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Three-component reaction between dichlorocarbene, acetylenic esters and aromatic aldehydes. Synthesis of functionalised furans.

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The zwitterionic intermediate created from the reaction between dichlorocarbene and acetylenic esters is trapped by aromatic aldehydes to afford polyfunctionalised furans in fairly good yields.

Keywords: aromatic aldehydes, acetylenic esters, dichlorocarbene, functionalised furans

Furan moieties are common substructure in numerous natural products, such as the kallolides[1] and combranolides.[2] These heterocycles are also found in numerous commercial products, including pharmaceuticals, fragrances and dyes.[3] Accordingly, many strategies have been developed for the preparation of furans.[4] The addition of dimethoxycarbene to dimethyl acetylenedicarboxylate was reported to produce a diionic intermediate which could be trapped with electrophiles such as aromatic aldehydes to yield dihydrofurans.[5] Here we report an efficient route to polysubstituted furans using dichlororocarbene, generated in phase transfer conditions ($CHCl_3$, 50% NaOH, benzyltrimethylammonium chloride), acetylenic esters and aromatic aldehydes. Thus the reaction between dichlorocarbene, dimethyl acetylenedicarboxylate, and *p*-chlorobenzaldehyde at ambient temperature in phase transfer conditions leads to dimethyl 2-chloro-5-(4-chlorophenyl)furan-3,4-dicarboxylate **3a** in 75% yield (Scheme 1).

The structures of compounds **3a–e** were deduced from their elemental analyses and their IR, ^1H NMR and ^{13}C NMR spectra. For example the ^1H NMR spectrum of **3a** exhibited two singlets (δ 3.62, 3.91) identified as methyl protons along with two multiplets (δ 7.34, 7.62) for aromatic protons. The ^1H decoupled ^{13}C NMR spectrum of **3a** showed 12 distinct resonances in agreement with the proposed structure. The absorption bonds for ester groups appear at 1752 and 1724 cm^{-1} in IR spectrum of **3a**.

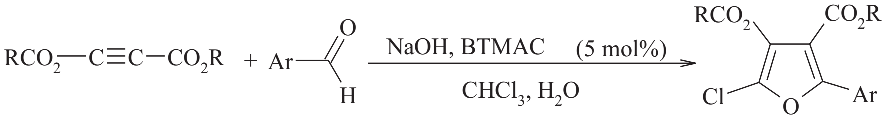
The proposed mechanism for production of compound **3a** is shown in Scheme 2. The addition of dichlorocarbene to dimethyl acetylenedicarboxylate leads to diionic intermediate **4** which is trapped by aldehyde to produce dihydrofuran **5**. Dihydrofuran **5** loses hydrogen chloride in the reaction conditions to yield the product **3a**.

In summary, the reaction of acetylenic esters and dichlorocarbene in the presence of aromatic aldehydes provide a simple and efficient route to the synthesis of functionalised furans. The mild experimental conditions, availability of the non-expensive reagents, rapid conversion and high yields of the products are the attractive features of the present protocol.

Experimental

All melting points are uncorrected. Elemental analyses were performed using a Heraeus CHN–O–Rapid analyser. 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. ^1H, and ^{13}C NMR spectra were recorded on BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^1H, and ^{13}C NMR spectra were obtained on solution in $CDCl_3$ using TMS as internal standard. Column chromatography was performed with Merck silica gel 60, 230–400 mesh. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Dimethyl 2-chloro-5-(4-chlorophenyl)furan-3,4-dicarboxylate **(3a):** To a magnetically stirred solution of 0.28 g dimethyl acetylene-

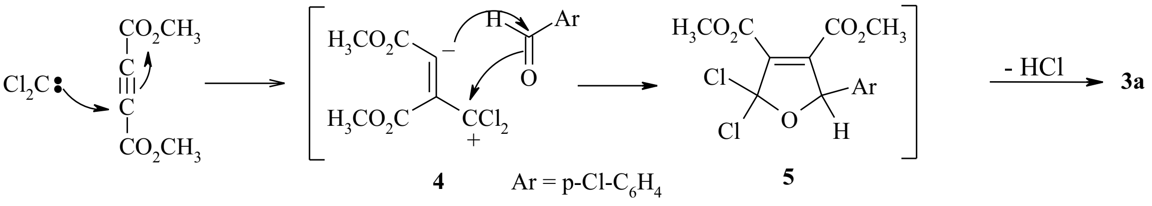


1	R
a	CH_3
b	CH_2CH_3

2	Ar
a	*p*-Cl-C_6H_4
b	*p*-Br-C_6H_4
c	*p*-CH_3-C_6H_4

3	R	Ar	Yield%
a	CH_3	*p*-Cl-C_6H_4	75
b	CH_3	*p*-Br-C_6H_4	68
c	CH_3	*p*-CH_3-C_6H_4	75
d	CH_2CH_3	*p*-Cl-C_6H_4	83
e	CH_2CH_3	*p*-CH_3-C_6H_4	81

