2,2,2-Trifluorodiazoethane: A Highly Selective Reagent for the Protection of Sulfonic Acids

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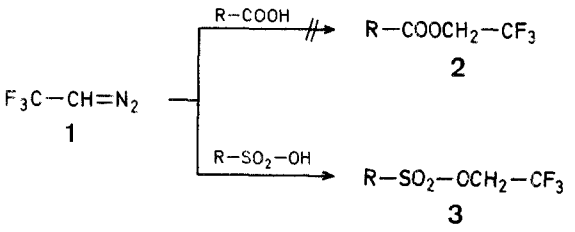
In the course of our studies on the synthesis of selective derivatization reagents for electron capture detection in negative ion mass spectrometry we studied some reactions of 2,2,2-trifluorodiazoethane (**1**), which is readily available as an ethereal co-distillate from direct nitrosation of 2,2,2-trifluoroethylamine[1]. In contrast to the well known reactivity of most other diazo compounds[2,3], no 2,2,2-trifluoroethyl esters (**2**) are formed if **1** is exposed to various carboxylic acids (e.g. acetic acid, citric acid, 4-methylbenzoic acid, 4-nitrobenzoic acid) at 20 °C for 24 h. However, sulfonic acids react rapidly with **1** to give 2,2,2-trifluoroethyl sulfonates (**3**) in good to excellent yields (Table)[4].

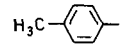
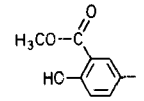


The selectivity of the reaction may be demonstrated with the synthesis of **3d** and **3e**. Thus, 3-sulfopropionic acid as well as 5-sulfosalicylic acid are exclusively converted by **1** to the corresponding sulfonates, leaving the carboxylic groups uneffected. Subsequent esterification using diazomethane results in the clean formation of the mixed esters **3d** and **3e**.

In contrast to the corresponding methyl or ethyl sulfonates, all 2,2,2-trifluoroethyl sulfonates prepared are highly crystalline and are stable towards pyridine (48 h, 20 °C). Due to a different mechanism[6], sulfonate esters may be cleaved selectively in the presence of methyl carboxylates using sodium methoxide[7] (per mmol of **3**: 5 mmol of sodium methoxide in 3 ml of dry methanol; 2 h, 20 °C) to liberate sulfonic acids after acidification in quantitative yields. As a result, the title compound **1** may be regarded as the first selective reagent for convenient protective group transformations of sulfonic acids[8]. The method described might not only be useful in organic synthesis but also in analytical chemistry in order to separate acids of different acidity.

An attempted preparation of **1** utilizing the method of Ref.[9] was unsuccessful since *N*-2,2,2,-trifluoroethyl-*p*-toluenesulfonamide (m.p. 138 °C) could not be nitrosated under conventional reaction conditions (acetic acid, sodium nitrite, 0 °C). Thus, ethereal solutions of **1** were prepared according to Ref.[1]. In order to remove traces of unreacted 2,2,2-trifluoroethylamine, which rapidly precipitates the corresponding ammonium salt in the presence of a sulfonic acid, the ethereal co-distillates are washed with an aqueous solution of 10–20% citric acid prior to use in esterification. The concentration of 2,2,2-trifluorodiazoethane (**1**) in these bright greenish-yellow solutions may be readily determined spectrophotometrically taking a molar coefficient of extinction of ε (400 nm) = 11 ± 1 (solvent: diethyl ether or *n*-pentane). This value is obtained from iodine titration (according to Ref.[1]) and the methods applied for the quantitation of other diazoalkanes.[10]

