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Reaction of ethyl 4,4,4-trifluoroacetoacetate enolate with 3-bromo-1,1,1-trifluoroacetone: synthesis of 2,4-bis(trifluoromethyl)furan

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Abstract

The potassium enolate of ethyl 4,4,4-trifluoroacetoacetate **1** reacts with 3-bromo-1,1,1-trifluoroacetone **2** in DMSO solution to yield three products. Ethyl 2,4-bis(trifluoromethyl)-4-hydroxydihydro-3-furoate **3** is generated via C-acylation. The hydrated trifluoromethyl ketone **4** is formed by O-alkylation and **4** reacts further with **2** to give the di-O-alkylated ketone hydrate **5**. Compound **3** undergoes dehydration to the furan derivative **6** on reaction with Ac_2O–$ZnCl_2$.

Keywords: Ethyl-4,4,4-trifluoroacetoacetate; 3-Bromo-1,1,1-trifluoroacetone; C-acylation; 2,4-Bis(trifluoromethyl)furan; 2-Methyl-5-trifluoromethylfuran

1. Introduction

Bégué and coworkers reported that the reaction of the enolate of ethyl 4,4,4-trifluoroacetoacetate **1** with alkyl and benzyl halides results in products formed by C-alkylation, O-alkylation, and di-C-alkylation [1–4]. Feist and Benary showed that haloacetones react with acetoacetic ester enolates to yield 2,4-disubstituted dihydrofuran derivatives, formed via C-acylation [5,6]. By contrast, Bambury et al. [7] reported that **1** and chloroacetone provided a 64% yield of C-alkylated product in the presence of potassium iodide which, after acid catalyzed cyclization, ester hydrolysis and decarboxylation, gave 2-trifluoromethyl-5-methylfuran. In light of these disparate results and our interest in preparing trifluoromethyl substituted furans, we explored the reaction of **1** with 3-bromo-1,1,1-trifluoroacetone **2**.

2. Results and discussion

We now report that the reaction of **1** with **2** in polar aprotic solvents follows competing courses, which result in two major and one minor products: (1) nucleophilic attack of carbanion **1** at the strongly electrophilic carbonyl carbon of **2** (C-acylation) to yield ethyl 2,4-bis(trifluoromethyl)-4-hydroxydihydro-3-furoate **3** (Scheme 1), and (2) S_N2 attack by the oxyanion **1** at the carbon alpha to carbonyl in **2**, with displacement of bromide ion (O-alkylation) to form the ketone hydrate **4**. The third product is believed to be the di-O-alkylated ketone hydrate **5**, derived from **4** (Scheme 2). There was no evidence of products formed by C-alkylation.

A variety of conditions were examined (Table 1) in an attempt to optimize the yield of **3**. In most cases, the yields were similar, with the best results when **1** and **2** were premixed and added to potassium hydride in DMSO, with short reaction times. However, under these conditions, O-alkylation is typically enhanced [4]. Column chromatography on silica gel was found to be the best method of separation and isolation of the products.

These new compounds were characterized by elemental analysis, mass spectrometry, and IR and NMR (^1H and ^{13}C, and ^{19}F) spectroscopy. The spectral data for **3** and the chemistry described below clearly establish the dihydrofuran structure. In contrast to previous studies [5,6], **3** does not readily undergo dehydration to the furan, even in the presence of *p*-toluenesulfonic acid, since the CF_3 group strengthens the C–OH bond and destabilizes the incipient carbocation. However, treatment of **3** with acetic anhydride and $ZnCl_2$ gave an 80% yield of ethyl 2,4-bis(trifluoromethyl)-3-furoate **6**. Aromatization to the furan is probably facilitated by initial formation of monoacetate **7**, followed by rapid elimination. With a large excess of acetic anhydride, **7** was the predominant

