1-Ethoxy-3-trifluoromethyl-1,3-butadiene and Congeners as Diels−Alder Components Opening an Entry to Functionalized (Trifluoromethyl)benzenes and -pyridines

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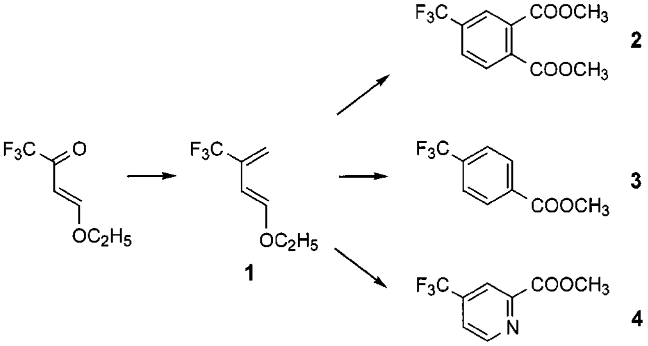
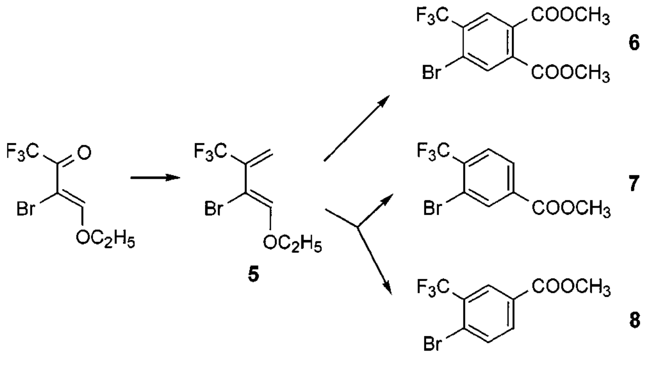
1-Ethoxy-3-trifluoromethyl-1,3-butadiene and its 2-bromo- and 2-phenyl-substituted derivatives have been prepared by Wittig methylenation of the corresponding 4-ethoxy-1,1,1-trifluoro-3-buten-2-ones, which in turn are readily accessible from trifluoroacetic acid. The electron-rich/electron-poor dienes combine smoothly with dimethyl acetylenedicarboxylate and methyl propiolate to provide trifluoromethyl-substituted phthalates (**2**, **6** and **10**) or benzoates (**3**, **7**, **8** and **11**). Satisfactory yields [of 4-(trifluoromethyl)pyridinecarboxylic acids **4** and **12**] can even be achieved with methyl cyanoformate, a less reactive dienophile, if a large excess of the dienophile is employed.

A few years ago we reported that Diels−Alder cycloaddition reactions between 3-trifluoromethyl-1-trimethylsilyloxy-1,3-butadiene and electron-poor dienophiles provide trifluoromethyl-substituted arenes and heterocycles.[1] A drawback of the method, however, was the lengthy preparation of the key starting material by one of two five-step procedures. We have now found a way to replace the dienic component by a more readily accessible equivalent.

The Lewis acid-catalyzed condensation of trifluoroacetyl chloride or trifluoroacetic acid anhydride (technical bulk products) with ethyl vinyl ether is known to afford 4-ethoxy-1,1,1-trifluoro-3-buten-2-one.[2] This ketone was converted by means of a Wittig reaction into (*E*)-1-ethoxy-3-trifluoromethyl-1,3-butadiene (**1**). Diene **1** reacted at 100 °C with stoichiometric amounts of dimethyl acetylenedicarboxylate, methyl propiolate or methyl cyanoformate by cycloaddition and subsequent thermal or base-assisted elimination of ethanol to give dimethyl 4-(trifluoromethyl)phthalate (**2**, 78%), methyl 4-(trifluoromethyl)benzoate (**3**, 77%) or methyl 4-trifluoromethyl-2-pyridinecarboxylate (**4**, 24%), respectively. The yield of the latter product could be improved considerably (to 60% by gas chromatography, 45% of isolated compound) by using a sixfold excess of the dienophile.



Analogously, (*Z*)-2-bromo-1-ethoxy-3-trifluoromethyl-1,3-butadiene (**5**) was made by olefination of (*Z*)-3-bromo-4-ethoxy-1,1,1-trifluoro-3-buten-2-one. When this diene was heated in the presence of dimethyl acetylenedicarboxylate or methyl propiolate, dimethyl 4-bromo-5-(trifluoromethyl)phthalate (**6**, 56%) or a 5:1 mixture of regioisomers (28%), composed of methyl 3-bromo-4-(trifluoromethyl)benzoate (**7**) and methyl 4-bromo-3-(trifluoromethyl)benzoate (**8**), were obtained, respectively.



