An efficient one-pot synthesis of trifluoromethyl-substituted cyclobutene derivatives

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Reaction between 1,1,1-trifluorobutane-2,4-dione derivatives and electron-deficient ethyl phenylpropyolate in the presence of triphenylphosphine leads to 4-acyl-2-phenyl-3-trifluoromethylcyclobut-2-ene-1-carboxylate derivatives in good yields.

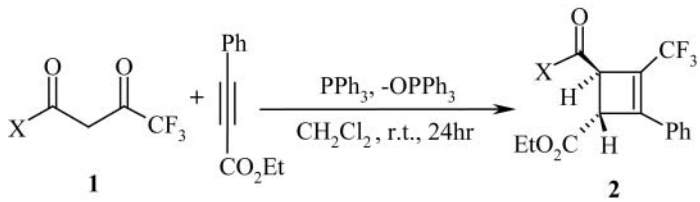
Keywords: cyclobutene derivatives, intramolecular Wittig reaction, CH-acid, triphenylphosphine, 1,1,1-trifluorobutane-2,4-dione

The intramolecular Wittig reaction has become a favourite method of cycloalkene synthesis.[1] 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.[2] Cyclobutenes are important intermediates in organic synthesis. [3] Fluorine-containing compounds have attracted much interest because of their unique chemical, physical, and biological activities.[4-9] The three-component reaction between triphenylphosphine, acetylenic esters and an organic acidic compound has been reported to produce phosphorus yields. Recently, we reported the reaction of acetylene dicarboxylic diester with 1,1,1-trifluorobutane-2,4-dione in the presence of triphenylphosphine for the synthesis of trifluoromethylated cyclobutene derivatives.[10] In continuation of our previous work on the reaction between trivalent phosphorus nucleophiles in the presence of acidic organic compounds,[10–12] we report here the results of our studies on the reaction between ethyl phenylpropiolate and triphenylphosphine in the presence of 1,1,1-trifluorobutane-2,4-dione derivatives **1**.

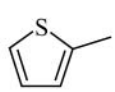
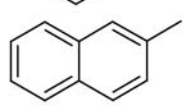
When ethyl phenylpropyolate was treated with triphenylphosphine in dichloromethane in the presence of 1,1,1-trifluorobutane-2,4-dione **1a**, ethyl 4-acetyl-2-phenyl-3-trifluoromethyl-cyclobut-2-ene-1-carboxylate **2a** was obtained in 86% yield (Scheme 1).

The structure of these products was confirmed by their spectral and analytical data. The ^{1}H NMR spectrum of compound **2a** showed a triplet (δ = 1.19 ppm, J = 7 Hz) and a quartet (δ = 4.16 ppm, J = 7 Hz) for ethyl protons. A single signal at 2.27 ppm related to methyl protons. Two methine protons showed two doublets at 3.98 and 4.04 ppm ($^3J_{HH}$ = 1.5 Hz) in agreement with a *trans* arrangement of these protons.[13] The aromatic protons resonated between 7.37 and 7.50 ppm. ^{13}C NMR spectrum of compound **2a** exhibited 14 signals in agreement with the proposed structure. The above structural assignments made on the basis of NMR spectroscopy were supported by IR spectra. The IR spectrum of compound **2a** showed absorption bonds at 1702 and 1676 cm^{-1} for the carbonyl groups.

On the basis of the well established chemistry of trivalent phosphorus nucleophiles,[14–19] it is reasonable to assume that compound **2** results from the initial addition of triphenylphosphine to the ethyl phenylpropyolate and subsequent protonation of the 1:1 adduct by 1,1,1-trifluorobutane-2,4-dione derivatives (Scheme 2). Then the positively charged ion **3** is attacked by the conjugate base of the CH-acid to form



1 **2**

1,2	X	%Yield
a	CH_3	86
b		92
c		89
d		88

Scheme 1 Reaction between 1,1,1-trifluorobutane-2,4-dione derivatives and electron-deficient ethyl phenylpropyolate in the presence of triphenylphosphine

