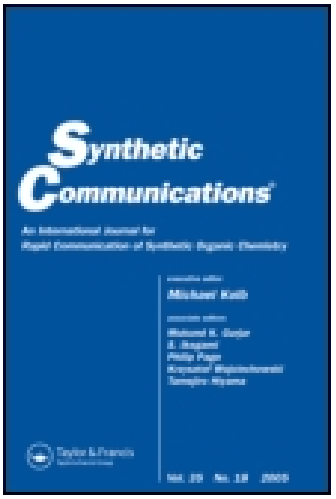

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Efficient One-Pot Synthesis of Alkyl 2-(Bromomethyl)-2-(4-aryl)-4-alkoxy-5-oxo-2,5-dihydrofuran-3-carboxylate

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EFFICIENT ONE-POT SYNTHESIS OF ALKYL 2-(BROMOMETHYL)-2-(4-ARYL)-4-ALKOXY-5-OXO-2,5-DIHYDROFURAN-3-CARBOXYLATE

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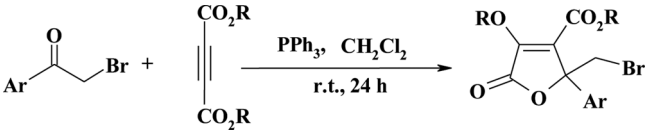
GRAPHICAL ABSTRACT



Abstract *One-pot, three-component reaction of different phenacyl bromides and dialkyl-acetylenedicarboxilates was carried out with triphenylphosphine and functionalized oxodihydrofuran derivatives in excellent yields.*

Keywords Acetylenic esters; oxodihydrofurans; phenacyl bromides; triphenylphosphine

Multicomponent condensation reactions (MCRs), because of atom economy, simplicity, and amenability to automated synthesis, have advantages over other organic synthesis methods. The development of new MCRs is an interestingly research topic in applied sciences.[1–3] Dihydrofurans are the most important heterocycles commonly found in a large variety of naturally occurring substances.[4,5] The development of new and efficient methods for their synthesis remains an area of current interest, and a whole series of new synthetic methods have appeared in the literature.[6–19] Among synthetic methodologies for dihydrofurans, nonionic as well as ionic procedures have been exploited. Radical[5] or carbenoid[10–12] additions to olefins have been utilized as non-ionic procedures. Among ionic reaction conditions, dihydrofuran syntheses via tandem nucleophilic reaction of 1,3-dicarbonyl compounds[13–15] or ylides[16–20] with enones have been reported. Nucleophilic addition of triphenylphosphine to activated acetylene is well known to produce a reactive zwitterionin intermediate,[21–23] which may be trapped by acidic organic compounds

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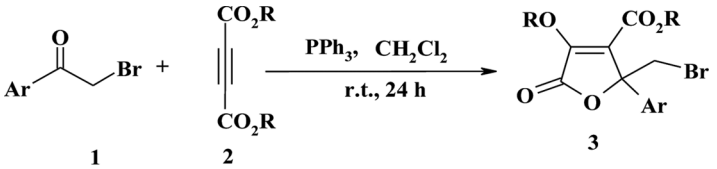


1 2 3

3	Ar	R	%Yield*
a	4-Cl C_6H_5	CH_3	88
b	4-Cl C_6H_5	C_2H_5	86
c	4-Cl C_6H_5	*t*-Bu	92
d	4-Br C_6H_5	CH_3	85
e	4-Br C_6H_5	C_2H_5	80
f	4-Br C_6H_5	*t*-Bu	90

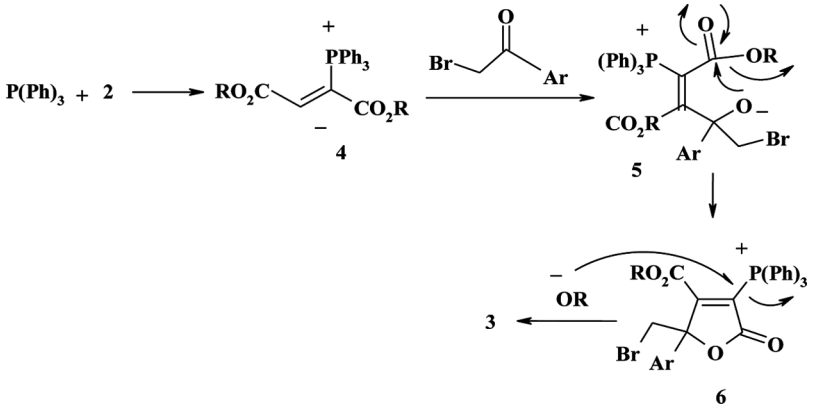
* Isolated yields

Scheme 1. Condensation of acetylenic esters and arylphenacyl bromides in the presence of triphenylphosphine.