Finally, 1-ethoxy-2-phenyl-3-trifluoromethyl-1,3-butadiene (**9**) was prepared, again by Wittig methylenation of the

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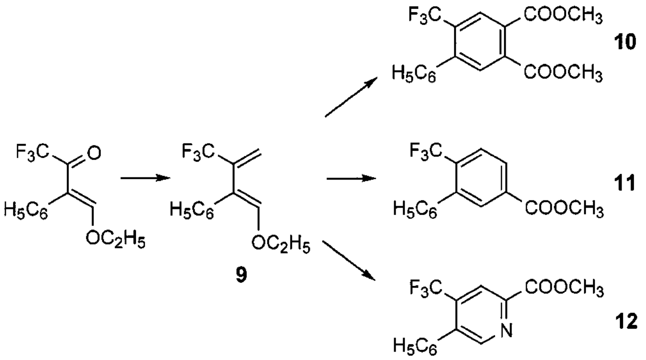
corresponding ketone precursor. Upon reaction with dimethyl acetylenedicarboxylate, methyl propiolate or methyl cyanoformate the expected cycloadducts dimethyl 4-phenyl-5-(trifluoromethyl)phthalate (**10**; 72%), methyl 3-phenyl-4-(trifluoromethyl)benzoate (**11**; 75%) and methyl 5-phenyl-4-trifluoromethyl-2-pyridinecarboxylate (**12**; 14%), respectively, were formed.



Experimental Section

General: Details concerning standard operations and abbreviations can be found in previous publications from this laboratory.[3−5] ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 400, 101 and 376 MHz, respectively, all samples having been dissolved in deuterochloroform. Mass spectra were obtained by chemical ionization in an ammonia atmosphere at 96 eV ionization potential and 100 °C source temperature.

Ketones

3-Bromo-4-ethoxy-1,1,1-trifluoro-3-buten-2-one: Bromine (40 g, 13 mL, 0.25 mol) was added dropwise, over 30 min, to a solution of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one[2] (42 g, 0.25 mol) in dichloromethane (0.25 L) at −25 °C. The yellow mixture was treated with triethylamine (25 g, 35 mL, 0.25 mmol) for 1 h at 25 °C before being poured into water (0.25 L). The organic layer was separated, washed with water (2 × 0.10 L), dried, concentrated and distilled; b.p. 89−91 °C/11 Torr; m.p. −2 to 0 °C; n_D^{20}: 1.4689; yield: 49.4 g (80%). ^{1}H NMR: δ = 7.98 (s, 1 H), 4.41 (q, J = 7.2 Hz, 2 H), 1.49 (t, J = 7.2 Hz, 3 H). ^{19}F NMR: δ = −69.6 (s). MS: m/z (%) = 248 (100) [M$^+$], 247 (25), 179 (38). $C_6H_6BrF_3O_2$ (247.01): calcd. C 29.18, H 2.45; found C 29.17, H 2.31.

4-Ethoxy-1,1,1-trifluoro-3-phenyl-3-butene-2-one: 1,1,1-Trifluoro-3-phenyl-2-propanone[6] (47 g, 0.25 mol), ethyl orthoformate (83 mL, 74 g, 0.50 mol) and acetic acid anhydride (47 mL, 51 g, 0.50 mol) were heated together to 120 °C for 2 h and, after the addition (at 25 °C) of zinc dichloride (3.4 g, 25 mmol), to 140 °C for 20 h. Distillation provided a colorless liquid; b.p. 94−95 g; yield: 36.6 g (60%). ^{1}H NMR: δ = 7.73 (s, 1 H), 7.3 (m, 3 H), 7.2 (m, 2 H), 4.23 (q, J = 7.2 Hz, 2 H), 1.36 (t, J = 7.2 Hz, 3 H). ^{19}F NMR: δ = −69.7 (s). MS: m/z (%) = 263 (16), 262 (100) [M + NH_4^+], 245 (32) [M$^+$ + 1], 244 (7) [M$^+$]. $C_{12}H_{11}F_3O_2$ (244.21): calcd. C 59.02, H 4.54; found C 59.25, H 4.53.

The absence of any NOE effect between the methine hydrogen at C-4 and the hydrogens at the *ortho* position of the phenyl ring makes the (*E*)-configuration probable.