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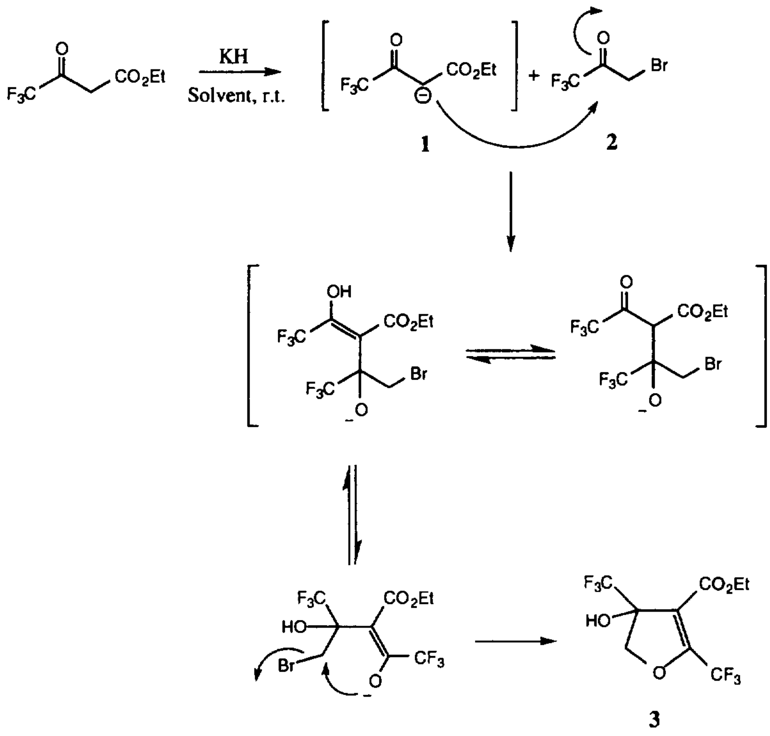


Scheme 1.

product, accompanied by a small amount of **6** (Scheme 3). Indeed **6**, as well as other products, formed when **7** was heated with potassium acetate in moist THF. Alkaline hydrolysis of **6** provided 2,4-bis(trifluoromethyl)-3-furoic acid **8** in near quantitative yield. Compounds **6**, **7** and **8** have not been described previously. Decarboxylation of **8** on heating with $CuSO_4$ and quinoline gave an 85% yield of the known 2,4-bis(trifluoromethyl)furan **9** [8] as summarized in Scheme 4. Compound **9** was prepared previously by reaction of 2,4-furandicarboxylic acid with SF_4 [8], a method which is limited by the lack of commercial availability of the acid. Our approach also obviates the use of SF_4.

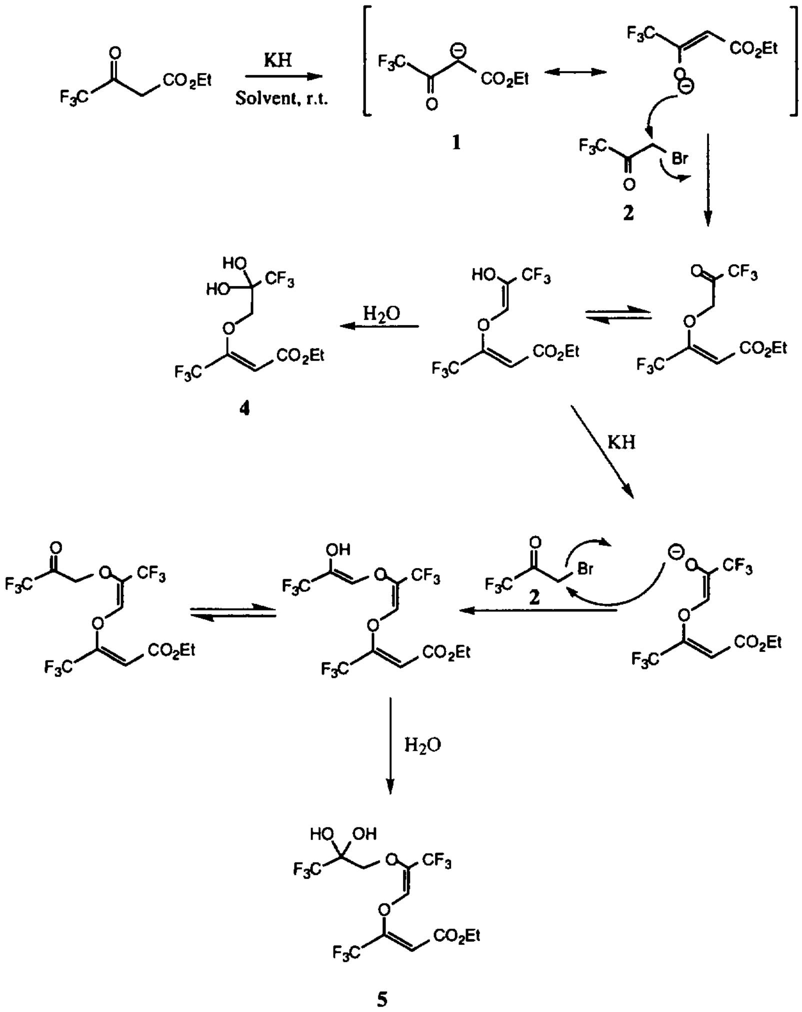
In related studies, the alkylation of **1** with chloroacetone provides **10** (64%) [7]. Hydrolysis and decarboxylation of **10** using DMSO and sodium chloride [9,10] gave a 73% yield of the new diketone **11**. Cyclization of **11** provided 2-methyl-5-trifluoromethylfuran **12** [7] in 42% yield (Scheme 5). This represents a shorter and improved route to **12**.