Scheme 1



Scheme 2

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dicarboxylate (2 mmol), 0.28g of 4-chlorobenzoldehyde (2 mmol) and 0.02 g benzyltrimethylammonium chloride (0.1 mmol) in 20 ml $CHCl_3$ was added 5 ml of 50% solution of NaOH in water over 2 min. The reaction mixture was stirred for more two hours. 50 ml saturated solution of ammonium chloride was added and the mixture was extracted with chloroform (2 × 20 ml). The organic phase was washed with water (2 × 30), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed over silica gel (60, 230–400 mesh), eluting by hexane-ethyl acetate (10: 1). The solvent was evaporated under reduced pressure and the product was obtained as colourless oil, 0.49 g, yield 75%, IR (neat) (ν_{max}/cm^{-1}): 1752 and 1724 (2 C=O ester). Anal. Calcd. for $C_{14}H_{10}Cl_2O_5$ (329.13): C, 51.09; H, 3.06; Found C, 51.2; H, 3.0%. ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 3.62 (3 H, s, OCH_3), 3.91 (3 H, s, OCH_3), 7.37 (2 H, d $^2J_{HH}$ = 9 H_Z, 2 CH), 7.59 (2 H, d $^2J_{HH}$ = 9 H_Z, 2 CH). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): 51.9 and 53.2 (2 OCH_3), 99.9, 117.8, 144.1, 156.2 (4 C, Furan moiety), 128.1, 129.0, 129.8, 136.3 (C_6H_4 carbons), 162.3 and 164.9 (2 CO, ester). MS, *m/z* (%): 329 (M$^+$, 10).

Dimethyl 2-chloro-5-(4-bromophenyl)furan-3,4-dicarboxylate **(3b):** Colourless oil, 0.51 g, yield 68%, IR (neat) (ν_{max}/cm^{-1}): 1741 and 1722 (2 C=O ester). Anal. Calcd. for $C_{14}H_{10}BrClO_5$ (373.58): C, 45.01; H, 2.70; Found C, 44.8; H, 2.8%. ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 3.62 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 7.52–7.60 (4 H, m, C_6H_4). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): 51.9 and 53.2 (2 OCH_3), 99.9, 117.8, 144.2, 156.2 (4 C, Furan moiety), 128.5, 130.0, 130.8, 132.1 (C_6H_4 carbons), 162.3 and 164.9 (2 CO, ester). MS, *m/z* (%): 374 (M$^+$, 10).

Dimethyl 2-chloro-5-(4-methylphenyl)furan-3,4-dicarboxylate **(3c):** Colourless oil, 0.46 g, yield 75%, IR (neat) (ν_{max}/cm^{-1}): 1751 and 1724 (2 C=O ester). Anal. Calcd. for $C_{15}H_{13}ClO_5$ (308.71): C, 58.36; H, 4.24; Found C, 58.2; H, 4.2%. ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 2.39 (3 H, s, CH_3), 3.62 (3 H, s, OCH_3), 3.96 (3 H, s, OCH_3), 7.23 (2 H, d $^2J_{HH}$ = 9 H_Z, 2 CH), 7.52 (2 H, d $^2J_{HH}$ = 9 H_Z, 2 CH). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): 20.42 (CH_3), 50.8 and 52.1 (2 OCH_3), 98.5, 117.7, 144.1, 157.6 (4 C, Furan moiety), 127.4, 128.1, 128.3, 139.6 (C_6H_4 carbons), 161.9 and 164.4 (2 CO, ester). MS, *m/z* (%): 308 (M$^+$, 14).

Diethyl 2-chloro-5-(4-chlorophenyl)furan-3,4-dicarboxylate **(3d):** Colourless oil, 0.59 g, yield 83%, IR (neat) (ν_{max}/cm^{-1}): 1744 and 1715 (2 C=O ester). Anal. Calcd. for $C_{16}H_{14}Cl_2O_5$ (357.18): C, 53.80; H, 3.95; Found C, 53.8; H, 3.7%. ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 1.24 (3 H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 1.38 (3 H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 4.09 (2 H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 4.41 (2 H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 7.42 (2 H, d $^2J_{HH}$ = 9 H_Z, 2 CH), 7.63 (2 H, d $^2J_{HH}$ = 9 H_Z, 2 CH). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): 13.8 and 14.1 (2 CH_3), 60.9 and 62.6 (2 CH_2), 100.1, 117.7, 144.2, 156.3 (4 C, Furan moiety), 128.2, 129.0, 129.9, 136.3 (C_6H_4 carbons), 161.9 and 164.5 (2 CO, ester). MS, *m/z* (%): 357 (M$^+$, 10).

Diethyl 2-chloro-5-(4-methylphenyl)furan-3,4-dicarboxylate **(3e):** Colourless oil, 0.55 g, yield 81%, IR (neat) (ν_{max}/cm^{-1}): 1745 and 1732 (2 C=O ester). Anal. Calcd. for $C_{17}H_{17}ClO_5$ (336.77): C, 60.63; H, 5.09; Found C, 60.4; H, 5.2%. ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 1.20 (3 H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 1.40 (3 H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 2.38 (3 H, s, CH_3), 4.11 (2 H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 4.38 (2 H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 7.37 (2 H, d $^2J_{HH}$ = 9 H_Z, 2 CH), 7.60 (2 H, d $^2J_{HH}$ = 9 H_Z, 2 CH). ^{13}C NMR (125.8 MH_Z, $CDCl_3$): δ 13.8 and 14.1 (2 CH_3 of ethyl groups), 21.5 (CH_3), 60.8 and 62.5 (2 CH_2), 99.7, 117.7, 145.3, 156.7 (4 C, Furan moiety), 126.9, 128.5, 129.3, 140.6 (C_6H_4 carbons), 162.1 and 164.7 (2 CO, ester). MS, *m/z* (%): 337 (M$^+$, 22).

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