Dienes

(*E*)-1-Ethoxy-3-trifluoromethyl-1,3-butadiene (1): An "instant ylide" [7,8] mixture containing methyl triphenylphosphonium bromide and sodium amide (0.10 mol each) was vigorously stirred in diethyl ether (0.20 L) for 30 min at 25 °C. At 0 °C, (*E*)-4-ethoxy-1,1,1-trifluoro-3-buten-2-one[2] (17 g, 0.10 mol) was added. After 60 min, the reaction mixture was poured whilst stirring into ice-cold hexanes (0.40 L). The liquid phase was decanted from the viscous precipitate, filtered through a pad of kieselguhr (diatomite) and concentrated. According to gas chromatography (30 m DB-1, 30 → 100 °C [20 °C/min], dodecane as an internal standard; 30 DB-1701, same conditions), the product was formed in 75% yield. Upon distillation, even if performed in the presence of some hydroquinone, a non-negligible fraction of the product was lost by polymerization; colorless liquid; b.p. 44−46 °C/45 Torr; n_D^{20}: 1.4032; yield: 14.3 g (43%). ^{1}H NMR: δ = 6.81 (d, J = 12.9 Hz, 1 H), 5.45 (d, J = 12.9 Hz, 1 H), 5.44 (s, 1 H), 5.30 (s, 1 H), 3.87 (q, J = 7.2 Hz, 2 H), 1.33 (t, J = 7.2, 3 H). ^{19}F NMR: δ = −67.2 (s). MS: m/z (%) = 167 (11) [M$^+$ + 1], 166 (94) [M$^+$], 138 (31), 118 (50), 99 (34), 90 (100). $C_7H_9F_3O$ (256.23): calcd. C 50.61, H 5.46; found C 50.54, H 5.41.

(*Z*)-2-Bromo-1-ethoxy-3-trifluoromethyl-1,3-butadiene (5): This compound was prepared analogously from 3-bromo-4-ethoxy-1,1,1-trifluoro-3-buten-2-one (37 g, 0.15 mol) and isolated as a colorless liquid; b.p. 54−56 °C/11 Torr; n_D^{20}: 1.4565; yield: 13.2 g (36%). ^{1}H NMR: δ = 6.91 (s, 1 H), 5.85 (q, J = 2.4 Hz, 1 H), 5.82 (s, 1 H), 4.09 (q, J = 7.3 Hz, 2 H), 1.37 (t, J = 7.3 Hz, 3 H). ^{19}F NMR: δ = −67.2 (s). MS: m/z (%) = 247 (39), 246 (100) [M$^+$], 245 (76), 244 (99), 243 (26). $C_7H_8BrF_3O$ (245.04): calcd. C 34.31, H 3.29; found C 34.35, H 3.15.

The (*Z*)-configuration of the diene **5** was demonstrated by the consecutive treatment with *tert*-butyllithium (2 equivalents, in diethyl ether at −100 °C for 15 min) and methanol which afforded (*E*)-1-ethoxy-3-trifluoromethyl-1,3-butadiene (**1**).

(*E*)-1-Ethoxy-2-phenyl-3-trifluoromethyl-1,3-butadiene (9): This compound was prepared analogously from 4-ethoxy-1,1,1-trifluoro-3-phenyl-3-buten-2-one (24 g, 0.10 mol) and isolated as a colorless liquid; b.p. 47−48 °C/0.3 Torr; yield: 8.0 g (33%). ^{1}H NMR: δ = 7.3 (m, 4 H), 7.2 (m, 1 H), 6.54 (s, 1 H), 5.73 (s, 1 H), 5.26 (s, 1 H), 3.95 (q, J = 7.0 Hz, 2 H), 1.28 (t, J = 7.0 Hz, 3 H). ^{19}F NMR: δ = −64.6 (s). MS: m/z (%) = 260 (13) [M + NH_4^+], 244 (18), 243 (100) [M$^+$ + 1], 242 (32) [M$^+$]. $C_{13}H_{13}F_3O$ (242.24): calcd. C 64.46, H 5.41; found C 64.23, H 5.38.

The (*E*) configuration was assigned on the basis of NOESY cross peaks. Marked nuclear Overhauser spin transfer was observed between the *endo*-methylene hydrogen at C-4 and both the methine hydrogen at C-1 and the aromatic hydrogens. In contrast, no nuclear interaction was found between the methine hydrogen at C-1 and the phenyl ring.

