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Novel and Efficient Route for the Synthesis of 4-Aryl-Substituted 2(5H)-Furanones

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Abstract: 4-Aryl-substituted 2(5H)-furanones were prepared by reaction of diethylphosphono acetic acid and phenacyl bromides, followed by an intramolecular Horner–Emmons-type cyclization. Both the reactions were carried out in situ to give the desired 4-aryl substituted 2(5H)-furanone derivatives.

Keywords: DBU, diethylphosphono acetic acid, furanone, Horner–Emmons cyclization, phenacyl bromides

α,β-Unsaturated γ-butyrolactones [2(5H)-furanones] possess interesting biological properties such as antiulcer, antibiotic, insecticidal, fungicidal, antimicrobial, and antitumor activities.[1–4]

The synthesis of 4-substituted 2(5H)-furanone is more challenging than the corresponding three or five analogs.[3,4] Considering the importance and challenging synthesis of 2(5H)-furanones, much attention has been paid to the preparation of 4-substituted 2(5H)-furanones. The majority of these methods involve transition-metal-catalyzed coupling leading to the desired 2(5H)-furanones. The most widely used reactions are Stille,[5] Suzuki,[6] and Suzuki–Miyaura[7] couplings.

The major drawback of the Stille cross-coupling reaction is the annoying preparation of organotin compounds and difficult removal of the toxic organotin by-products. Development of Suzuki coupling reaction along with the

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ready availability of boronic acids has attracted wide attention for the synthesis of 4-substituted 2(5H)-furanones. Difficulty in the synthesis of 4-bromo-2(5H)-furanone and stability of β-tetronic acid triflate under normal reaction conditions are the major drawbacks of the Suzuki coupling reaction. Recently, Wu et al.[4] used 4-tosyl-2(5H)-furanone instead of β-tetronic acid triflate in the Suzuki coupling reaction. The ease of synthesis of 4-tosyl-2(5H)-furanone and its stability toward the standard Suzuki reaction conditions made this substrate more versatile for the synthesis of 4-aryl-2(5H)-furanones. Zhen-Yu et al.[8] used 4-tosyl-2(5H)-furanone under Suzuki–Miyaura cross couplings in the presence of nickel (0)/tricyclohexylphosphine [Ni(0)/PCy_3] catalyst to get 4-substituted-2(5H)-furanones. Wu et al.[9] used organozinc compounds instead of organoboronic acid with 4-tosyl-2(5H)-furanone in the presence of Ni(II) catalyst. Synthesis of 4-substituted-2(5H)-furanone in the presence of transition metal has also been reported.[10,11] Mehta et al.[12] synthesized 4-aryl-substituted 2(5H)-furanones via Heck reaction of diazonium salts with 2,5-dihydrofuran. Kagabu et al.[13] synthesized 4-aryl-substitited 2(5H)-furanones by treating β-arylcrotonic esters with selenium dioxide in acetic acid in the presence of a catalytic amount of perchloric acid. There are very few reports of the synthesis of 2(5H)-furanones without using a transition-metal catalyst.

Considering the earlier literature for the synthesis and importance of 2(5H)-furanones, there is a need for an easy, facile, and environmentally friendly process. The basic requirements for the desired schemes are (1) ease of availability of starting materials, (2) avoiding the use of transition-metal catalyst, (3) reaction conditions compatible with diverse functional groups, and (4) mild reaction condition. To satisfy all these conditions, we found that intramolecular Horner–Emmons-type cyclization is an ideal reaction to get suitably substituted furanone derivatives. The Horner–Emmons-type reaction is widely used in the preparation of E-disubstituted α,β-unsaturated olefins.[14,15]

In continuation of our research on the green chemistry, herein we report an easy and facile synthesis of 4-aryl-substituted 2(5H)-furanones. The furanone formation is the combination of the phenacyl ester formation followed by an intramolecular Horner–Emmons-type reaction to get cyclized product. The reaction can be carried out under mild conditions using a base such as triethylamine or 1,8-diazabicyclo [5,4,0]undec-7-ene (DBU), of which DBU is preferred.

The reaction of diethylphosphono acetic acid **(3)** with phenacyl bromides **(2)** under mild basic conditions led to the formation of phosphonate ester **(4)** in almost quantitative yield. The phosphonate ester was converted to 4-aryl-substituted 2(5H)-furanone **(1)** under an intramolecular Horner–Emmons-type cyclization reaction. Because of very high reactivity of phosphonate ester toward intramolecular Horner–Emmons

cyclization, it is very difficult to isolate this intermediate **(4)**, and we observed the formation of desired 4-aryl-substituted 2(5H)-furanone derivatives.

