ARTICLE INFO
Received 08 February 2021
Accepted 15 February 2021
Available online February 2021

THREE-COMPONENT ONE-STEP SYNTHESIS OF NEW NITRILES 3-(1*H*-INDOLE-3-YL)-2-CYANO-4,4,4-TRIFLUOROBUTANOIC ACID

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Abstract: A new highly electrophilic alkene – 2-(2,2,2-trifluoroethylidene)malononitrile **1** and nitriles of 3-(1*H*-indole-3-yl)-2-cyano-4,4,4-trifluorobutanoic acid **2a** - **f** on its basis were synthesized. Compounds **2a**, **b** were obtained by C^3-alkylation of indole derivatives **4a**, **b** by alkene **1** with high yields, which, however, do not compensate for the low yield of **1**. To increase the common yield of target nitriles **2**, a three-component one-step reaction of trifluoroacetaldehyde ethyl hemiacetal, malononitrile and **4c** - **f** indole derivatives was developed. The maximum yields of **2c** - **f** compounds are achieved when all the reagents are mixed simultaneously in the equimolar ratio and the catalytic amount of the organic base. The structure of the compounds was confirmed by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, mass spectrometry, and high-resolution mass spectrometry.

Keywords: 2-(2,2,2-trifluoroethylidene)malononitrile, nitriles 3-(1*H*-indole-3-yl)-2-cyano-4,4,4-trifluorobutanoic acid, three-component one-step synthesis, trifluoroacetaldehyde ethyl hemiacetal, indole and its derivatives, malononitrile.

Introduction

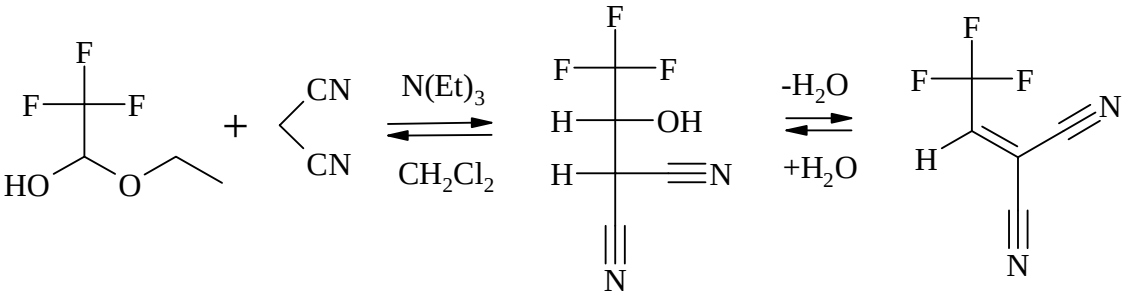
For many years, we systematically studied fluorinated highly electrophilic dicyanoethylenes synthesized from polyfluorocarbonyl compounds and malononitrile. [1 - 5]. One of the substrates that under mild conditions regeoselectively undergo C-alkylation at 3^d position by similar alkenes is indole and its derivatives. 3-Substituted indoles underlie the structures of many natural compounds, medicinal drugs, and plant growth regulators [5 - 7]. The synthesis of new fluorinated 3-substituted indoles expands the prospect of creating effective biologically active compounds. The classical scheme for the synthesis of fluorinated dicyanoethylenes involves the C-oxyalkylation of malononitrile with a fluorinated carbonyl compound in the presence of a base or Lewis acid,

followed by dehydration of the resulting alcohol. This method was used to obtain dicyanoethylenes from polyfluorinated ketones and trifluoropyruvic acid esters [2, 4 - 6].

In this paper, we studied methods for the synthesis of new nitriles 3-(1*H*-indole-3-yl)-2-cyano-4,4,4-trifluorobutanoic acid **2a - f** based on trifluoroacetaldehyde ethyl hemiacetal.