(Trifluoromethyl)phthalic Esters

Dimethyl 4-(Trifluoromethyl)phthalate (2): Diene **1** (3.3 g, 20 mmol) and dimethyl acetylenedicarboxylate (2.5 mL, 2.8 g, 20 mmol) were kept for 16 h at 100 °C. After the addition of acetone (50 mL) and potassium carbonate (5.5 g, 40 mmol) the mixture was heated for 1 h under reflux before being filtered through a pad of diatomite, concentrated and distilled; colorless liquid; b.p. 79−81 °C/0.5 Torr (ref.:[9−11] b.p. 115−135 °C/16 Torr); yield: 4.1 g (78%). ^{1}H NMR: δ = 8.04 (s, 1 H), 7.81 (d-like, slim m, 2 H), 3.95 (s, 6 H). ^{13}C NMR: δ = 167.2 (s), 166.4 (s), 135.7 (s), 133.0 (q, J = 34 Hz), 132.2 (s), 129.4 (s), 128.2 (q, J = 3 Hz,), 126.3 (q, J = 3 Hz), 123.1 (q, J = 273 Hz), 53.0 (2 C). ^{19}F NMR: δ = −63.2 (s). $C_{11}H_9F_3O_4$ (262.18): calcd. C 50.39, H 3.46; found. C 50.54, H 3.15.

Dimethyl 4-Bromo-5-(trifluoromethyl)phthalate (6): This compound was prepared analogously with diene **5** (4.9 g, 20 mmol) and isolated as colorless needles (from hexanes); m.p. 24−25 °C; b.p. 97−99 °C/0.3 Torr; yield: 3.8 g (56%). ^{1}H NMR: δ = 8.11 (s, 1 H), 8.00 (s, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H). ^{19}F NMR: δ = −63.7 (s). MS: *m*/*z* (%) = 360 (100) [M + NH_4^+], 343 (80), 342 (48) [M$^+$]. $C_{11}H_8BrF_3O_4$ (341.08): calcd. C 38.74, H 2.36; found C 38.74, H 2.28.

Dimethyl 2-Trifluoromethyl-1,1′-biphenyl-4,5-dicarboxylate (10): This compound was prepared analogously with diene **9** (4.8 g, 20 mmol) and isolated as colorless starlets after chromatography with a 1:20 (v/v) mixture of ethyl acetate and hexanes as the eluent; m.p. 71−73 °C (from hexanes); yield: 4.9 g (72%). ^{1}H NMR: δ = 8.19 (s, 1 H), 7.64 (s, 1 H), 7.4 (m, 3 H), 7.3 (m, 2 H), 3.97 (s, 3 H), 3.94 (s, 3 H). ^{13}C NMR: δ = 167.2 (s), 166.2 (s), 144.9 (s), 137.8 (s), 135.4 (s), 132.4 (s), 130.6 (q, *J* = 31 Hz), 129.9 (2 C), 128.6 (s), 128.5 (2 C), 128.1 (s), 127.4 (q, *J* = 5 Hz), 123.1 (q, *J* = 275 Hz), 53.0 (2 C). ^{19}F NMR: δ = −57.9 (s). $C_{17}H_{13}F_3O_4$ (338.28): calcd. C 60.36, H 3.87; found C 60.29, H 3.84.

(Trifluoromethyl)benzoic Esters

Methyl 4-(Trifluoromethyl)benzoate (3): Diene **1** (3.3 g, 20 mmol) and methyl propiolate (1.7 mL, 1.7 g, 20 mmol) were mixed and heated for 16 h at 100 °C. The reaction was worked up as described in the preceding section; colorless liquid; b.p. 84−86 °C/9 Torr (ref.:[12] b.p. 94.3−94.8 °C/21 Torr); yield: 3.1 g (77%). ^{1}H NMR: δ = 8.16 (d, *J* = 8.3 Hz, 2 H), 7.71 (d, *J* = 8.3 Hz, 2 H), 3.96 (s, 3 H). ^{19}F NMR: δ = −63.6 (s).

Methyl 3-Bromo-4-(trifluoromethyl)benzoate (7) and Methyl 4-Bromo-3-(trifluoromethyl)benzoate (8): According to NMR spectroscopy, the two compounds were obtained as a 5:1 mixture when diene **5** (4.9 g, 20 mmol) was used under otherwise identical conditions; colorless viscous liquid; b.p. 99−103 °C/4 Torr; yield: 3.8 g (28%). ^{1}H NMR: δ = 8.39 (s, 0.85 H), 8.37 (s, 0.15 H), 8.08 (d, *J* = 8.3 Hz, 0.85 H), 8.06 (dd, *J* = 8.3, 1.9 Hz, 0.15 H), 7.83 (d, *J* = 8.3 Hz, 0.15 H), 7.79 (d, *J* = 8.3 Hz, 0.85 H), 3.99 (s, 2.55 H), 3.98 (s, 0.45 H). ^{19}F NMR: δ = −63.4 (s, 0.45 F), −63.6 (s, 2.55 F). $C_9H_6BrF_3O_2$ (283.04): calcd. C 38.19, H 2.14; found C 38.33, H 2.16.

