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BISTRIFLUOROMETHYLATION OF ACRYLAMIDE FOR TRIFLUOROMETHYLATED SYNTHETIC BLOCKS

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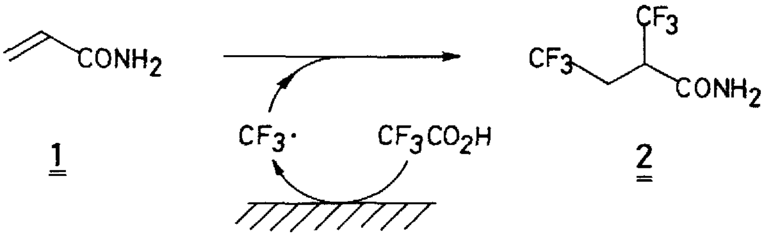
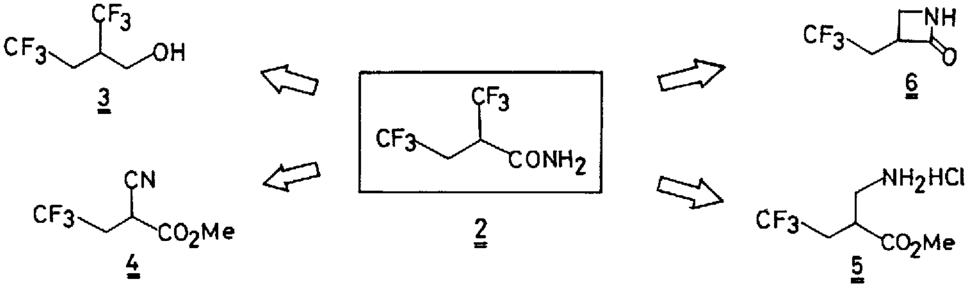
Summary; 4,4,4-Trifluoro-2-trifluoromethylbutyrylamide has been electrochemically prepared and transformed into the carbon-five synthetic blocks such as β-amino acid and β-lactam bearing trifluoromethyl group.

Organofluorine compounds have been accepting an increasing attention due to their unique natures as the medicinal, agricultural, and electronics materials.[1] 1,2-Bistrifluoromethylated aliphatic compounds would be potentially useful precursors for trifluoromethylated synthetic blocks but have never been successfully employed because their preparations are not straightforward.[2] Reaction of the electrochemically generated trifluoromethyl radical with olefins would be promising for the purpose. However, a synthetically successful electrochemical trifluoromethylation from TFA is very few.[3] Here, we describe a novel electrochemical bistrifluoromethylation of acrylamide **1** in which two trifluoromethyl groups are selectively incorporated into the α- and β-positions on the activated double bond.[4] A mixture of TFA (4.3 ml, 56.3 mmol), **1** (1 g, 14.1 mmol), NaOH (224 mg, 5.6 mmol) dissolved in MeCN (115 ml) and H_2O (15 ml) was electrolyzed in an undivided cell at 0°C. A constant current (200 mA/cm^2) was applied for 2.5 h (1 F/mol to TFA) using two platinum electrodes (2 x 1.5 cm^2).



A usual workup and a simple distillation gave 4,4,4,-trifluoro-2-trifluoromethylbutyrylamide (*2*) as crystals (35%).[5] *The current efficiency for* trifluoromethyl radical formation from TFA is acceptable since 1.1 F/mol electricity is enough to consume a total of TFA. The higher current density (200 mA/cm^2) is critical for the bistrifluoromethylation in contrast to trifluoromethyldimerization of methylacryrate where a moderate current density (50 mA/cm^2) is usable. Presumably, the trifluoromethylated radical intermediate bearing $CONH_2$ group would adsorb more strongly on the platinum electrode by the aid of the amino nitrogen atom so as to meet with another attack of trifluoromethyl radical at the higher current density.

The bistrifluoromethylated compound 2 is a promising and versatile precursor for aliphatic trifluoromethylated synthetic blocks due to the two CF_3 groups. Some preliminary results of the transformation of 2 are shown in the scheme. Hydrogen chloride catalyzed hydrolysis of 2 provides the corresponding carboxylic acid which is esterified with diazomethane followed by $LiAlH_4$ reduction, affording 3 (70% from 2). Compound 2 was transformed to α-cyanoester **4** by sodium hydroxide catalyzed carbomethoxylation of CF_3 group in MeOH (85%) and subsequent dehydrative cyanation of $CONH_2$ group (P_2O_5 at 220 °C, 80%). Hydrogenation of **4** (PtO_2 in AcOH) gave the β-amino acid 5 (70%), which was transformed to the β-lactam **6** by the use of ethylmagnesium bromide (55%).



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References

1) R. Filler and Y. Kobayashi, "Biomedicinal Aspects of Fluorine Chemistry," Kodansha, Tokyo (1982).

2) Conventional trifluoromethylative reagents such as metal complexes of trifluoromethyl iodide and N-trifluoromethyl-N-nitrosotrifluoromethanesulfonamide are unfeasible for 1,2-bistrifluoromethylation. ; Y. Kobayashi, K. Yamamoto, and I. Kumadaki, Tetrahedron Lett., **42**, 4071 (1979); T. Kitazume and N. Ishikawa, Chem. Lett., 1981, 1679; T. Umemoto, and A. Ando, Bull. Chem. Soc. Jpn., 59, 447 (1986).

3) C. J. Brookes, P. L. Coe, D. M. Owen, A. E. Pedler, and J. C. Tatlow, J. Chem. Soc., Chem. Commun., **1974**, 323; R. N. Renaud, P. J. Champagne, and M. Savard, Can. J. Chem., 57, 2617 (1979); N. Muller, J. Org. Chem., **48**, 1370 (1983).

4) N. Muller, J. Org. Chem. **51**, 263 (1986); Muller reported a preparation of 2,2,2-trifluoroethylmalonic acid (9% yield) via 4,4,4-trifluoro-2-trifluoromethylbutanoic acid which was unisolable.

5) mp;90-92°C; ^{19}F-NMR (δ. from C_6F_6 in $CDCl_3$); 93.99 (d, J=8.5Hz), 93.23 (t, J=10.3Hz), ^{13}C-NMR ($CDCl_3$); 29.4 (q, J=30.6Hz), 43.2 (q, J=28.2Hz), 123.6 (q, J=280.2Hz), 124.9 (q, J=276.6Hz), 164.9 (s); MS m/e=209 (M^+).

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