofuran (X) was obtained in acetic anhydride. Alkaline hydrolysis of X also leads to resinification.



IX X

An azide, which was converted, without purification, to urethane XI, was obtained from acid hydrazide IV by the action of sodium nitrite and hydrochloric acid.

## EXPERIMENTAL

The analytical data and physical constants for the compounds obtained are presented in Table 1.

5-Trifluoromethylfuran-2-carboxylic Acid (I). A 31.2-g (0.2 mole) sample of furan-2,5-dicarboxylic acid and 30 ml of anhydrous HF were placed in a 250-ml autoclave, after which the autoclave was cooled with liquid nitrogen and evacuated, and 65 g (0.6 mole) of sulfur tetrachloride was condensed in it. The autoclave was then heated at 40°C for 24 h, after which it was cooled to 10-15°C, and the gaseous products were removed. Crushed ice was added carefully to the residue with cooling, and the mixture was made alkaline with 15% KOH. The alkaline solution was refluxed with charcoal and filtered, and the filtrate was acidified with concentrated HCl. The precipitate was removed by filtration, and the filtrate was extracted with ether (two 50-ml portions). The ether was removed by distillation, the residue was added to the principal product, and the combined products were dissolved in ether. The solution was filtered to remove the furan-2,5-dicarboxylic acid. The ether was removed by distillation to give 23.4 g (65%) of a product with mp 118-119°C (from benzene—hexane) [1].

Methyl 5-Trifluoromethylfuran-2-carboxylate (II). A mixture of 36 g (0.2 mole) of acid I, 150 ml of methanol, and 3 ml of concentrated sulfuric acid was refluxed for 14 h, after which the methanol was removed by distillation, and the residue was poured into 150 ml of ice water. The organic layer was separated, and the aqueous layer was extracted with ether (three 50-ml portions). The ether extract was added to the organic layer, and the mixture was washed with 5% sodium bicarbonate solution and water and dried with $MgSO_4$. The ether was removed by distillation, and the residue was distilled to give 28.8 g of II.

5-Trifluoromethylfuran-2-carboxylic Acid Chloride (III). A mixture of 18 g (0.1 mole) of acid I and 30 ml (0.42 mole) of $SOCl_2$ was refluxed for 6 h, after which it was worked up to give 18.5 g of III.

5-Trifluoromethylfuran-2-carboxylic Acid Hydrazide (IV). A mixture of 9.7 g (0.05 mole) of ester II, 6 ml (0.1 mole) of 85% hydrazine hydrate, and 6 ml of ethanol was refluxed for 20 h, after which the ethanol was removed by distillation, and the residue was crystallized to give 8.1 g of IV.

2-Cyano-5-trifluoromethylfuran (V). A mixture of 9.4 g (0.05 mole) of 5-trifluoromethylfuran-2-carboxamide and 10 g (0.07 mole) of $P_2O_5$ was heated, after which nitrile V was removed by distillation. The yield was 7.5 g.

5-Trifluoromethyl-2-hydroxymethylfuran (VI). A) A solution of 18 g (0.1 mole) of acid I in 50 ml of ether was added dropwise to a suspension of 3.1 g (0.08 mole) of $LiAlH_4$ in 80 ml of ether at a rate that ensured gentle refluxing of the solution. The solution was then refluxed for another 2 h and allowed to stand overnight. A 5-ml sample of 5% KOH was added, and the mixture was filtered. The solid material was washed twice with 20-ml portions of ether. The ether extracts were dried with $MgSO_4$, the ether was removed by distillation, and the residue was distilled to give 10.8 g of VI.

B) Compound VI was obtained by reaction under similar conditions of 9.7 g (0.05 mole) of ester II with 1.4 g (0.037 mole) of $LiAlH_4$. The yield was 5.1 g.

C) Compound VI was obtained by reaction of 9.9 g (0.05 mole) of acid chloride IV and 1.4 g (0.037 mole) of $LiAlH_4$. The yield was 4.6 g.

5-Trifluoromethylfurfural (VII). A 16.6-g (0.1 mole) sample of alcohol VI and 20 ml (0.65 mole) of nitrogen tetroxide were mixed at —10°C, and the mixture was maintained at —10°C for 15 min, at 0° for 2 h, and at 20° for 15 h. Ether (100 ml) was added, and the mixture was washed with 5% sodium bicarbonate solution and water and dried with $MgSO_4$. The ether was removed by distillation, and the residue was distilled. The yield was 12.8 g.

β-(5-Trifluoromethyl-2-furyl)acrylic Acid (VIII). A mixture of 3.28 g (0.02 mole) of aldehyde VII, 2.06 g (0.02 mole) of malonic acid, and 2 ml of pyridine was heated on a boiling-water bath for 2 h, after which it was cooled and treated with 20 ml of 10% HCl. The precipitate was removed by filtration and crystallized. The yield was 3.05 g.

5-Trifluoromethyl-2-acetamidofuran (X). A 9.05-g (0.05 mole) sample of nitro compound IX was dissolved in a mixture of 20 ml of acetic anhydride and 30 ml of acetic acid, after which argon was blown through the system, and 0.5 g of platinum black was added. Hydrogenation was carried out at room temperature until the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration, the filtrate was poured into a saturated solution of $CH_3COONa$, and the mixture was extracted with ether. The ether extracts were washed with water and dried with $MgSO_4$. The ether was removed by distillation, and the residue was crystallized. The yield was 3.6 g.

5-Trifluoromethyl-2-ethoxycarbonylaminofuran (XI). A 4.9-g (0.025 mole) sample of hydrazide IV was dissolved in 3 ml of HCl and 35 ml of water, the solution was cooled, and 1.8 g (0.025 mole) of sodium nitrite in 5 ml of water was added gradually while maintaining the temperature at 5-7°C. The solution was extracted with ether (three 20-ml portions), and the ether extracts were dried for 5 min with $CaCl_2$ and filtered. Absolute alcohol (20 ml) was added to the filtrate, and the ether was removed by distillation. The alcohol solution was refluxed for 10 h, and the alcohol was removed carefully by vacuum distillation without heating (an explosion is possible). The residue was crystallized. The yield was 2.6 g.

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