such an alcohols. Reaction between dimethyl acetylenedicarboxylate and triphenylphosphine in the presence of alcohols has been reported to produce phosphorus ylide as an intermediate or final product. When α-hydroxy carbonyl compounds were used, the intramolecular Wittig reaction of the ylide intermediate afforded oxygen heterocycles.[24,25] Similar reactions have been developed for the synthesis of a variety of carbocycles and heterocycles, using N-H,[25,26] O-H, S-H[27] and C-H[28] acidic compounds to trap the zwitterionic DMAD-PPh_3 intermediate in condition of our precision studies on the reaction of PPh_3-DMAD zwitterions with organic acidic compounds.[29]

Here we report that the reaction of different phenacyl bromides, dialkyl acetylenedicarboxylates, and triphenylphosphine afforded oxodihydrofuran derivatives in good yields. Treatment of dimethyl acetylenedicarboxylate (DMAD) with triphenylphosphine and 4-chlorophenacyl bromide in dichloromethane at room temperature after 24 h afforded methyl 2-(bromomethyl)2-(4-chlorophenyl)4-methoxy-5-oxo-2,5-dihydrofuran-3-carboxylate (**3a**) in 88% yield (Scheme 1).

The mass spectrum of **3a** displayed a molecular ion peak at $m/z = 374$. The ^{1}H NMR spectrum of **3a** exhibits two sharp lines at $\delta = 3.83$ and 4.32 ppm for the protons of two methoxy groups. The methylene protons resonate at 4.34 ppm as an AB quartet ($\delta_1 = 4.12$, $\delta_2 = 4.56$, $^2J_{HH} = 11$ Hz). The aromatic protons resonated between 7.27 and 7.50 ppm. ^{13}C NMR spectrum of compound **3a** shows 12 distinct signals, which is consistent with the proposed structure. This assignment was supported by the infrared (IR) spectrum of compound **3a**, which exhibited absorption bonds at 1781 and 1711 cm^{-1} due to carbonyl groups. Although the mechanistic details of the reaction are not known, a plausible mechanism may be advanced to rationalize product formation (Scheme 2).[30] The initial addition of triphenylphosphine on DAAD (**2**) led to a diionic intermediate **4**, followed by addition of



Scheme 2. Suggested mechanism for formation of compound **3**.

the anion **4** to the carbonyl group of arylphenacyl bromide (**1**) to form intermediate **5**. This then loosed an alkoxide ion and cyclized to intermediate **6.** The elimination of triphenylphosphine by the alkoxide ion led to oxodihydrofuran derivatives **3**. In summary, the reaction of different arylphenacyl bromides and dialkyl acetylenedicarboxilates was carried out with triphenylphosphine, and functionalized oxodihydrofuran derivatives **3a–f** were obtained in good yields.

The present procedure has the advantages that not only is the reaction performed under neutral conditions but also the starting materials and reagents can be mixed without any activation or modification. The procedure described here provides an acceptable one-pot method for the preparation of alkyl 2-(bromomethyl)-2-(4-aryl)-4-alkoxy-5-oxo-2,5-dihydrofuran-3-carboxylate.

EXPERIMENTAL

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer at the analytical laboratory of the Islamic Azad University, Yazd branch. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Preparation of Compounds 3a–f

A mixture of triphenylphosphine (1 mmol) in 2 mL dichloromethane was added to a magnetically stirred solution of phenacyl bromides **1** (1 mmol) in 20 mL dichloromethane and dialkyl acetylenedicarboxylate **2** (1 mmol) in 10 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.

Methyl 2-(Bromomethyl)-2-(4-chlorophenyl)-4-methoxy-5-oxo-2,5-dihydrofuran-3-carboxylate (3a)

Yield: 88%; yellow oil. IR (KBr) (ν_{max}, cm^{-1}): 1781 and 1711 (C=O). Analyses: Calcd. for $C_{14}H_{12}BrClO_5$, C, 44.77; H, 3.22%. Found: C, 44.82, H, 3.16%. MS (m/z, %): 374 (7). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 and 4.32 (6 H, 2 s, 2 OCH_3), 4.34 (2 H, AB quartet, $^2J_{HH} = 11$ Hz, CH_2), 7.27–7.50 (4 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 36.93 (CH_2), 52.45 and 60.05 (2 O*C*H_3), 84.26 (C-O), 123.46, 134.65 (olefinic carbons), 127.39, 129.04, 135.42, 149.50 (aromatic), 161.75, 164.72 (2 C=O ester).