Results and discussion

The study of the reaction of trifluoroacetaldehyde ethyl hemiacetal (TFAE) with malononitrile in the presence of catalytic amounts of triethylamine showed that the C-hydroxyalkylation product **3** is spontaneously dehydrated to form alkene **1**. The presence of **1** in the reaction mass in an amount of ~ 5% is confirmed by ^{1}H and ^{19}F NMR spectroscopy (Scheme 1). It was found that in the reaction mixture, alkene **1** is unstable and enters into various reactions with the formation of unknown by-products. An attempt to increase the yields of alkene **1** by changing the ratio of the starting compounds (TFAE and malononitrile) did not lead to positive results. An increase of the reaction temperature and/or the contact time of the reagents leads only to the tarring of the reaction mass. The use of other basic catalysts instead of triethylamine, such as DABCO, pyridine, quinoline, K_2CO_3, in different ratios, or the use of their mixtures with triethylamine, does not give the better results. Incomplete conversion of two consecutive reversible reactions and their final product - highly reactive alkene **1**, which easily enters into side irreversible reactions with the initial and/or intermediate compounds, significantly complicate its synthesis. Nevertheless, high reactive dicyanoethylene **1** was isolated by distillation from the reaction mass with a yield of 7%.



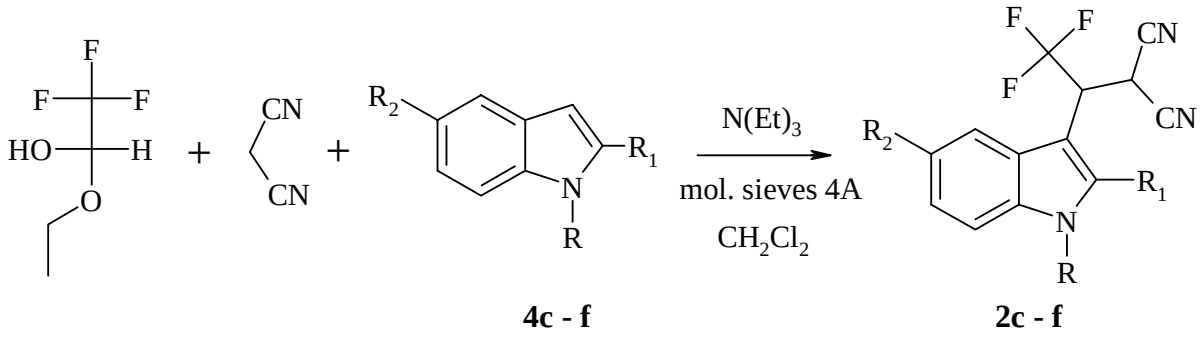
3 **1**

Scheme 1. *Two-steps scheme of the synthesis of 2-(2,2,2-trifluoroethylidene)malononitrile **1**. Under the conditions of synthesis, TFAE is gradually hydrolyzed by the released reaction water.*

The reaction of indole and 2-methylindole with alkene **1** in dichloromethane leads to the almost quantitative formation of nitriles 3-(1*H*-indole-3-yl)-2-cyano-4,4,4-trifluorobutanoic acid **2a** and **b**, which are isolated with yields of 92 % and 89 %, respectively. However, the low yield of alkene **1** stimulated the authors to search for new, alternative methods for the synthesis of target compounds **2**.

The spontaneous formation of alkene **1** at the C-oxyalkylation stage allowed using **1** for C^3-alkylation of indole **4** derivatives without prior it from the reaction mass. The addition of N-methylindole **4c** to the reaction mass four hours after its preparation from equimolar amounts of TFAE, malononitrile, and a catalytic amount of triethylamine in dichloromethane resulted in the formation of compound **2c** with a yield of 74 %.

It is known that TFAE reacts with indole only at high temperature or in the presence of Friedel - Crafts catalysts or under microwave irradiation [8 - 11]. At room temperature, under reaction conditions, TFAE does not react with indole, and therefore cannot compete with alkene **1** in the substitution reaction of indole **4** derivatives. Comparing the data from the literature and our experiment, it became obvious that all the reagents can be mixed simultaneously. For comparison, compound **2c** was obtained a second time, but now all the reagents were mixed simultaneously. In this one-step synthesis performance, compound **2c** was isolated with a yield of 81%. This allowed in this work to implement the strategy of *in situ* synthesis of highly reactive alkene 2-(2,2,2-trifluoroethylidene)malononitrile **1** in the presence of indole **4** derivatives and take placed a three-component one-step reaction under basic catalysis (Scheme 2). Compounds **2c - f** are formed as a result of a regeoselective electrophilic attack of intermediate **1** at position 3 of indole **4** derivatives, the formation of which in the reaction mass was confirmed by ^1H and ^{19}F NMR spectroscopy.



