A facile stereoselective synthesis of functionalised cyclobutenes and electron-deficient 1,3-dienes

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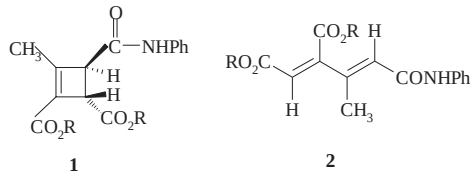
Protonation of the 1:1 intermediate produced in the reaction between dialkyl acetylenedicarboxylates and triphenylphosphine by ethyl 4,4,4-trifluoroacetoacetate leads to vinyltriphenylphosphonium salts: the positively charged ion reacts with the anion of ethyl 4,4,4-trifluoroacetoacetate to form ylides **5a–c**, which undergo intramolecular Wittig reaction to produce 1-ethyl 2,3-dialkyl 4-(trifluoromethyl)-3-cyclobutene-1,2,3-tricarboxylate, which undergo electrocyclic ring-opening reactions in boiling toluene to produce highly electron-deficient 1, 3-dienes in fairly good yields.

Keywords: ethyl 4,4,4-trifluoroacetoacetate, triphenylphosphine, dialkyl acetylenic ester, intramolecular Wittig reaction

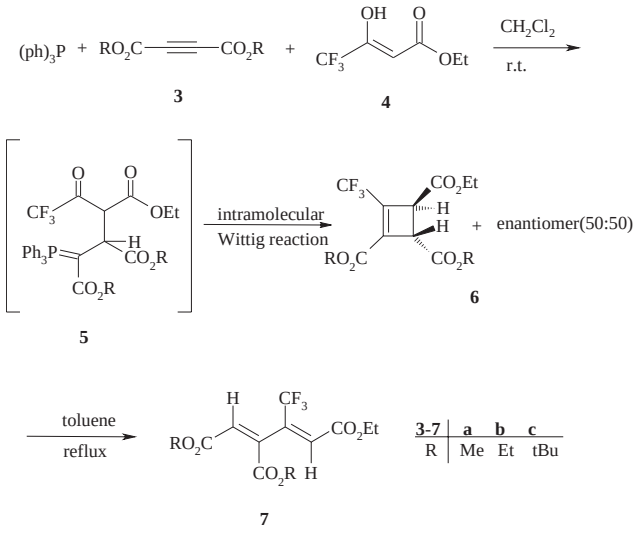
Cyclobutenes are important intermediates in organic synthesis,[1,2] and their synthesis continues to attract much attention. Although the common 5-, 6-and 7-membered ring cycloalkenes are produced fairly easily by intramolecular Wittig reaction, the formation of cyclopropenes and cyclobutenes has not received much attention.[3,4] We have recently described synthesis of cyclobutene derivatives from the stereoselective intramolecular Wittig reaction of a vinyltriphenylphosphonium salt with acetoacetanilide in boiling benzene.[5] Cyclobutenes **1** undergo electrocyclic ring-opening reaction in boiling toluene to produce highly electron-deficient 1,3-dienes **2**.



Scheme 1

As part of our current studies on the development of new routes to carbocyclic systems, we now report a facile synthesis of functionalised cyclobutenes **6** *via* an intramolecular Wittig reaction. Compounds **6a–c** undergo electrocyclic ring-opening reactions to produce electron-deficient 1,3-dienes **7a–c** in fairly high yields. Thus reaction of ethyl 4,4, 4-trifluoroacetoacetate **4** with dialkyl acetylenedicarboxylate **3** in the presence of triphenyl-phosphine leads to the corresponding cyclobutene derivatives **6**, which are converted into electron-deficient 1,3-dienes **7**.