3. Experimental details

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Column chromatography was performed with 63-200 mm silica gel from EM Science. The ^1H, ^{13}C, and ^{19}F NMR spectra were obtained on a Varian Unity 400 MHz spectrophotometer and, where indicated, a JEOL model FX90Q, in the specified deuterated solvent at 30 °C, and are reported in ppm. For samples prepared in deuteriochloroform, the chemical shifts are expressed relative to internal tetramethylsilane (TMS). The upfield ^{19}F chemical shifts are expressed relative to external trifluorotrichloroethane. For samples prepared in d_6-acetone the downfield chemical shifts are expressed relative to TMS. The electron impact (EI) mass spectra (ms) were determined with a Hewlett-Packard HP-5971A spectrometer. The negative fast atom bombardment (neg-FAB) and the electron impact-direct probe (EI-dp) mass spectra were determined on a VG Autospec spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 series II instrument. Gas chromatography was performed on an HP-5890 series II instrument equipped with an HP-5 Column-30 meter, injector 250 °C, detector 285 °C, rate 8 °C min^{-1}, 0.2 ml injection. IR spectra for solids were recorded using the attenuated total reflectance (ATR) method (corrected) with a Mattson RS FTIR spectrophotometer. IR spectra for liquids were recorded with an Applied Systems React IR 1000, Millersville, MD. Ethyl-4,4,4-trifluoroacetoacetate and 1,1,1-trifluoro-3-bromoacetone were used as received from Aldrich Chemical Company. Solvents were purchased anhydrous and used without further drying.

3.1. General procedure for reaction of the enolate of ethyl-4,4,4-trifluoroacetoacetate (1) with 3-bromo-1,1,1-trifluoroacetone (2)

Ethyl-4,4,4-trifluoroacetoacetate 4.0 g (0.022 mol) was added dropwise to a stirred solution of anhydrous solvent (THF, DMSO, DME) containing 0.023 mol of hydride (NaH or KH). When the evolution of hydrogen ceased, an equimolar amount of **2** was added. The mixture was stirred (see



Scheme 2.

Table 1
Conditions examined

Base	Solvent	Time (h)	Temperature (°C)	Yield (%) [a]		
				3	4	5
NaH	DMSO	1.5	25	20(19)	57(13)	12
KH	DMSO	1.5	25	24 [b]	23	<1
KH	THF	28	25	21(20)	24(2)	3
NaH	THF	3	68	12	[c]	
NaH/KI	Acetone	53	50	22	[c]	
NaH/KI	DME	20	86	17	[c]	
NaH/KI	DME	3	86	10	[c]	
NaH/KI	DME	62	25	21	[c]	