Table. Compounds **3** prepared

Product No. R	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	^{1}H-N.M.R.[c] δ [ppm]	^{13}C-N.M.R.[d] δ [ppm]
3a[e] 	87 (>95)	39–40° (n-C_6H_{14})	$C_9H_9F_3O_3S$ (254.2)	2.47 (s, 3H, CH_3); 4.36 (q, 2H, J = 8.0 Hz, OCH_2); 7.39 (d, 2H_{arom}, J = 8.6 Hz); 7.83 (d, 2H_{arom}, J = 8.6 Hz)	21.7 (CH_3); 64.9 (q, J = 38 Hz, OCH_2); 122 (q, J = 278 Hz, CF_3); C_{arom}: 128.5, 130.7, 132.4, 146.6
3b n-$C_{12}H_{25}$	91 (>95)	41–42° (CH_3OH/H_2O)	$C_{14}H_{27}F_3O_3S$ (332.4)	0.88 (t, 3H, J = 6.1 Hz, CH_3); 1.27 (br.s, 23H, CH_2); 1.88 (m, 2H, CH_2SO_3); 4.50 (q, 2H, J = 8.1 Hz, OCH_2)	14.1 (CH_3); 22.7, 23.4, 28,1, 28.5, 28.9, 29.4, 29.7, 32.0; 51.7 (CH_2SO_3); 63.7 (q, J = 38 Hz, OCH_2); 122.4 (q, J = 278 Hz, CF_3)
3c[f] $HOOC-CH_2-CH_2-$	93 (>95)	105–106° (C_2H_5OAc/ n-C_6H_{14})	$C_5H_7F_3O_5S$ (236.2)	2.96 (t, 2H, J = 6.8 Hz); 3.58 (t, 2H, J = 6.8 Hz); 4.53 (q, 2H, J = 7.8 Hz, OCH_2)	33.7 (CH_2CO_2); 50.7 (CH_2SO_3); 67.8 (q, J = 38 Hz, OCH_2); 125.1 (q, J = 277 Hz, CF_3); 180.2 (CO_2)
3d[f] $H_3COOC-CH_2-CH_2-$	78 (>95)	39° (n-C_6H_{14})	$C_6H_9F_3O_5S$ (250.2)	2.90 (t, 2H, J = 7.1 Hz); 3.58 (t, 2H, J = 7.1 Hz); 3.76 (s, 3H, OCH_3); 4.53 (q, 2H, J = 8.0 Hz, OCH_2)	28.3 (CH_2CO_2); 46.8 (CH_2SO_3); 52.7 (OCH_3); 64.2 (q, J = 38 Hz, OCH_2); 122.5 (q, J = 278 Hz, CF_3); 170.3 (CO_2)
3e[g] 	67 (78)	81.5° (n-C_6H_{14})	$C_{10}H_9F_3O_6S$ (314.2)	4.03 (s, 3H, OCH_3); 4.39 (q, 2H, J = 7.8 Hz, OCH_2); 7.17 (d, 1H_{arom}, J = 8.8 Hz); 7.98 (dd, 1H_{arom}, J = 2.4/8.8 Hz); 8.47 (d, 1H_{arom}, J = 2.4 Hz); 11.4 (s, 1H, OH)	53.2 (OCH_3); 64.7 (q, J = 38 Hz, OCH_2); 122.2 (q, J = 278 Hz, CF_3); 169.5 (CO_2); C_{arom}: 113.1, 119.7, 125.7, 131.8, 134.9

[a] Yield after recrystallization, in brackets yield determined by ^{1}H-N.M.R. spectroscopy (internal standard for quantification: benzylideneacetone, δ_{CH_3} = 2.38 ppm/$CDCl_3$).

[b] Satisfactory microanalyses obtained: C +0.30, H ±0.20, S +0.24.

[c] Solvent $CDCl_3$; shifts relative to internal tetramethylsilane (80 MHz).

[d] Proton-decoupled (20 MHz), singlets reported unless otherwise noted; solvent $CDCl_3$ (**3a**, **3b**, **3d**, **3e**) and D_2O/0.5 molar K_2HPO_4 (**3c**), internal standard sodium 3-(trimethylsilyl)-propionate-d_4.

[e] Ref.[5]: m.p. 41 °C.

[f] Prepared from 3-sulfopropionic acid anhydride (**3c**), with subsequent esterification with diazomethane (**3d**).

[g] Prepared from 5-sulfosalicylic acid dihydrate in 1,4-dioxan, with subsequent esterification with diazomethane.

Selective Esterification; Synthesis of 3d:

3-Sulfopropionic acid anhydride (40.6 mg, 0.3 mmol) is dissolved in 2–3 drops of water. Acetone (5 ml) is then added, followed by a 15–20 fold excess of ethereal **1**. After 2h at room temperature the solution is concentrated under reduced pressure to give pure crystalline **3c**; yield: 68.0 mg (96%). The residue is redissolved in ethyl acetate (2 ml) and excess ethereal diazomethane is added at 0 °C until a yellow colour persists. Evaporation in vacuo leaves pure **3d** as judged from T.L.C. analysis [silica gel, solvent system: ethyl acetate/n-hexane, 1/1(v/v), R_f 0.58] and ^{1}H-N.M.R. spectrum; yield: 65.0 mg (87%). The oily residue is dissolved in a minimum n-hexane to give the analytical pure crystalline product after cooling (−40 °C).

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[4] A quantitative ^{1}H-N.M.R. study showed 90% conversion of p-toluenesulfonic acid monohydrate (0.013 mmol in 1 ml of tetrahydrofuran) to **3a** (at 20 °C) after 30 min (**1**: 16 fold excess of a 0.07 molar ethereal solution).

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