Ethyl 2-(Bromomethyl)-2-(4-chlorophenyl)-4-ethoxy-5-oxo-2,5-dihydrofuran-3-carboxylate (3b)

Yield: 86%; yellow oil. IR(KBr) (ν_{max}, cm^{-1}): 1779, 1719 (C=O). Analyses: Calcd. for $C_{16}H_{16}BrClO_5$, C, 47.61; H, 4.00%. Found: C, 47.54, H, 4.08%. MS (m/z, %): 402 (11). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 and 1.37 (6 H, 2 t, $^3J_{HH} = 7$ Hz, 2 CH_3), 4.25 (2 H, AB quartet, $^2J_{HH} = 11$ Hz, CH_2), 4.26 and 4.64 (4 H, 2 q, $^3J_{HH} = 7$ Hz, 2 OCH_2), 7.29–7.43 (4 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.41 and 15.94 (2CH_3), 37.53 (CH_2), 61.99 and 69.11 (2O*C*H_2), 84.75 (C-O), 124.92, 135.72 (olefinic carbons), 127.86, 129.42, 135.25, 149.60 (aromatic), 161.76, 165.42 (2 C=O ester).

t-Butyl 2-(Bromomethyl)-2-(4-chlorophenyl)-4-t-butoxy-5-oxo-2,5-dihydrofuran-3-carboxylate (3c)

Yield: 92%; yellow oil. IR (KBr) (ν_{max}, cm^{-1}): 1775, 1720 (C=O). Analyses: Calcd. for $C_{20}H_{24}BrClO_5$, C, 52.25; H, 5.26%. Found: C, 52.31, H, 5.40%. MS (m/z, %): 458 (7). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 and 152 (18 H, 2 s, 2 *t*-Bu), 4.22 (2 H, AB quartet, $^2J_{HH} = 11$ Hz, CH_2), 7.11–7.54 (4 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 30.12 and 30.62 (6 CH_3 of 2 *t*-Bu), 38.26 (CH_2), 82.68 and 83.07 (2 C of 2 *t*-Bu), 84.93 (C-O), 124.80, 135.61 (olefinic carbons), 128.88, 129.75, 135.14, 149.53 (aromatic), 161.82, 165.57 (2 C=O ester).

Methyl 2-(Bromomethyl)-2-(4-bromophenyl)-4-methoxy-5-oxo-2,5-dihydrofuran-3-carboxylate (3d)

Yield: 85%; yellow oil. IR (KBr) (ν_{max}, cm^{-1}): 1778, 1708 (C=O). Analyses: Calcd. for $C_{14}H_{12}Br_2O_5$, C, 40.03; H, 2.88%. Found: C, 40.15, H, 2.95%. MS (m/z, %): 418 (9). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 and 4.30 (6 H, 2 s, 2 OCH_3), 4.37 (2 H, AB quartet, $^2J_{HH} = 11$ Hz, CH_2), 7.25–7.71 (4 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 36.85 (CH_2), 52.45 and 60.12 (2 O*C*H_3), 84.19 (C-O), 123.40, 134.68 (olefinic carbons), 127.22, 129.00, 135.51, 149.42 (aromatic), 161.60, 165.39 (2 C=O ester).

Ethyl 2-(Bromomethyl)-2-(4-bromophenyl)-4-ethoxy-5-oxo-2,5-dihydrofuran-3-carboxylate (3e)

Yield: 80%, yellow oil. IR (KBr) (ν_{max}, cm^{-1}): 1773, 1705 (C=O). Analyses: Calcd. for $C_{16}H_{16}Br_2O_5$, C, 42.89; H, 3.60%. Found: C, 42.75, H, 3.68%. MS (m/z, %): 446 (10). ^1H NMR (500 MHz, $CDCl_3$): δ 1.28 and 1.42 (6 H, 2 t, $^3J_{HH} = 7$ 7 Hz, 2 CH_3), 4.30 (2 H, AB quartet, $^2J_{HH} = 11$ Hz, CH_2), 4.25 and 4.69 (4 H, 2 q, $^3J_{HH} = 7$ Hz, 2 OCH_2), 7.25–7.77 (4 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.38 and 15.96 ($2CH_3$), 37.54 (CH_2), 61.92 and 69.08 ($2OCH_2$), 84.72 (C-O), 124.90, 135.76 (olefinic carbons), 127.88, 130.21, 135.19, 149.67 (aromatic), 161.71, 165.32 (2 C=O ester).

t-Butyl 2-(Bromomethyl)-2-(4-bromophenyl)-4-t-butoxy-5-oxo-2,5-dihydrofuran-3-carboxylate (3f)

Yield: 90%, yellow oil, IR(KBr) (ν_{max}, cm^{-1}): 1779, 1705 (C=O). Analyses: Calcd. for $C_{20}H_{24}Br_2O_5$, C, 47.64; H, 4.80%. Found: C, 47.77, H, 4.71%. MS (m/z, %): 502 (5). ^1H NMR (500 MHz, $CDCl_3$): δ 1.30 and 157 (18 H, 2 s, 2 *t*-Bu), 4.17 (2 H, AB quartet, $^2J_{HH} = 11$ Hz, CH_2), 7.28–7.69 (4 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 30.05 and 30.71 (6 CH_3 of 2 *t*-Bu), 38.12 (CH_2), 82.60 and 83.14 (2 C of 2 *t*-Bu), 84.98 (C-O), 124.76, 135.52 (olefinic carbons), 128.83, 129.70, 135.08, 149.61 (aromatic), 161.84, 165.69 (2C=O ester).

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