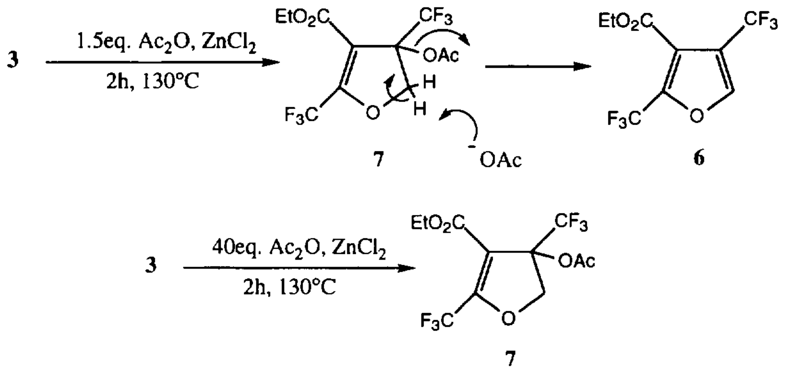
[a] Yields determined via gas chromatography (GC) with pentadecane as an internal standard, and are based on conversion of **1**, except where noted. Values in parentheses are isolated yields.

[b] Reactants were added premixed.

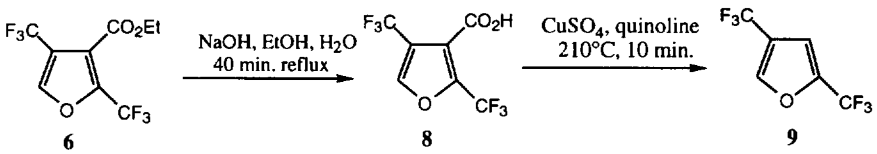
[c] Yield of **3** is the isolated overall yield, the yields of **4** and **5** were not determined.

Dimethoxy ethane (DME), tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), potassium iodide (KI).

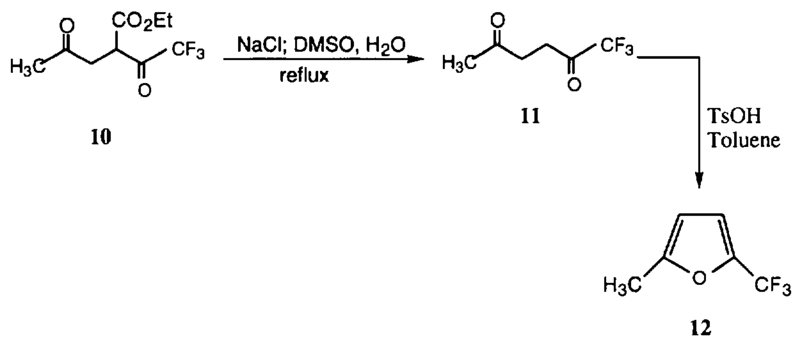
Table 1), whereupon the solution was quenched with 100 ml of an 8% aqueous sulfuric acid solution. Ether (80 ml) was added to facilitate extraction of the organics. The aqueous phase was subsequently extracted 2× with 60 ml of ether, and the organic phases were combined and dried over magnesium sulfate ($MgSO_4$). The crude material was evaporated under reduced pressure, being careful not to exceed 25 °C on the rotovap bath temperature, owing to the volatility of the



Scheme 3.



Scheme 4.



Scheme 5.

products. The residue was purified by column chromatography on silica gel, eluting with hexane:ethyl acetate (95:5).

3.2. *Ethyl-2,4 bis(trifluoromethyl)-4-hydroxydihdyro-3-furoate (3) (nc)*

This compound was obtained in 24% yield as a white solid (ether), mp 28 °C. IR: 3456 cm^{-1} OH (b), 1706 cm^{-1} ester CO (s), 1656 cm^{-1} C=C (s). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 4.8 (d, 1H, J = 11.5 Hz, methylene CH$_2$), 4.7 (s, 1H, OH), 4.6 (d, 1H, J = 11.7 Hz, methylene CH$_2$), 4.6–4.31 (q, 2H, J = 7.2 Hz, CH$_2$), 1.34 (t, 3H, CH$_3$). ^{19}F NMR (CDCl$_3$, 376 MHz): δ −68.3, −80.0. ^{13}C NMR (CDCl$_3$, 100 MHz): δ 162.1, 156.1 (q, J = 40.5 Hz, ring C-2), 124.0 (q, J = 285 Hz, CF$_3$), 117.2 (q, J = 274 Hz, CF$_3$), 160.2, 83.7 (q, J = 32 Hz), 77.7, 62.3, 13.7. ms: (EI) *m/z* 294 (M$^+$), 249 (M-45), 225 (M-69), other ions at *m/z* 179, 121. ms: (EI-dp) *m/z* 249 (M-45), 225 (M-69), 179. Analysis calculated for $C_9H_8F_6O_4$: C, 36.73; H, 2.72. Found: C, 36.59; H, 2.87.