On the basis of the chemistry of trivalent phosphorus nucleophiles,[6,7] it is reasonable to assume that cyclobutene **6** results from initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the reactive 1:1 adduct by ethyl 4,4,4-trifluoroacetoacetate. Then the positively charged ion reacts with the anion of ethyl 4,4, 4-trifluoroacetoacetate to form ylide **5**, which immediately undergoes an intramolecular Wittig reaction to produce the cyclobutene derivatives **6a–c**. Compounds **6a–c** undergo an electrocyclic ring-opening reaction in boiling toluene to produce electron deficient 1,3-dienes **7a–c** in fairly good yields. The ^{1}H NMR spectra of the cyclobutene derivatives **6a–c** displayed signals at about δ=3.7 and δ=3.8 for the two methine groups, which appear as singlets, in agreement with the *trans* geometry for these protons.[8] The ^{13}C NMR spectra of **6a–c** exhibited two signals at about δ=45–45.5 for two allylic carbon atoms and two signals at about δ=138.5–141.5 (q, $^2J_{FC}$ 40.5 Hz) and 138.5–140 (q, $^3J_{FC}$ 5.2 Hz) for two olefinic carbon atoms. The ^{19}F NMR spectra of **6a–c** exhibited one signal at about δ= –65 for the CF_3 groups.



Scheme 2

The ^{1}H NMR spectra of the butadiene derivatives **7a–c** displayed signals at about δ=6.2 and δ=6.4 for two olefinic protons. The ^{13}C NMR spectra of **7a–c** exhibited four signals in the olefinic region. The ^{19}F NMR spectra of **7a–c** also displayed one singlet peak at about δ= –61 for the CF_3 group.

The structural assignments made on the basis of NMR spectra for compounds **6**–**7** were supported by measurments of their IR spectra. Of special interest are the strong carbonyl absorption bands at 1680–1750 cm^{-1} for these compounds.Although the presence of the ^{19}F nucleus complicated both ^{1}H and ^{13}C NMR spectra of **6**–**7**, it helps in assignment of the signals by the long-range coupling with ^{1}H and ^{13}C nuclei. In conclusion,we have found that this reaction leads to a facile synthesis of highly functionalised cyclobutenes,which are converted into electron-deficient 1,3-dienes on the basis of conrotatory opening.

Exprimental

Dialkyl acetylenedicarboxylates, triphenylphosphine and ethyl 4,4,4-trifluoroaceto-acetate were obtained from Fluka (Buchs, Switzerland) and were used without further purification. ^{1}H, ^{13}C and ^{19}F NMR spectra were measured with a Bruker DRX-500 AVANCE spectrometer at 500, 125.8 and 470.59 MHz, respectively. IR spectra were recorded on a UNICAM IR-1100 spectrometer. Elemental analyses for C and H were performed using a Heraeus CHN-O-Rapid analyser.

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Preparation 1-ethyl 2,3-dimethyl-4-(trifluoromethyl)-3-cyclobutene-1,2,3-tricarboxy-late **6a**. *General procedure:* To a magnetically stirred solution of ethyl 4,4,4-trifluoroacetoacetate (0.3682 g, 2 mmol) and triphenylphosphine (0.52 g, 2 mmol) in CH_2Cl_2 (10 ml) was added, dropwise, a mixture of dimethylacetylenedicarboxylate (0.28 g, 2 mmol) in CH_2Cl_2 (4 ml) at –10˚C over 10 min. The mixture was allowed to stand at 5 ˚C for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel (Merck silica gel, 230–400 mesh) column chromatography using hexane: ethyl acetate (1:4) as eluent. The solvent was removed under reduced pressure and compound **6a** was obtained. The other compounds, *i.e.* **6b** and **6c** also were synthesised with the same procedure except that the corresponding acetylenic esters were used. Compound **6a** (0.434 g, yield 70%) was obtained as yellow viscous oil. IR (KBr) (ν_{max}, cm^{-1}): 1689, 1709 and 1748 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.19 (3H, t, $^3J_{HH}$ 7.11 Hz, CH_3), 3.67 and 3.73 (6H, 2s, 2OMe), 3.75 (1H, s, CH), 3.81 (1H, q, $^4J_{FH}$ 2.1 Hz, CH), 4.14 (2H, q, $^3J_{HH}$ 7.11 Hz, OCH_2); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 13.69 (CH_3), 45.48 (CH), 45.58 (q, $^3J_{FC}$ 2 Hz, CH), 52.41 and 52.55 (2OMe), 61.77 (OCH_2), 119.89 (q, $^1J_{FC}$ 271.91 Hz, CF_3), 138.94 (q, $^3J_{FC}$ 5.28 Hz, ^{13}C=C–CF_3), 139.91 (q, $^2J_{FC}$ 40.50 Hz, ^{13}C–CF_3),159.0, 167.57 and 168.64 (3C=O) ; ^{19}F NMR (470.59 MHz, $CDCl_3$): δ_F –65.05; Anal. Calcd for $C_{12}H_{13}F_3O_6$: C, 46.46; H, 4.22, Found: C, 46.1; H, 4.19.