In conclusion, we report herein a versatile method for the efficient and facile synthesis of 4-aryl-substituted 2(5H)-furanones using easily available diethylphosphono acetic acid and phenacyl bromides. The ease of formation of phenacyl ester and its subsequent Horner–Emmons-type cyclization make the process very simple and highly efficient, and at the same time, the entire sequence can be carried out in one pot.

EXPERIMENTAL

All the 2-bromo-1-substituted phenyl ethanone derivatives were synthesized according the literature procedure.[16] Diethylphosphono acetic acid obtained from Aldrich was used directly for the experiments. ^{1}H NMR spectra were recorded using $CDCl_3$ or dimethylsulfoxide (DMSO) as solvent with tetramethylsilane (TMS) as an internal standard on Bruker 300-MHz and 400-MHz instruments.

Preparation of (Diethoxy-phosphoryl)-acetic Acid 2-Benzo[1,3]dioxol-5-yl-2-oxo-ethyl Ester

Diethylphosphono acetic acid (0.520 g, 3.24 mmol) was added to a mixture of 1-benzo[1,3]dioxol-5-yl-ethanone (0.5 g, 2.16 mmol) in dimethyl formamide (10 mL) under nitrogen. The reaction mixture was cooled to 0–5°C. Triethyl amine (1 mL, 6.48 mmol) was added. The mixture was stirred at 0–5°C for 0.5 h. Completion of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was quenched in water (50 mL). The compound was extracted in ethyl acetate (20 mL × 3). The organic layer was dried over sodium sulfate (4 g), and the solvent was removed under reduced pressure to get an oily crude compound, which was purified by flash column chromatography using silica gel (eluent: ethyl acetate) to afford the title compound (0.75 g, 97.26%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, 6H, $J = 6.8$ Hz); 3.13 (d, 2H); 4.20 (q, 4H, $J = 6.8$ Hz); 5.24 (s, 2H); 6.07 (s, 2H); 6.86 (d, 1H, $J = 8$ Hz); 7.39 (d, 1H, $J = 1.6$ Hz); 7.49 (d, 1H, $J = 8.4$ Hz). ESI-MS (359, $M + H)^+$.

General Procedure for the Preparation of 4-Aryl Substituted 2(5H)-Furanones Derivatives

Diethylphosphono acetic acid (1.0 mmol) was added to a mixture of phenacyl bromide derivative (1.0 mmol) in dimethyl formamide (10 mL).

The reaction mixture was cooled to 0–5°C, and DBU (3 mmol) was added. The mixture was stirred at 0–5°C for 0.5 h and allowed to warmed to 25–35°C, then stirred for another 0.5 h. Completion of reaction was monitored by TLC. The mixture was quenched in 10% aq. HCl (30 mL), and the compound was extracted by adding ethyl acetate (20 mL × 3). Combined organic layer was washed with water (50 mL). The organic layer was dried over sodium sulfate (4 g), and the solvent was removed under reduced pressure to get oily crude compound, which was purified by flash column chromatography using silica gel (230–400 mesh; eluent: petroleum ether–ethyl acetate) to afford 4-aryl-substituted 2(5H)-furanone derivatives **1a–1i**. The products were characterized by IR, ^{1}H NMR, and ESI-MS spectroscopy.

Data

Compound **1a**

4-Phenylfuran-2(5H)-one. Yield = 62%, mp 91°C (lit. 87°C).[13] ^{1}H NMR (400 MHz, DMSO): δ 5.38 (d, 2H, J = 1.6 Hz); 6.73 (d, 1H); 7.53 (m, 3H); 7.68 (m, 2H). IR (KBr): 3058, 1795, 1732, 1616, 1450, 1151, 894 cm^{-1}. ESI-MS: 160.8 (M^+).

Compound **1b**

4-(4-Methyl-phenyl)furan-2(5H)-one. Yield 75%, mp 115°C (lit. 117°C).[13] ^{1}H NMR (300 MHz, DMSO): δ 2.35 (s, 3H); 5.33 (d, 2H, J = 1.55 Hz); 6.63 (s, 1H); 7.30 (d, 2H, J = 8.03 Hz); 7.59 (d, 2H, J = 8.13 Hz). IR (KBr): 1789, 1730, 1618, 1161, 1043 cm^{-1}. ESI-MS (197, $M + Na^+$).

