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A novel approach to the synthesis of highly functionalized furans

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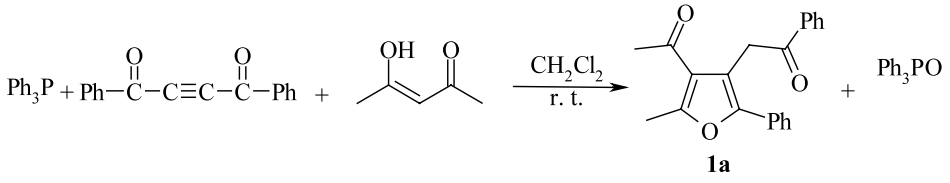
Abstract—The reaction of dibenzoylacetylene and enol systems, such as acetylacetone, 5,5-dimethylcyclohexane-1,3-dione, 1-naphthol, 2-naphthol, 2,7-dihydroxynaphthalene, or 8-hydroxyquinoline in the presence of triphenylphosphine leads to tetrasubstituted furans in 65–83% yields.

Furan moieties are common substructures 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] We wish to report an efficient synthetic route to polysubstituted furans using dibenzoylacetylene and an enol system such as acetylacetone, 5,5-dimethylcyclohexane-1,3-dione, 1-naphthol, 2-naphthol, 2,7-dihydroxynaphthalene, or 8-hydroxyquinoline in the presence of triphenylphosphine. Thus, the reaction between acetylacetone and dibenzoylacetylene in the presence of triphenylphosphine at ambient temperature in dichloromethane, leads to the highly functionalized furan derivative **1a** in 74% yield[5] (Scheme 1).

Table 1 contains the results of our study. The structures of compounds **1a**–**1f** were deduced from their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **1a** exhibited[5] three singlets identified as methyl (δ 2.43 and 2.74) and methylene (δ 4.61) protons along with multiplets (δ 7.2–8.4) for the aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum of **1a** showed 17 distinct resonances in agreement with the proposed structure. The mass spectra of the products displayed molecular ions at appropriate m/z values.

We have not yet established a mechanism for the formation of the furan derivatives **1a**–**f**, but a reasonable possibility is indicated in Scheme 2. On the basis of the well established chemistry of trivalent phosphorus nucleophiles[6–8] it is reasonable to assume that compound **1a** results from the initial addition of triphenylphosphine to dibenzoylacetylene and subsequent protonation of the 1:1 adduct by acetylacetone. Then the positively charged ion is attacked by the conjugate base of acetylacetone to produce ylide **2**. Such an addition product may isomerize under the reaction conditions to produce the betaine **3**, which undergoes a 1,3-hydrogen shift and subsequent ring closure followed by elimination of triphenylphosphine



Scheme 1.

Keywords: tetrasubstituted furans; fused furans; dibenzoylacetylene; triphenylphosphine.
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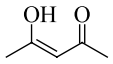
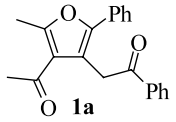
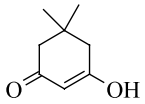
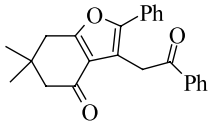
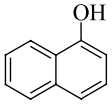
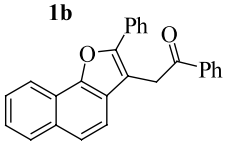
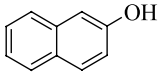
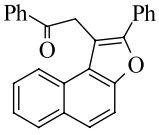
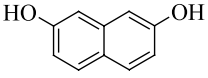
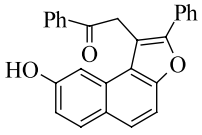
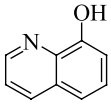
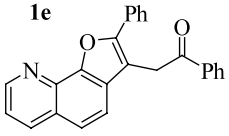
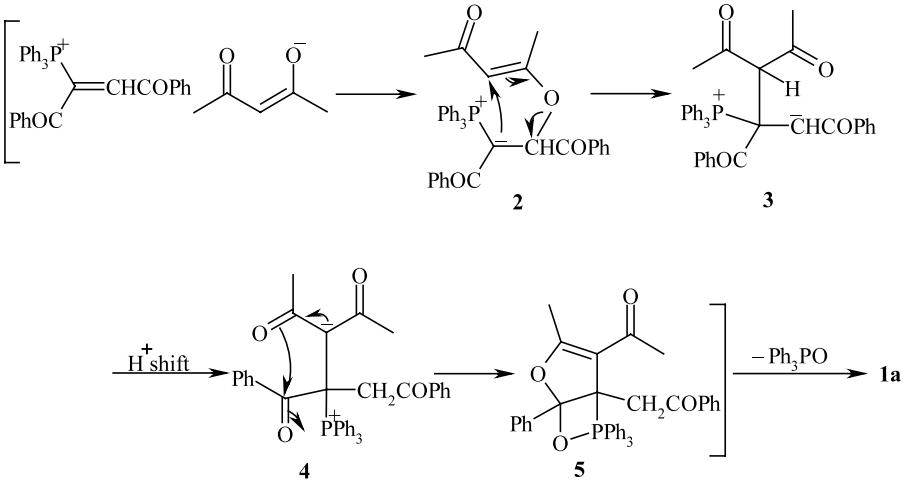
Table 1. Condensation–cyclization reaction of dibenzoylacetylene with 1,3-dicarbonyl compounds, hydroxynaphthalenes, or 8-hydroxyquinoline in the presence of triphenylphosphine