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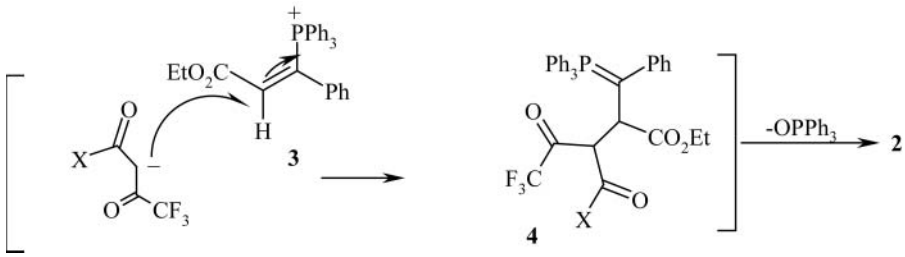

Scheme 2 Suggested mechanism for formation of compounds **2a–d**.

phosphorane **4**, which undergoes an intramolecular Wittig reaction to produce triphenylphosphine oxide and product **2**.

Conclusion

In summary, the procedure described here provides an acceptable one-pot method for the preparation of 4-acyl-2-phenyl-3-trifluoromethylcyclobut-2-ene-1-carboxylate derivatives. The present procedure carries the advantage that, not only the reaction is performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

Experimental

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed at the analytical laboratory of Science and Research Unit of Islamic Azad University. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a shimadzu IR-470 spectrometer.^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Typical procedure for the preparation of compounds **4a–d**

To a magnetically stirred solution of 1,1,1-trifluorobutane-2,4-dione derivative **1** (2 mmol) and ethyl phenylpropyolate (2 mmol) in 10 mL dichloromethane was added a mixture of triphenylphosphine (2 mmol) in 2 mL dichloromethane at room temperature. The reaction mixture was then allowed to stir for 24 h. The solvent was evaporated at reduced pressure and the residue was purified by silica gel column chromatography using hexane–ethyl acetate (3:1) as eluent. The solvent was removed under reduced pressure to afford the product.

Spectral data

Ethyl 4-acetyl-2-phenyl-3-trifluoromethylcyclobut-2-ene-1-carboxylate **(2a):** White powder, Yield: 86%; m.p. 137–139°C, IR (KBr) (ν_{max}, cm^{-1}): 1702, 1676 (C=O), 1595 (C=C). Anal. Calcd for $C_{16}H_{15}F_3O_3$: C, 61.54; H, 4.84. Found: C, 62.12; H, 4.98%. MS (*m/z*, %): 312 (M$^+$, 18), 241 (34), 105 (19), 77 (14), 43 (85) . ^{1}H NMR (500 MHz, δ, $CDCl_3$): 1.19 (3 H, t, $^3J_{HH}$ = 7 Hz, CH_3), 2.27 (3 H, s, CH_3), 3.98 (1 H, d, $^3J_{HH}$ = 1.5 Hz, CH), 4.04 (1 H, d, $^3J_{HH}$ = 1.5 Hz, CH), 4.16 (2 H, q, $^3J_{HH}$ = 7 Hz, OCH_2), 7.37–7.50 (5 H, m, aromatic). ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 13.8 (*C*H$_3$), 28.3 (*C*H$_3$), 45.6 and 51.9 (2 *C*H), 61.5 (O*C*H$_2$), 117.2 (CF$_3$, q, $^1J_{CF}$ = 270 Hz), 126.1 (C- CF$_3$, q, $^2J_{CF}$ = 38 Hz), 148.2 (C=C– CF$_3$, q, $^3J_{CF}$ = 6 Hz), 120.8, 127.2, 128.4, 130.6 (phenyl moiety), 169.6 (C=O, ester), 204.0 (C=O).