Compound **1c**

4-(4-Isobutylphenyl)furan-2(5H)-one. Yield 79%, mp 154°C. ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.92 (d, 6H, J = 6.8 Hz); 1.90 (m, 1H); 2.52 (d, 2H, J = 5.1 Hz); 5.21 (d, 2H, J = 1.6 Hz); 6.33 (t, 1H, J = 1.6 Hz); 7.23 (d, 2H, J = 8.4 Hz); 7.42 (d, 2H, J = 8.4 Hz). IR (KBr): 2950, 1795, 1737, 1622, 1164, 896 cm^{-1}. ESI-MS: 216.9 $(M + H)^+$.

Compound **1d**

4-(3,4-Dimethylphenyl)furan-2(5H)-one. Yield 78%, mp 120°C. ^{1}H NMR (400 MHz, DMSO): δ 2.26 (s, 6H); 5.33 (d, 2H, J = 0.80 Hz); 6.61 (brs,

1H); 7.28 (d, 1H, $J = 7.60$ Hz); 7.44 (d, 2H, $J = 8.00$ Hz); 7.49 (brs, 1H). IR (KBr): 3093, 2943, 1797, 1728, 1618, 1448, 1325, 1197, 896, 823 cm^{-1}. ESI-MS: 188.8 $(M + H)^+$.

Compound **1e**

4-(Biphenyl-4-yl)furan-2(5H)-one. Yield 68%, mp 176°C. ^1H NMR (400 MHz, DMSO): δ 5.41 (d, 2H, $J = 1.6$); 6.77 (1H, brs); 7.40 (t, 1H, $J = 7.6$ Hz); 7.49 (t, 2H, $J = 7.6$ Hz); 7.75 (d, 2H, $J = 5.4$ Hz); 7.70–7.83 (4H, m). IR (KBr): 3080, 2962, 1792, 1732, 1612, 1487, 1326, 1173, 894 cm^{-1}. ESI-MS: 236.9 $(M + H)^+$.

Compound **1f**

4-(4-Methoxyphenyl)furan-2(5H)-one. Yield 80%, mp 120°C (lit. 121°C).[13] ^1H NMR (400 MHz, DMSO): δ 3.81 (s, 3H); 5.32 (d, 2H, $J = 1.2$ Hz); 6.56 (brs, 1H); 7.03 (d, 2H, $J = 8.81$ Hz); 7.65 (d, 2H, $J = 8.81$ Hz). IR (KBr): 3113, 2931, 1792, 1735, 1571, 1427, 1238, 1163, 895 cm^{-1}. ESI-MS: 190.8 $(M + H)^+$.

Compound **1g**

4-(Benzo[d][1,3]dioxol-5-yl)furan-2(5H)-one. Yield 80%, mp > 200°C. ^1H NMR (400 MHz, DMSO): δ 5.29 (d, 2H, $J = 0.8$ Hz); 6.11 (s, 2H); 6.59 (brs, 1H); 7.03 (d, 1H, $J = 8.00$ Hz); 7.19 (d, 1H, $J = 8.00$ Hz); 7.38 (s, 1H). IR (KBr): 3097, 2866, 1807, 1720, 1681, 1606, 1269, 1232, 993 cm^{-1}. ESI-MS: 204.9 $(M + H)^+$.

Compound **1h**

4-(4-(Methylthio)phenyl)furan-2(5H)-one. Yield 76%, mp 101°C. ^1H NMR (300 MHz, DMSO): δ 2.48 (s, 3H); 5.33 (d, 2H, $J = 1.8$ Hz); 6.67 (t, 1H, $J = 1.61$ Hz); 7.3 (d, 2H, $J = 8.53$ Hz); 7.6 (d, 2H, $J = 8.57$ Hz). IR (KBr): 3085, 1801, 1716, 1681, 1411, 1172, 898 cm^{-1}. ESI-MS: 206.9 $(M + H)^+$.

Compound **1i**

4-(4-Fluorophenyl)furan-2(5H)-one. Yield 60%, mp 144°C. ^1H NMR (400 MHz, DMSO): δ 5.36 (d, 2H, $J = 1.6$ Hz); 6.71 (brs, 1H); 7.34

(m, 2H); 7.79 (m, 2H). IR (KBr): 3114, 3070, 1786, 1737, 1624, 1228, 1161, 991 cm^{-1}. ESI-MS: 178.8 $(M + H)^+$.

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