1,2,3-triethyl-4-(trifluoromethyl)-3-cyclobutene-1,2,3-tricarboxylate **6b**: Yellow oil (0.425 g, yield 63%) : IR (KBr) (ν_{max}, cm^{-1}): 1680, 1704 and 1748 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.20–1.25 (9H, m, $3CH_3$), 3.76 and 3.81 (2H, 2s, 2CH), 4.15–4.24 (6H, m, $3OCH_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 13.71, 13.78 and 13.89 ($3CH_3$), 45.48 (q, $^3J_{CF}$ 2.13 Hz, CH), 45.79 (CH), 61.71, 61.73 and 61.92 ($3OCH_2$), 117.84(q, $^1J_{FC}$ 271.89 Hz, CF_3), 139.54 (q, $^3J_{FC}$ 5.27 Hz, ^{13}C=C–CF_3), 139.61 (q, $^2J_{FC}$ 40.50 Hz, ^{13}C–CF_3), 158.62, 167.68 and 168.24 (3 C=O); ^{19}F NMR (470.59 MHz, $CDCl_3$): δ_F –65.15; Anal. Calcd for $C_{14}H_{17}F_3O_6$: C, 49.71; H, 5.07, Found: C, 49.31; H, 5.03.

1-ethyl 2,3-di-tert-butyl-4-(trifluoromethyl)-3-cyclobutene-1,2,3-tricarboxylate **6c**: Yellow oil (0.597 g, yield 75%) ; IR (KBr) (ν_{max}, cm^{-1}): 1684, 1709 and 1743 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.24 (3 H, t, $^3J_{HH}$ 7.11 Hz, CH_3), 1.43 and 1.45 (18H, 2s, $2CMe_3$), 3.69 and 3.70 (2H, 2s, 2CH), 4.19 (2H, q, $^3J_{HH}$ 7.11 Hz, $2OCH_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 13.88 (CH_3), 27.77 and 27.83 ($2CMe_3$), 45.17 (q, $^3J_{FC}$ 2.06 Hz, CH), 47.03 (CH), 61.79 (OCH_2), 82.32 and 83.11 ($2^{13}CMe_3$), 118.03 (q, $^1J_{FC}$ 271.92 Hz, CF_3), 138.46 (q, $^2J_{FC}$ 40.12 Hz, ^{13}C–CF_3), 141.38 (q, $^3J_{FC}$ 5.16 Hz ^{13}C=C–CF_3), 157.96, 167.47 and 168.13 (3C=O); ^{19}F NMR (470.59 MHz, $CDCl_3$); δ_F –64.56; Anal. Calcd for $C_{18}H_{25}F_3O_6$: C, 54.82; H, 6.39, Found: C, 54.50; H, 6.35.