Ethyl 2-phenyl-4-(thiophene-2-carbonyl)-3-trifluoromethyl-cyclobut-2-ene-1-carboxylate 4-acyl-2-phenyl-3-trifluoromethylcyclobut-2-ene-1-carboxylate **(2b)**: White powder, Yield: 92%; m.p. 130–132°C, IR (KBr) (ν_{max}, cm^{-1}): 1726, 1654 (C=O), 1575 (C=C). Anal. Calcd for $C_{19}H_{15}F_3O_3S$: C, 59.99; H, 3.97. Found: C, 60.34; H, 3.80%. MS (*m/z*, %): 380 (M$^+$, 16), 307 (19), 111 (92), 83 (13), 39 (50) . ^{1}H NMR (500 MHz, δ, $CDCl_3$): 1.22 (3 H, t, $^3J_{HH}$ = 7 Hz, CH_3), 4.10 (1 H, d, $^3J_{HH}$ = 1.5 Hz, CH), 4.22 (2 H, q , $^3J_{HH}$ = 7 Hz, OCH_2), 4.80 (1 H, d, $^3J_{HH}$ = 1.5 Hz, CH), 7.17–7.85 (8 H, m, aromatic).^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 13.9 (*C*H$_3$), 46.9 and 47.8 (2*C*H), 61.6 (O*C*H$_2$), 119.1 (CF$_3$, q, $^1J_{CF}$ = 270 Hz), 126.3 (C- CF$_3$, q, $^2J_{CF}$ = 38 Hz), 148.1 (C=C–CF$_3$, q, $^3J_{CF}$ = 6 Hz), 128.4, 132.9, 135.1, 142.5 (thionyl moiety), 127.8, 128.5, 129.7, and 130.5 (phenyl moiety), 169.5 (C=O, ester), 188.2 (C=O).

Ethyl 4-benzoyl-2-phenyl-3-trifluoromethyl-cyclobut cyclobut-2-enecarboxylate **(2c)**: White powder, Yield: 89%; m.p. 142–144°C, IR (KBr) (ν_{max}, cm^{-1}): 1737, 1698 (C=O), 1571 (C=C). Anal. Calcd for $C_{21}H_{17}F_3O_3$: C, 67.38; H, 4.58. Found: C, 67.66; H, 4.73%. MS (*m/z*, %): 374 (M$^+$, 6), 329 (14), 301 (12), 105 (90), 77 (88), 51 (27) . ^{1}H NMR (500 MHz, δ, $CDCl_3$): 1.22 (3 H, t, $^3J_{HH}$ = 7 Hz, CH_3), 4.02 (1 H, d, $^3J_{HH}$ = 1.5 Hz, CH), 4.25 (2 H, q , $^3J_{HH}$ = 7 Hz, OCH_2), 4.91 (1 H, d, $^3J_{HH}$ = 1.5 Hz, CH), 7.32-8.20 (10 H, m, aromatic).^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 14.1 (*C*H$_3$), 47.1 and 47.4 (2*C*H), 61.8 (O*C*H$_2$), 119.4 (CF$_3$, q, $^1J_{CF}$ = 270 Hz), 126.9 (C- CF$_3$, q , $^2J_{CF}$ = 38 Hz), 147.7 (C=C–CF$_3$, q, $^3J_{CF}$ = 6 Hz), 127.9, 128.5, 128.9, 129.9, 130.6, 132.9, 133.9, 135.3 (phenyl moiety), 169.8 (C=O ,ester), 195.7 (C=O).