3.3. *O-alkylated ketone hydrate (4) (nc)*

This compound was obtained in 57% yield as a white solid (chloroform or methylene chloride), mp 105–109 °C. IR: 3307 cm^{-1} OH (b), 1720 cm^{-1} ester CO. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.4 (broad s, 2H, hydrate protons), 4.3 (m, 2H, ester CH$_2$), 3.7 (m, 1H, vinyl proton), 2.7 (m, 2H, methylene protons), 1.3 (t, 3H, CH$_3$). ^{19}F NMR (CDCl$_3$, 376 MHz): δ −66, −85. ^{13}C NMR (d_6-acetone, 100 MHz): δ 174 (ester CO), 129 (q, J = 284 Hz), 128 (q, J = 284 Hz), 108 (q, J = 35 Hz), 107 (q, J = 52 Hz), 66, 52, 39, 19. ms: (negative-FAB) *m/z* 311 (M-1), 293 (M-1-H$_2$O). ms: (EI-dp) *m/z* 249 (M-45), 225 (M-69), other ions at *m/z* 197, 179, 169, 151, 125. Analysis calculated for $C_9H_{10}F_6O_5$: C, 34.62; H, 3.21. Found: C, 34.69; H, 3.26.

3.4. *Di-O-alkylated ketone hydrate (5) (nc)*

This compound was obtained in 12% yield as a white solid (chloroform or methylene chloride), mp 107–111 °C. IR: 3349 cm^{-1} OH (b), 1722 cm^{-1} ester CO, 1664 cm^{-1} C=C. ^{1}H NMR (CDCl$_3$, 90 MHz): δ 5.1 (b, 2H, hydrate protons), 4.3–3.7 (complex multiplet, 4H, ester CH$_2$, vinyl protons), 2.4 (m, 2H, methylene protons), 1.3 (t, 3H, CH$_3$). ^{19}F NMR (CDCl$_3$, 376 MHz): δ −83.5, −84.7, −85.9. ^{13}C NMR (d_6-acetone, 22.5 MHz): δ 167 (ester CO), 129 (q, J = 285 Hz, CF$_3$), 128 (q, J = 285 Hz, CF$_3$), 127 (q, J = 285 Hz, CF$_3$), 108 (q, J = 34 Hz), 107 (q, J = 34 Hz), 63, 55, 47, 40, 37, 14. ms: (EI) m/z 404 (M-H_2O), 359 (M-H_2O-OEt), 335 (M-H_2O-CF_3). Analysis calculated for $C_{12}H_{11}F_9O_6$: C, 34.12; H, 2.61. Found: C, 34.19; H, 2.60.

3.5. *Ethyl-2,4-bis(trifluoromethyl)-3-furoate (**6**) (nc)*

To a sealed 5 ml vial, with stirring bar, was added 0.53 g (1.8 mmol) **3**, 1.5 eq. acetic anhydride, and 10 mol% zinc chloride. The mixture was immersed in a preheated (125 °C) oil bath for 2 h. The resulting solution was quenched with 1% potassium carbonate until pH > 10, extracted 3 × 30 ml ether, and dried over $MgSO_4$. The mixture was filtered and evaporated under reduced pressure (bath temperature less than 21 °C). The residue was purified by column chromatography on silica gel, eluted with hexane:ethyl acetate (98:2), to provide a clear liquid, 0.42 g (82%). IR: 1742 cm^{-1} ester CO. ^1H NMR ($CDCl_3$, 90 MHz): δ 7.9 (s, 1H), 4.4 (m, 2H, ester CH_2), 1.4 (t, 3H, CH_3). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −60.4, −63.6. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159 (ester CO), 146 (q, J = 44 Hz), 144 (q, J = 6 Hz), 121 (q, J = 268 Hz, CF_3), 119 (q, J = 39 Hz), 118 (q, J = 270 Hz, CF_3), 117, 62, 14. ms: (EI) m/z 276 (M^+), 261 (M-15), 248 (M-28), 231 (M-45), 207 (M-69). Analysis calculated for $C_9H_6F_6O_3$: C, 39.14; H, 2.19. Found: C, 39.23; H, 2.28.