4c - f **2c - f**

Scheme 2. *Three-Component one-step synthesis of nitriles 3-(1H-indole-3-yl)-2-cyano-4,4,4-trifluorobutanoic acid **2c - f**.*
c) *R=Me, R_1=R_2=H;* ***d)*** *R=Bnz, R_1=R_2=H;* ***e)*** *R=R_1=H, R_2=Br;* ***f)*** *R=R_2=H, R_1=Ph.*

Maximum yields of **2c - f** compounds (56 - 81 %) were achieved when equimolar amounts of TFAE, malononitrile, and **4c - f** indole derivatives were mixed simultaneously in the presence of a catalytic amount of triethylamine at room temperature. The C^3-alkylation reaction of indole derivatives **4c - f** wins the competition with the side transformations of the alkene **1** formed *in situ,* providing high yields of the products of the main reaction-the target nitriles **2**.

Thus, an effective method has been developed for the synthesis of new nitriles 3-(1*H*-indole-3-yl)-2-cyano-4,4,4-trifluorobutanoic acid **2**, which are of great interest in the search for biologically

active compounds. The use of a three-component one-step synthesis involving TFAE opens up new possibilities in the synthesis of trifluoromethyl-substituted compounds. Currently, one-step multicomponent reactions have become a valuable tool in modern organic synthesis for reducing stages, increasing the efficiency of synthesis methods, and reducing their cost [12, 13]. The maximum transformation of initial compounds into final products **2** (80 - 85 %) provides almost complete absence of chemical waste, that is, in this case, the principle of "atom economy" is implemented, which is one of the main principles for "green chemistry" [14].

Experimental part

All the original compounds were purchased from Merck and Sigma-Aldrich and used without further purification. All eluents and solvents: petroleum ether with t_{bp} = 40-70°C (PE), EtOAc (EA), C_6H_6, DCM and NEt_3 were purified by distillation before use. Merck Kieselgel 60 F254 TLC plates were used for reaction control and substance detection. The products were purified by column chromatography using Merck Kieselgel 60 silica gel (0.06-0.20 mm).

The ^{1}H, ^{13}C DEPT 135 and ^{19}F NMR spectra were recorded on a Bruker Avance^{TM}400 spectrometer with operating frequencies of 400, 100, and 376 MHz, respectively. Chemical shifts of protons were determined relative to the residual $CDCl_3$ signals (7.26 ppm) and recalculated to the $SiMe_4$ signal. Chemical shifts of ^{19}F NMR were determined with the suppression of the spin-spin coupling relative to trifluoroacetic acid as an external standard and recalculated to the $CFCl_3$ signal.

Electron impact (70 eV) mass spectra were obtained with a Finnigan Polaris Q instrument equipped with an ion trap. The samples were introduced *via* either the direct inlet. The mass spectrum of compound **2e** containing a bromine atom contains data for ions containing the ^{79}Br isotope. Electrospray ionization (ESI) high resolution mass spectrometry was carried out with a Bruker micrOTOF II instrument operating in positive (capillary voltage of 4500 V) and negative (capillary voltage of 3200 V) ion modes. Operating mass range was *m*/*z* 50 - 3000 Da, calibration was either internal or external (Electrospray Calibrant Solution, Fluka). The samples were introduced *via* a syringe inlet as a solution in MeCN, MeOH, and water at flow rate of 3 μl×min^{-1}. Nebulizer gas was nitrogen (flow rate of 4 l×min^{-1}), inlet temperature was 180°C [15].

2-(2,2,2-Trifluoroethylidene)malononitrile (1)

The dichloromethane (5.0 ml), malononitrile (3.3 g, 0.05 mol), trifluoroacetaldehyde ethyl hemiacetal (7.2 g, 0.05 mol) and triethylamine (0.35 g) were added sequentially into a round-bottom flask with magnetic stir bar under the argon atmosphere. The reaction mixture was stirred at room temperature for overnight. When the reaction done, the solvent was removed under reduced

pressure, the reaction mass was cooled and P_2O_5 (14.2 g, 0.1 mol) was added. A top-down refrigerator and a trap with dry ice are placed. The reaction mass was gently heated at a reduced pressure (~20 mmHg). Alkene **1** after top-down refrigerator is collected in a trap with dry ice. Obtained transparent oil with a sharp irritating smell, 0.52 g, yield 7%, t_{bp} 80-85°C at ~ 20 mm Hg. The substance is tarred for a week at 5°C.

^{1}H NMR ($CDCl_3$, δ, ppm., *J*/Hz): 7.13 (1H, q, 6.3 Hz, CF_3-CH=).

