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A Simple and Efficient Method of Preparing α-Bromo Carboxylic Acids

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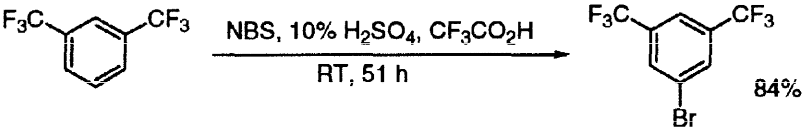
Abstract

A new and convenient method for α-bromination of aliphatic carboxylic acids is reported. Heating carboxylic acids for 16 hours at 85 °C in trifluoroacetic acid with 1.5 equivalents of N-bromosuccinimide and a catalytic amount of concentrated H_2SO_4 leads to good yields of the respective α-bromocarboxylic acids.

In recent years we have been actively searching for new and more powerful methods of electrophilic aromatic bromination. Recently we reported the development of a novel reagent [*N*-bromosuccinimide/CF_3CO_2H/H_2SO_4] which is effective in monobrominating highly electron-deficient benzene derivatives, such as 1,3-bis(trifluoromethyl)benzene [1].



During optimization experiments, an attempt was made to use acetic acid as solvent in place of the more expensive trifluoroacetic acid. Although no aromatic bromination occurred, it was observed that all of the NBS had been rapidly consumed. Examination of the ^1H NMR spectrum of the reaction mixture showed a new singlet at δ 3.2 ppm, which indicated that a reaction had indeed occurred. Isolation and characterization led to the determination that this product, which could be obtained in high yield and high purity, was α-bromoacetic acid.

α-Bromocarboxylic acids are important synthetic intermediates, and the Hell-Volhard-Zelinsky reaction [2-6], including more recent variations, [7,8] is currently the most convenient method for the preparation of such compounds. Therefore, the generality of this new bromination method was examined, along with experiments designed to optimize reaction conditions and yields. It was soon discovered that the reaction could be conveniently and

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effectively carried out in trifluoroacetic acid at the 0.1 mole scale (using 1.5 equiv. of NBS and 2.5 mL concentrated H_2SO_4/50 mL TFA) for general preparation of α-bromo derivatives of aliphatic carboxylic acids. The yields of the α-bromo acids prepared from various aliphatic carboxylic acids by the new method are given in the Table below:

$$R_1R_2CHCO_2H \xrightarrow[85\ ^{\circ}C,\ 16\ h]{NBS,\ H_2SO_4,\ CF_3CO_2H} R_1R_2CBrCO_2H$$

R = H or alkyl

Table. Yields of α-Bromo Carboxylic Acids

Substrate	*Yield (%)*[a]	*Substrate*	*Yield (%)*[a]
Acetic acid	88	Isobutyric acid	86
Propionic acid	89	Pentanoic acid	86
Butyric acid	87	Hexanoic acid	82

[a] 90-90% purity after one distillation; >95% after two distillations (see example below)

Among solvents examined (THF, $CHCl_3$, CH_2Cl_2) trifluoroacetic acid was by far the best. The optimal ratio of H_2SO_4/TFA for the reaction was found to be 2.5 mL/50 mL. Dibromo products were not formed significantly in any of the reactions, even with the 50% excess of NBS being used. Phenyl-substituted carboxylic acids, such as phenylacetic acid, were not good substrates for the reaction, because they apparently undergo preferential aromatic bromination.

The absence of dibromo products, coupled with the fact that elemental bromine does not work in place of NBS in the reaction, under otherwise identical conditions, leads us to believe that the mechanism of the reaction involves formation of some derivative of the carboxylic acid which more easily enolizes. One such possible derivative would be the hypobromite, RCO_2Br. Studies directed at elucidating the mechanism are currently underway.

Typical Experimental Procedure: Hexanoic acid (11.6 g (0.1 mol), NBS (26.7 g, 0.15 mol), 2.5 g concentrated H_2SO_4, and 50 mL of CF_3CO_2H are placed in a 250 mL round bottomed flask equipped with magnetic stirrer and reflux condenser which is vented into a gas absorption trap containing water. The reaction mixture is heated to 85 °C, at which temperature the reaction commences. After stirring for 16 hours, the solvent was removed under aspirator pressure, and the product was distilled in vacuo (110-120 °C/5 mm Hg) to give a product of > 90% purity, containing some succinimide. Redistillation at 134-136 °C/9 mm Hg, gives 14.3 g (73%) product of > 95% purity.

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