Methyl 2-Trifluoromethyl-1,1′-biphenyl-5-carboxylate (11): This compound was prepared analogously with diene **9** (4.8 g, 20 mmol) and isolated as a colorless liquid; b.p. 87−89 °C/0.2 Torr; yield: 4.2 g (75%). ^{1}H NMR: δ = 8.12 (d, *J* = 8.3 Hz, 1 H), 8.01 (s, 1 H), 7.83 (d, *J* = 8.3 Hz, 1 H), 7.4 (m, 3 H), 7.3 (m, 2 H), 3.97 (s, 3 H). ^{13}C NMR: δ = 165.8 (s), 141.8 (s), 138.8 (s), 133.1 (s), 132.8 (s), 132.1 (q, *J* = 30 Hz), 128.9 (s, 2 C), 128.3 (s), 128.0 (s), 127.9 (s, 2 C), 126.4 (q, *J* = 5 Hz), 123.6 (q, *J* = 275 Hz), 52.5 (s). ^{19}F NMR: δ = −57.8 (s). $C_{15}H_{11}F_3O_2$ (338.28): calcd. C 64.29, H 3.96; found C 64.02, H 4.00.

(Trifluoromethyl)pyridinecarboxylic Esters

Methyl 4-Trifluoromethyl-2-pyridinecarboxylate (4): A solution of 1-ethoxy-3-trifluoromethyl-1,3-butadiene (**1**; 4.8 g, 20 mmol) and methyl cyanoformate (1.6 mL, 1.7 g, 20 mmol) in toluene (20 mL) was heated under reflux (to approx. 110 °C) for 24 h before the product was absorbed on silica gel (50 mL) and eluted with a 1:3 (v/v) mixture of ethyl acetate and hexanes; colorless prisms; m.p. 29−31 °C (from hexanes at −75 °C); b.p. 87−89 °C/13 Torr; yield: 1.18 g (24%). The yield, as determined by gas chromatography (30 m, DB-FFAP, 100 °C; 30 m, DB-1701, 120 °C), increased to 38%, 52% and 60% when a twofold, fourfold and sixfold excess of cyanoformate was used, respectively. The pyridine ester **4** was isolated in 45% yield (2.2 g) from the last reaction. ^{1}H NMR: δ = 8.96 (d, *J* = 5.1 Hz, 1 H), 8.37 (s, 1 H), 7.23 (d, *J* = 5.1 Hz, 1 H), 4.06 (s, 3 H). ^{13}C NMR: δ = 164.4 (s), 150.8 (s), 149.2 (s), 139.6 (q, *J* = 35 Hz), 122.4 (s, *J* = 274 Hz), 122.3 (q, *J* = 4 Hz), 120.9 (q, *J* = 4 Hz), 53.2 (s). ^{19}F NMR: δ = −65.3 (s). MS: *m*/*z* (%) = 224 (17), 223 (79) [M + NH_4^+], 207 (32), 206 (100) [M$^+$ + 1], 205 (6) [M$^+$]. $C_8H_6F_3NO_2$ (205.14): calcd. C 46.84, 2.95; found C 46.75, H 2.75.

Methyl 5-Phenyl-4-trifluoromethyl-2-pyridinecarboxylate (12): This compound was prepared by reaction between the diene **9** (4.9 g, 20 mmol) and methyl cyanoformate (1.6 mL, 1.7 g, 20 mmol), worked up in the same way as specified for the (trifluoromethyl)-phthalic esters above and isolated as slightly yellowish needles after chromatography on silica (50 mL) with a 1:20 (v/v) mixture of ethyl acetate and hexanes as the eluent; m.p. 64−65 °C (from heptanes); yield: 0.78 g (14%). ^{1}H NMR: δ = 8.79 (s, 1 H), 8.47 (s, 1 H), 7.5 (m, 3 H), 7.4 (m, 2 H), 4.08 (s, 3 H).). ^{13}C NMR: δ = 164.6 (s), 152.9 (s), 147.6 (s), 138.9 (s), 137.0 (q, *J* = 32 Hz), 134.8 (s), 129.1 (s), 128.9 (s, 2 C), 128.4 (s, 2 C), 123.2 (q, *J* = 276 Hz), 121.3 (q, *J* = 5 Hz), 53.3 (s). ^{19}F NMR: δ = −59.8 (s). $C_{14}H_{10}F_3NO_2$ (281.23): calcd. C 59.79, H 3.58, N 4.98; found C 59.78, H 3.72, N 5.00.

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