^{19}F NMR ($CDCl_3$, δ, ppm.): -62.91 (s, -CF_3).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 146 $[M]^+$ (10.7).

General procedure for the synthesis of nitriles 3-(1H-indole-3-yl)-2-cyano-4,4,4-trifluorobutanoic acid 2a, b by C-alkylation of indole derivatives 4a, b with alkene 1

The dichloromethane (3.0 ml), indole derivatives **4a, b** (1.78 mmol) and alkene **1** (0.26 g, 1.78 mmol) in 1 ml DCM were added sequentially into a round-bottom flask with magnetic stir bar under the argon atmosphere at 0-5°C. The reaction mixture was stirred for 4 hours. When the reaction done, solution was diluted with dichloromethane (20 ml) and filtered through a 1 cm layer of silica gel and the solvent was removed under reduced pressure to give the desired product.

2-[2,2,2-Trifluoro-1-(1H-indole-3-yl)-ethyl]malononitrile (2a)

Obtained: 0.42 g, yield 92 %, light yellow rosin-shaped oil, R_f = 0.5 (PE+EA, 0.8+0.2).

^{1}H NMR ($CDCl_3$, δ, ppm., *J*/Hz): 4.37-4.45 (2H, m, overlap of two signals -CH-); 7.24-7.64 (5H, m, Ar); 8.54 (1H, br. s., NH).

^{13}C NMR DEPT 135 ($CDCl_3$, δ, ppm., *J*/Hz): 25.29 (s,-<u>C</u>H$(CN)_2$); 42.40 (q, 30.5 Hz, CF_3-<u>C</u>H-); 102.54; 110.71 (s, -CN); 110.81 (s, -CN); 112.06; 117.73; 121.08; 123.44; 124.47 (q, 280.9 Hz, -CF_3); 124.72; 126.13; 135.60.

^{19}F NMR ($CDCl_3$, δ, ppm.): -67.89 (s, -CF_3).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 262.9 $[M]^+$ (9.4); 198.2 $[M\text{-}CH(CN)_2]^+$ (100).

HRMS (ESI, neg. ions), $C_{13}H_8F_3N_3$, found m/z: 262.0595 $[M\text{-}H]^-$. Calculated: 262.0598.

2-[2,2,2-Trifluoro-1-(2-methyl-1H-indole-3-yl)ethyl]malononitrile (2b)

Obtained: 0.44 g, 89% yield, light beige powder, R_f = 0.2 (PE+EA, 0.8+0.2).

^{1}H NMR ($CDCl_3$, δ, ppm., *J*/Hz): 2.32 (3H, s, -Me); 4.21-4.30 (1H, m, CF_3-CH-); 4.92 (1H, d, 9.6 Hz, -CH$(CN)_2$); 6.95-7.45 (4H, m, Ar); 10.37 (1H, br. s., NH).

^{13}C NMR DEPT 135 ($CDCl_3$, δ, ppm., *J*/Hz): 11.46 (s, -Me); 23.58 (s, -CH$(CN)_2$); 43.37 (q, 30.7 Hz, CF_3-CH-); 97.98; 110.92 (s, -CN); 111.16; 111.27 (s, -CN); 118.02; 119.85; 121.30; 124.72 (q, 281.7 Hz, -CF_3); 125.15; 135.45; 136.98.

^{19}F NMR ($CDCl_3$, δ, ppm.): -65.64 (s, -CF_3).

MS (EI, 70 eV), *m/z* (I_{rel} (%)):277 $[M]^+$ (6.6); 212.1 $[M\text{-}CH(CN)_2]^+$ (100). HRMS (ESI, neg. ions), $C_{14}H_{10}F_3N_3$, found m/z: 276.0759 $[M\text{-}H]^-$. Calculated: 276.0754.

Three-component one-pot synthesis of 2-[2,2,2-trifluoro-1-(1-methyl-1H-indole-3-yl) ethyl]malononitrile (2c)

The DCM (3.0 ml), malononitrile (0.132 g, 2.0 mmol), trifluoroacetaldehyde ethyl hemiacetal (0.288 g, 2.0 mmol), triethylamine (0.1 g) and molecular sieves 4A were added sequentially into a round-bottom flask with magnetic stir bar under the argon atmosphere. The reaction mixture was stirred at room temperature for four hours. Then, with a syringe add N-methylindole **4c** (0.262 g, 2 mmol) dissolved in 1 ml of DCM. After a day, the reaction mixture was diluted (20 ml) with a mixture of DCM and PE (1/1) and transferred to a chromatographic column containing 100 ml of silica gel. The reaction mass is eluted with a mixture of DCM with PE (1/1), gradually increasing the solvent gradient by adding EA to 3%. The solution of the purified product is evaporated at reduced pressure and then re-evaporated with 20 ml of DCM. Received: 0.41 g, 74% yield, light yellow rosin-shaped oil, R_f = 0.4 (PE+EA, 0.8+0.2).