Entry	Starting enol/naphthol	Product	Yield (%)[a]
a		 **1a**	74
b		 **1b**	65
c		 **1c**	83
d		 **1d**	80
e		 **1e**	85
f		 **1f**	76

[a]Isolated yields.



Scheme 2.

oxide to produce 2-(4-acetyl-5-methyl-2-phenylfuran-3-yl)-1-phenylethanone **1a**.

In summary, we have found a simple and efficient method for the preparation of some tetrasubstituted furans and functionalized fused furans. The present method carries the advantage 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.

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5. The procedure for the preparation of 2-(4-acetyl-5-methyl-2-phenylfuran-3-yl)-1-phenylethanone **1a** is described as an example. To a magnetically stirred solution of 0.52 g triphenylphosphine (2 mmol) and 0.20 g acetylacetone (2 mmol) in 20 mL CH_2Cl_2 was added a mixture of 0.47 g dibenzoylacetylene (2 mmol) in 5 mL CH_2Cl_2 at −5°C for 2 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 12 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–400 mesh) column chromatography using 4:1 hexane/ethyl acetate mixture as eluent. The product **1a** was obtained as a white powder, mp 145–147°C, 0.47 g, yield 74%. IR (KBr) (ν_{max}/cm^{-1}): 1677, 1651. Anal. calcd for $C_{21}H_{18}O_3$ (318): C, 79.22; H, 5.70; Found: C, 79.2; H, 5.7%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43 and 2.74 (6H, 2 s, 2 Me), 4.61 (2H, s, CH_2), 7.2–8.4 (10H, m, 2 C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 15.71 and 30.42 (2 CH_3), 35.50 (CH_2), 114.59 and 123.46 (2 C), 126.72, 128.15, 128.19, 128.49, 128.59, 132.9 (10 CH), 129.9 and 137.07 (2 C), 150.30 and 157.30 (2 C–O), 194.15 and 197.33 (2 C=O). MS, m/z: 319 (M^++1). **1b**: White powder, mp 140–143°C, 0.46 g, yield 65%. IR (KBr) (ν_{max}/cm^{-1}): 1672, 1663. Anal. calcd for $C_{24}H_{22}O_3$ (358): C, 80.42; H, 6.19; Found: C, 80.4; H, 6.2%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (6H, s, 2 Me), 2.38, 2.75 and 4.31 (6H, 3 s, 3 CH_2), 7.2–8.0 (10H, m, 2 C_6H_5); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 28.46 (2 Me), 34.73, 36.52 and 37.50 (3 CH_2), 52.81 (CMe$_2$), 118.45 and 122.28 (2 C), 127.45, 127.94, 128.27, 128.59, 129.49 and 133.48 (10 CH), 130.96 and 135.80 (2 C), 145.53 and 165.89 (2 C–O), 193.22 and 194.93 (2 C=O). MS, m/z: 359 (M^++1). **1c**: White powder, mp 155–157°C; 0.60 g, yield 83%. IR (KBr) (ν_{max}/cm^{-1}): 1670. Anal. calcd for $C_{26}H_{18}O_2$ (362): C, 86.16; H, 5.01; Found: C, 86.2; H, 5.1%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.57 (2H, s, CH_2), 7.37–7.63 (10H, m, H_m and H_p of 2 C_6H_5 and H_5–H_8), 7.76 (2H, d $^3J_{HH}$ = 7.4 Hz, H_o of Ph), 7.89 (1H, d $^3J_{HH}$ = 8.1 Hz, H_4), 8.00 (2H, d $^3J_{HH}$ = 7.4 Hz, H_o of COPh), 8.36 (1H, d $^3J_{HH}$ = 8.1 Hz, H_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 35.06 (CH_2), 