Preparation of 4-ethyl 1,2-dimethyl (1Z,3Z)–3-(trifluoromethyl)-1,3-butadiene-1,2,4-tricarboxylate **7a**: Compound **6a** was refluxed in toluene for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel (Merck silica gel, 230–400 mesh) column chromatography using hexane:ethyl acetate (9:1) as eluent. The solvent was removed under reduced pressure and **7a** was obtained as a yellow viscous oil (yield 67%); IR (KBr) (ν_{max},cm^{-1}): 1717, 1721, 1734 (C=O); ^{1}H NMR(500 MHz, $CDCl_3$); δ_H 1.28 (3H, t, $^3J_{HH}$ 7.12 Hz, CH_3), 3.76 and 3.85 (2OMe), 4.25 (2H, q, $^3J_{HH}$ 7.12 Hz, OCH_2), 6.25 and 6.42 (2H, 2s, 2CH); ^{13}C NMR (125.8 MHz; $CDCl_3$): δ_C 13.88 (CH_3), 52.52 and 53.26 (2OMe), 62.24 (OCH_2), 121.18 (q, $^1J_{FC}$ 276.69 Hz, CF_3), 125.31 (^{13}C=C–C-CF_3), 131.04 (q, $^3J_{FC}$ 3.02 Hz, ^{13}C=C–CF_3), 131.37 (q, $^2J_{FC}$ 33.33, ^{13}C–CF_3), 139.69 (^{13}C–C–CF_3), 163.44, 164.4 and 165.37 (3C=O, ester); ^{19}F NMR (470.59 MHz, $CDCl_3$): δ_F –60.91; Anal. Calcd for $C_{12}H_{13}F_3O_6$: C, 46.46; H, 4.22, Found: C, 46.21; H, 4.20.

4-ethyl 1,2-diethyl (1Z, 3Z)-3-(trifluoromethyl)-1,3-butadiene-1,2,4-tricarboxylate **7b**: Yellow viscous oil, yield 58%; IR (KBr)(ν_{max},cm^{-1}): 1715, 1723, 1730 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$); 1.21–1.32 (9H, m, $3CH_3$), 4.20, 4.25 and 4.30 (2H, 2s, 2CH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 13.81, 13.89 and 14.04 ($3CH_3$), 61.65, 62.18 and 62.55 (3 OCH_2), 121.23 (q, $^1J_{FC}$ 276.57 Hz, CF_3), 125.84 (^{13}C=C–C–CF_3), 130.75 (q, $^3J_{FC}$ 3.02 Hz, ^{13}C=C–CF_3), 131.88 (q, $^2J_{FC}$ 33.08 Hz, ^{13}C–CF_3), 139.47 (^{13}C–C–CF_3), 163.51, 163.96 and 164.84 (3C=O, ester); ^{19}F NMR (470.59 MHz, $CDCl_3$): δ_F –60.60; Anal. Calcd for $C_{14}H_{17}F_3O_6$: C, 49.71; H, 5.07, Found: C, 49.20; H, 5.01.

4-ethyl 1,2-di-tert-butyl (1Z, 3Z)-3-(trifluoromethyl)-1,3-butadiene-1,2,4-tri carboxylate **7c**: Yellow oil (yield 53%); IR (KBr) (ν_{max},cm^{-1}): 1718, 1724, 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H1.28 (3H, $^3J_{HH}$ 7.14 Hz, CH_3), 1.46 and 1.49 (18H, 2s, $2CMe_3$), 4.23 (2H, q, $^3J_{HH}$ 7.14 Hz, OCH_2), 6.11 and 6.37 (2H, 2s, 2CH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 13.89 (CH_3), 27.78 and 28 ($2CMe_3$), 61.97 (OCH_2), 82.34 and 83.68 ($2OCMe_3$), 121.35 (q, $^1J_{FC}$ 276.07, CF_3), 127.69 (^{13}C=C–C–CF_3), 129.84 (q, $^3J_{FC}$ 3.02 Hz, ^{13}C=C–CF_3), 133.60 (q, $^2J_{FC}$ 33.45 Hz, ^{13}C–CF_3), 138.95 (^{13}C–C–CF_3), 163.21, 163.52 and 163.58 (3C=O, ester); ^{19}F NMR (470.57 MHz, $CDCl_3$): δ_F –60.31; Anal. Calcd for $C_{18}H_{25}F_3O_6$: C, 54.82; H, 6.39, Found: C, 54.25; H, 6.32.

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