^{1}H NMR ($CDCl_3$, δ, ppm., *J*/Hz): 3.82 (3H, s, -Me); 4.36-4.44 (2H, m, overlap of two signals -CH-); 7.25-7.63 (4H, m, Ind); 7.44 (1H, br. s., H(2) Ind).

^{13}C NMR DEPT 135 ($CDCl_3$, δ, ppm., *J*/Hz): 25.44 (s, -CH$(CN)_2$); 33,28 (s, N-Me); 42.53 (q, 30.4 Hz, CF_3-CH-); 100.90; 110.19; 110.65 (s, -CN); 110.72 (s, -CN); 117.81; 120.82; 123.08; 124.49 (q, 281.4 Hz, -CF_3); 126.92; 128.82; 136.61.

^{19}F NMR ($CDCl_3$, δ, ppm.): -67.98 (s, -CF_3).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 277 $[M]^+$ (14.3); 212 $[M\text{-}CH(CN)_2]^+$ (100).

HRMS (ESI, neg. ions), $C_{14}H_{10}F_3N_3$, found m/z: 276.0751 $[M\text{-}H]^-$. Calculated: 276.0754.

General procedure for producing of nitriles 3-(1H-indole-3-yl)-2-cyano-4,4,4-trifluoro-butanoic acid 2c - f by three-component one-step synthesis

The dichloromethane (3.0 ml), malononitrile (0.264 g, 4.0 mmol), indole derivatives **4c - f** (4.0 mmol), trifluoroacetaldehyde ethyl hemiacetal (0.58 g, 4.0 mmol), triethylamine (0.15 g) and molecular sieves 4A were added sequentially into a round-bottom flask with magnetic stir bar under the argon atmosphere. The reaction mixture was stirred at room temperature for overnight. After

completion of the reaction, the solvent was removed under reduced pressure, and the crude residue was purified by silica gel column chromatography with PE/DCM as eluent, gradually increasing the solvent gradient by adding ethyl acetate to 3%. The solution was evaporated at low pressure and then re-evaporated with 20 ml of DCM to give the desired product.

2-[2,2,2-Trifluoro-1-(1-methyl-1H-indole-3-yl)ethyl]malononitrile (2c)

Obtained: 0.9 g, 81% yield, light yellow rosin-shaped oil, R_f = 0.4 (PE+EA, 0.8+0.2).
The spectral data are given earlier.

2-[1-(1-Benzyl-1H-indole-3-yl)-2,2,2-trifluoroethyl]malononitrile (2d)

Obtained: 1.09 g, 78% yield, light yellow rosin-shaped oil, R_f = 0.4 (PE+EA, 0.8+0.2).

^{1}H NMR ($CDCl_3$, δ, ppm., *J*/Hz): 4.40-4.42 (2H, m, overlap of two signals -CH-); 5.39 (2H, s, -CH_2-); 7.11-7.64 (9H, m, Bnz, Ind,); 7.50 (1H, s, H(2) Ind).

^{13}C NMR DEPT 135 ($CDCl_3$, δ, ppm., *J*/Hz): 25.28 (s, -<u>C</u>H$(CN)_2$); 42.49 (q, 30.4 Hz, CF_3-<u>C</u>H-); 50.46 (s, -CH_2-); 101.70; 110.62 (s, -CN); 110.75; 110.80 (s, -CN); 118.04; 121.01; 123.23; 124.46 (q, 280.9 Hz, -CF_3); 126.73; 127.05; 127.98; 128.49; 128.97; 136.16; 136.40.

^{19}F NMR ($CDCl_3$, δ, ppm.): -67.85 (s, -CF_3).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 353 $[M]^+$ (8.9); 288 $[M\text{-}CH(CN)_2]^+$ (50.9); 91 $[C_7H_7]^+$ (100).

HRMS (ESI, neg. ions), $C_{20}H_{14}F_3N_3$, found m/z: 352.1076 $[M\text{-}H]^-$. Calculated: 352.1067.