Ethyl 4-(naphthalene-2-carbonyl)-2-phenyl-3-trifluoromethyl cyclobut-2-ene-1-carboxylate **(2d)**: White powder, Yield: 88%; m.p. 151–153°C, IR (KBr) (ν_{max}, cm^{-1}): 1722, 1668 (C=O), 1586 (C=C). Anal. Calcd for $C_{25}H_{19}F_3O_3$: C, 70.75; H, 4.51. Found: C, 70.98; H, 4.82%. MS (*m/z*, %): 424 (M$^+$, 15), 351 (20), 155 (90), 127 (85), 77 (15) . ^{1}H NMR (500 MHz, δ, $CDCl_3$): 1.28 (3 H, t, $^3J_{HH}$ = 7 Hz, CH_3), 4.11 (1 H, d, $^3J_{HH}$ = 1.5 Hz, CH), 4.29 (2 H, q , $^3J_{HH}$ = 7 Hz, OCH_2), 5.13 (1 H, dd, $^3J_{HH}$ = 1.5 Hz, $^5J_{HF}$ = 1.4 Hz, CH), 7.41–8.50 (12 H, m, aromatic). ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 14.2 (*C*H$_3$), 47.2 and 47.4 (2*C*H), 61.8 (O*C*H$_2$), 120.9 (CF$_3$, q, $^1J_{CF}$ = 270 Hz), 127.0 (C–CF$_3$, q, $^2J_{CF}$ = 38 Hz), 147.7 (C=C–CF$_3$, q, $^3J_{CF}$ = 6 Hz), 116.7, 118.8, 127.9, 128.8, 128.9, 129.7, 130.6, 132.5, 132.7 and 135.9 (naphthol moiety), 121.0, 127.0, 128.6, 130.5 (phenyl moiety), 169.9 (C=O, ester), 195.7 (C=O).

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References

1 K.B. Becker, *Tetrahedron*, 1980, **36**, 1717.
2 K.P.C. Vollhardt, *Synthesis*, 1975, 765.
3 H.W. Moore and O.H.W. Decker, *Chem. Rev*., 1986, **86**, 84.
4 T. Hiyama, *Organofluorine compounds*, Springer: Berlin, 2000.
5 M. Hudlicky, *Chemistry of organic fluorine compounds*, 2nd edn, Ellis Harwood, Chichester, 1976.
6 J.T. Welch and S. Eswarakrishnan eds, *Fluorine in bioorganic chemistry*, Wiley, New York, NY, 1991.
7 J. Prabhakaran, M. D.Underwood, R.V. Parsey, V. Arango, V.J. Majo, N.R. Simpson, R.V. Heertum, J.J. Mann and J.S.D. Kumar, *Med. Chem*., 2007, **15**, 1802.
8 R. Filler and Y. Kobayashi, *Biomedicinal aspects of fluorine chemistry*, Kodansha & Elsevier Biomedical, Tokyo, 1982.
9 R. Filler, Y. Kobayashi and L.M .Yagupolskii, *Organofluorine compounds in medical chemistry and biomedical application*, Elsevier, Amsterdam, 1993.
10 M.H. Mosslemin, I.Yavari, M. Anary-abbasinejad and M.R. Nateghi, *Synthesis*, 2004, **7**, 1029.
11 M.H. Mosslemin, M.Anary-Abbassinejad, A. Hassanabadi, M. Mohebat and M.R. Nateghi, *Synth. Commun*., 2009, **19**, 3482.
12 M. Anary-Abbasinejad, M.H. Mosslemin, A. Hassanabadi and M. Tabatabaee, *Synth. Commun*., 2008, **21** , 3700.
13 H. Gunther, *NMR spectroscopy*, 2nd edn, Wiley, New York, 1995, Chap. 9.
14 D.E.C. Corbridge, *Phosphorus an outline of the chemistry, biochemistry, and uses,* Elsevier, Amsterdam, 1995, 5th edn.
15 R. Engel, *Synthesis of carbon-phosphorus bonds*, CRC Press, Boca Raton, 1988.
16 J.I.G. Cadogan, *Organophosphorus in organic synthesis*, Academic Press, New York, 1979.
17 O.I. Kolodiazhnyi, Russ. *Chem. Rev*., 1997, **66**, 225.
18 H.J. Bestmann and R. Zimmermann, *Top. Curr. Chem*., 1983, **109**, 85.
19 B.E. Maryano and A.B. Reits, *Chem. Rev.*, 1989, **89**, 863.