3.6. *Acetate of 3 (7) (nc)*

To a sealed 5 ml vial, with stirring bar, was added 0.20 g of **3**, 40 eq. acetic anhydride, and 10 mol% zinc chloride. The mixture was submersed in a preheated (135 °C) oil bath for 2 h. The resulting solution was quenched with 1% potassium carbonate until pH > 10, extracted 3 × 30 ml ether, and dried over $MgSO_4$. The mixture was filtered and evaporated under reduced pressure (bath temperature less than 21 °C). The residue was purified by TLC with hexane:ethyl acetate (90:10), to provide a clear liquid, 0.13 g (55%). IR: 1766 cm^{-1} acetate CO, 1727 cm^{-1} ester CO, 1661 cm^{-1} C=C. ^1H NMR ($CDCl_3$, 90 MHz): δ 4.8 (broad s, 2H), 4.2 (m, 2H, ester CH_2), 2.2 (s, 3H, acetate CH_3), 1.3 (t, 3H, ester CH_3). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −67.8, −79.6. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169 (ester CO), 160, 158 (q, J = 40 Hz), 123 (q, J = 283 Hz, CF_3), 122, 118 (q, J = 274 Hz, CF_3), 88 (q, J = 33 Hz), 74, 62, 21, 14. ms: (EI) m/z 336 (M^+), 291 (M-45), 267 (M-69), 225, 209, 197, 179. Analysis calculated for $C_{11}H_{10}F_6O_5$: C, 39.29; H, 2.98. Found: C, 39.63; H, 3.10.

3.7. *2,4-Bis(trifluoromethyl)-3-furoic acid (**8**) (nc)*

To a 15 ml three-neck flask fitted with a condenser and stir bar was added 0.58 g of **6**, 5.5 g of ethanol, 0.18 g of 50% sodium hydroxide, and 1.2 g of water. The mixture was refluxed (77 °C) for 45 min. The resulting solution was quenched with 40 ml 8% sulfuric acid (pH < 2), extracted 3 × 30 ml ether, and dried over $MgSO_4$. The mixture was filtered and evaporated under reduced pressure to provide a white solid (hexane), mp 104–107 °C, 0.51 g (97%). IR: 2900 cm^{-1} CO_2H. ^1H NMR ($CDCl_3$, 90 MHz): δ 9.6 (s, 1H, CO_2H), 7.9 (s, 1H, H-5). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −60.5, −63.6. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164 (CO_2H), 147 (q, J = 44 Hz, C-4), 144 (q, J = 6 Hz, aromatic CH), 120 (q, J = 268 Hz, CF_3), 119 (q, J = 40 Hz), 118 (q, J = 270 Hz, CF_3). ms: (EI) m/z 247 (M-1), 231 (M-OH), 203 (M-CO_2H), 69. Analysis calculated for $C_9H_6F_6O_3$: C, 33.89; H, 0.81. Found: C, 33.81; H, 0.91.

3.8. *2,4-Bis(trifluoromethyl)furan (**9**)*

To a 10 ml two-neck flask with stirring bar and fitted with a 10 inch vigreaux column with condenser and dry ice trap, was added 0.28 g of **8**, 4 g quinoline, and 10 mol% copper sulfate. An argon sweep was maintained to carry the off gases to a dry ice trap. The mixture was submersed in a preheated (210 °C) oil bath for 10 min. The distillate was treated with $MgSO_4$, and the clear liquid drawn off by pipet to provide 0.21 g (90%) [8]. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.9 (s, 1H, H-5), 7.0 (s, 1H, H-3) (literature [8] 7.96, 7.09). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −60.9, −66.0. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144 (C-5), 121 (q, J = 267 Hz, CF_3), 119 (q, J = 39 Hz, C-4), 118 (q, J = 267 Hz, CF_3), 109 (C-3). ms: (EI) m/z 204 (M^+), 185, 154, 135 (M − 69).