2-[1-(5-Bromo-1H-indole-3-yl)-2,2,2-trifluoroethyl]malononitrile (2e)

Obtained: 0.77 g, yield 56 %, light yellow rosin-shaped oil, R_f = 0.2 (PE+EA, 0.8+0.2).

^{1}H NMR ($CDCl_3$, δ, ppm., *J*/Hz): 4.28-4.35 (1H, m, CF_3-CH-); 4.42 (1H, d, 5.2 Hz, -$CH(CN)_2$); 7.23 (1H, d, 6.2 Hz, H(7)); 7.33 (1H, br. d., 8.6 Hz, H(6)); 7.50 (1H, br. s., H(4)); 7.72 (1H, s, H(2)); 8.77 (1H, br. s., NH).

^{13}C NMR DEPT 135 ($CDCl_3$, δ, ppm., *J*/Hz): 25.33 (s, -<u>C</u>H$(CN)_2$); 42.51 (q, 30.7 Hz, CF_3-<u>C</u>H-); 102.33; 110.49 (s, -CN); 110.57 (s, -CN); 113.58; 114.53; 120.40; 124.27 (q, 281.0 Hz, -CF_3); 125.86; 126.58; 127.95; 134.39.

^{19}F NMR ($CDCl_3$, δ, ppm.): -67.94 (s, -CF_3).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 341 $[M]^+$ (11.6); 276 $[M\text{-}CH(CN)_2]^+$ (100).

HRMS (ESI, neg. ions), $C_{13}H_7BrF_3N_3$, found m/z: 339.9695 $[M\text{-}H]^-$. Calculated: 339.9703.

2-[2,2,2-Trifluoro-1-(2-phenyl-1H-indole-3-yl)ethyl]malononitrile (2f)

Obtained: 1.02 g, 75% yield, light beige powder, R_f = 0.3 (PE+EA, 0.8+0.2).

^{1}H NMR ($CDCl_3$, δ, ppm., *J*/Hz): 4.34-4.43 (1H, m, CF_3-CH-); 4.67 (1H, d, 10.4 Hz, -$CH(CN)_2$); 7.26-7.69 (9H, m, Ind+Ph); 8.56 (1H, br. s., NH).

^{13}C NMR DEPT 135 ($CDCl_3$, δ, ppm., *J*/Hz): 23.46 (s, -$\underline{C}H(CN)_2$); 43.64 (q, 30.5 Hz, CF_3-$\underline{C}$H-); 98.61; 110.69 (s, -CN); 110.99 (s, -CN); 111.99; 119.04; 120.30; 122.29; 124.51; 124.77 (q, 282.4 Hz, -CF_3); 128.72; 128.88; 129.24; 130.76; 136.20; 140.93.

^{19}F NMR ($CDCl_3$, δ, ppm.): -65.03 (s, -CF_3).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 339 $[M]^+$ (9.7); 274 $[M\text{-}CH(CN)_2]^+$ (100).

HRMS (ESI, neg. ions), $C_{19}H_{12}F_3N_3$, found m/z: 338.0921 $[M\text{-}H]^-$. Calculated: 338.0911.

2-(2,2,2-Trifluoro-1-hydroxyethyl)malononitrile (3)

The substance is not stable during storage and heating and was not purified individually. The CS of ^{1}H, ^{19}F NMR and the mass spectrum are given for the reaction mass of equimolar amounts of TFAE (7.2 g, 0.05 mol), malononitrile (3.3 g, 0.05 mol) and triethylamine (0.35 g) in DCM (5 ml) after reaction done. The CS of protons, multiplicity, and *J*-coupling depend on the composition of the mixture.

^{1}H NMR (no solvent, δ, ppm., *J*/Hz): 4.73 (1H, d, 2.3 Hz, -$CH(CN)_2$); 4.78-4.85 (1H, m, CF_3-CH-).

^{19}F NMR ($CDCl_3$, δ, ppm.): -77.25 (s, -CF_3).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 164 $[M]^+$ (2.1); 146 $[M\text{-}H_2O]^+$ (9.3).

Acknowledgments

This work was performed with the financial support from Ministry of Science and Higher Education of the Russian Federation. The contribution of Center for molecular composition studies of A.N. Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences (Moscow, Russia) is gratefully acknowledged. High resolution mass spectrometry was performed in the Department of Structural Studies of N.D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences (Moscow, Russia).

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