110.48 (C), 118.26 and 120.11 (2 CH), 121.33 (C), 123.48 and 125.14 (2 CH), 125.61 (C), 126.33, 127.23, 128.40, 128.74, and 128.85 (10 CH), 130.93 and 131.67 (2 C), 133.41 (CH), 136.44 (C), 149.68 and 152.34 (2 C–O), 196.37 (CO); MS, m/z: 363 (M^++1). **1d**: White powder, mp 130–133°C, 0.58 g, yield 80%. IR (KBr) (ν_{max}/cm^{-1}): 1675. Anal. calcd for $C_{26}H_{18}O_2$ (362): C, 86.16; H, 5.01. Found: C, 86.2; H, 5.0%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.86 (2H, s, CH_2), 7.34–7.56 (7H, m, 7 CH), 7.60 (2H, d $^3J_{HH}$ = 7.4 Hz, H_o of Ph), 7.65–7.76 (3H, m, 3 CH), 7.88 and 7.93 (2H, 2 d $^3J_{HH}$ = 7.9 Hz, H_3 and H_4), 8.12 (2H, d, $^3J_{HH}$ = 7.4 Hz, H_o of COPh); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 36.93 (CH_2), 110.85 (C), 112.48 and 122.41 (2 CH), 123.28 (C), 124.07, 125.88, 126.28, 127.68, 128.41, 128.54, 128.80, 128.91 and 129.28 (13 CH), 128.93 (C), 130.62 and 130.95 (2 C), 133.61 (CH), 136.56 (C), 152.24 and 153.21 (2 C–O), 196.70 (C=O). MS, m/z: 363 (M^++1). **1e**: White powder, mp 173–175°C, 0.64 g, yield 85%. IR (KBr) (ν_{max}/cm^{-1}): 3365, 1658. Anal. calcd for $C_{26}H_{18}O_3$ (378): C, 82.52; H, 4.79. Found: C, 82.6; H, 4.8%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.99 (2H, s, CH_2), 7.03 (1H, d $^3J_{HH}$ = 8.7 Hz, CH), 7.23 (1H, s, CH), 7.41 (1H, t $^3J_{HH}$ = 7.1 Hz, H_p of Ph), 7.48 (2H, t $^3J_{HH}$ = 7.5 Hz, H_m of Ph), 7.58 (2H, d $^3J_{HH}$ = 7.4 Hz, H_o of Ph), 7.60 (1H, t $^3J_{HH}$ = 7.1 Hz, H_p of Ph), 7.64 (2H, t $^3J_{HH}$ = 7.3 Hz, H_m of Ph), 7.73–7.88 (2H, m, 2 CH), 7.87 (1H, d, $^3J_{HH}$ = 8.7 Hz, CH), 8.23 (2H, d $^3J_{HH}$ = 7.8 Hz, H_o of Ph), 9.7 (1H, s, OH); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 37.01 (CH_2), 105.71, 109.39, 111.94 and 116.51 (4 CH), 122.33 and 125.00 (2 C), 126.52, 127.35, 128.89 (5 CH), 129.02 (C), 129.47 and 129.51 (4 CH), 130.06 and 130.51 (2 C), 131.15 and 134.28 (2 CH), 136.56, 151.80, 152.39 and 156.50 (4 C), 197.14 (C=O). MS, m/z: 363 (M^++1). **1f**: White powder, mp 180–182°C, 0.55 g, yield 76%. IR (KBr) (ν_{max}/cm^{-1}): 1670. Anal. calcd for $C_{25}H_{17}NO_2$ (363): C, 82.63; H, 4.72; N, 3.85. Found: C, 82.6; H, 4.7; N, 3.8%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.65 (2H, s, CH_2), 7.39–7.62 (9H, m, 9 CH), 7.83 (2H, d $^3J_{HH}$ = 7.8 Hz, H_o of Ph), 8.03 (2H, d $^3J_{HH}$ = 8.0 Hz, H_o of COPh), 8.2 (1H, d $^3J_{HH}$ = 8.2 Hz, CH), 8.99 (1H, d $^3J_{HH}$ = 4.1 Hz, N–CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 35.06 (CH_2), 110.41 (C), 119.38, 120.32 and 123.08 (3 CH), 126.51 (C), 127.78, 128.42, 128.77, 128.80 and 128.87 (9 CH), 129.71 and 130.32 (2 C), 133.55 (CH), 136.32 (C), 136.57 (CH), 136.64 (C), 148.59 (C), 150.07 (N–CH), 154.23 (C), 196.20 (C=O). MS, m/z: 364 (M^++1).
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