3.9. *1,1,1-Trifluoro-2,5-hexanedione (**11**) (nc)*

Ethyl-4,4,4-trifluoroacetoacetate (5.96 g) was added dropwise to 70 ml of dimethoxyethane containing 0.85 g of NaH. When the evolution of hydrogen ceased, an equimolar amount of chloroacetone was added dropwise followed by refluxing for 17 h. The solution was allowed to cool and a 100 ml water quench acidified to less than pH 2 with 8% H_2SO_4 added. The organic phase was extracted 3 × 60 ml with ethyl acetate and dried over $MgSO_4$. The mixture was filtered and distilled under reduced pressure to provide compound **10** in 65% yield [7]. To a 25 ml three-necked flask with magnetic stir bar and condenser was added compound **10** (1.92 g). To this was added 8.0 g DMSO, water (0.63 g), and NaCl (0.05 g). The resulting solution was immersed in an oil bath (110 °C) for 2.5 h. The solution was allowed to cool and 20 ml of water with 5 ml 8% H_2SO_4 was added. The two-phase mixture was extracted 3 × 60 ml with ether and dried over $MgSO_4$. The mixture was filtered and distilled under reduced pressure to provide **11** in 73% yield as a clear liquid, bp 23 °C (1 Torr). IR: (neat) 1752 cm^{-1} CF_3C=O, 1708 cm^{-1} CH_3C=O, 1300–1140 cm^{-1} CF_3. ^1H NMR ($CDCl_3$, 90 MHz): δ 2.9 (m, 4H), 2.2 (s, 3H). ms: (EI) m/z 168 (M^+), 153 (M-15), 125 (M-43), 99 (M-69), 69. Analysis calculated for $C_6H_7F_3O_2$: C, 42.86; H, 4.21. Found: C, 42.49; H, 4.40.

3.10. *2-Trifluoromethyl-5-methylfuran (**12**)*

To a 50 ml three-neck flask with stirring bar and fitted with a Dean-Stark trap, was added 30 ml of toluene and 0.18 g of

TsOH. The solution was allowed to reflux for 1 h, after which 0.51 g of **11** was added. The mixture was refluxed for an additional 55 h. The contents of the Dean-Stark trap were combined with the flask contents and quenched with 20 ml of 1% potassium carbonate. The resulting solution was phase separated and the resulting aqueous phase was extracted 2 × 5 ml of toluene. The organic extracts were combined and dried with $MgSO_4$ and found to contain 0.19 g (42%) **12**, as per GC/ms and GC Area%. IR [7]: (toluene) 1200–1100 cm^{-1} (CF_3). ms: (EI) m/z 150 (M^+), 131, 81 (M-CF_3).

Acknowledgements

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References

[1] C. Aubert, J.P. Bégué, M. Charpentier-Morize, G. Nee and B. Langlois, *J. Fluorine Chem., 44* (1989) 361.
[2] C. Aubert, J.P. Bégué, M. Charpentier-Morize, G. Nee and B. Langlois, *J. Fluorine Chem., 44* (1989) 377.
[3] J.P. Bégué, M. Charpentier-Morize and G. Nee, *J. Chem. Soc., Chem. Commun.*, (1989) 83.
[4] J.P. Bégué and D. Bonnet-Delpon, *Tetrahedron, 47* (1991) 3207.
[5] F. Feist, *Chem. Ber., 35* (1902) 1545.
[6] E. Benary, *Chem. Ber., 44* (1911) 493.
[7] R.E. Bambury, H.K. Yatkin and K.K. Wyckoff, *J. Heterocyclic Chem., 5* (1968) 95.
[8] V.V. Lyalin, R.V. Grigorash, L.A. Alekseeva and L.M. Yagupol'skii, *Zh. Org. Khim., 11* (1975) 1086.
[9] A.P. Krapcho, E.G.E. Jahngen, Jr., and A.J. Lovey, *Tetrahedron Lett., 13* (1974) 1091.
[10] A.P. Krapcho, J.F. Weimaster, J.M. Eldridge, E.G.E. Jahngen, Jr., A.J. Lovey and W.P. Stevens, *J. Org. Chem., 43* (1978) 138.