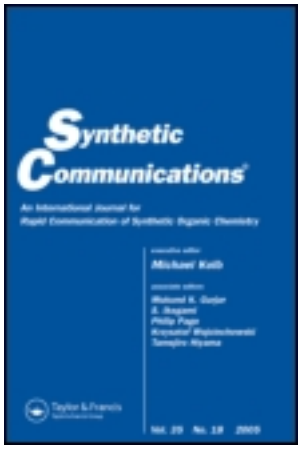

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ONE-POT SYNTHESIS OF 3,4-DIARYL-SUBSTITUTED 2(5*H*)-FURANONE AND ITS COMMERCIAL APPLICATION

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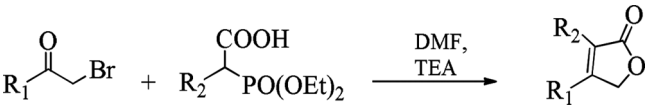
GRAPHICAL ABSTRACT



Abstract *One-pot synthesis of 3,4-diaryl substituted 2(5*H*)-furanones was established and its commercial application has been demonstrated by accomplishing total synthesis of rofecoxib, under mild reaction conditions, with good yields and purity.*

Keywords Diethylphosphono phenyl acetic acid; furanone; Horner–Wadsworth–Emmons reaction; phenacyl bromides; rofecoxib

INTRODUCTION

2(5*H*)-Furanones (butenolides) constitute an important class of oxygen heterocycles, found in several natural products and drugs with diverse biological activities such as antifungal, antibacterial, antiulcer, antitumor, insecticidal, cytotoxic, antimicrobial, and anti-inflammatory activities.[1–3] Rofecoxib (**1**) is one of the well-established bioactive drugs containing the 2(5*H*)-furanone ring system as an active pharmacophore.[4] It is a cyclooxygenase-2 (COX-2) inhibitor and exhibits anti-inflammatory, analgesic, and antipyretic activities.[5]

Knowing the pharmacological implication of furanone's ring system, various synthetic routes have been documented for the preparation of mono- and disubstituted 2(5*H*)-furanone derivatives,[6] and overall, synthesis of 3,4-diaryl/4-aryl-derivatives of 2(5*H*)-furanone is more challenging than that for the corresponding three- or five-substituted analogs.[7,8] The majority of literature methods reported

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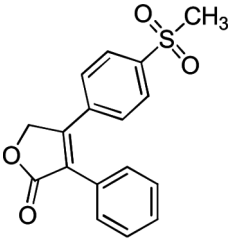
for the synthesis of substituted 2(5*H*)-furanones involve transition-metal-catalyzed coupling, palladium-catalyzed coupling reactions (Stille or Suzuki coupling, Suzuki–Miyaura cross-coupling) or use of expensive catalysts such as Grubbs catalyst.[7–10] Considering the biological importance and synthetic challenges of 3,4-diaryl-substituted 2(5*H*)-furanone derivatives, in the present communication, a one-pot, high-yielding synthesis of 3,4-diaryl-substituted 2(5*H*)-furanones, involving a intramolecular Horner–Wadsworth–Emmons-type cyclization reaction under mild conditions, has been reported. The generality of an efficient transformation has been demonstrated via several examples. Mechanistically, an involvement of the key intermediate has also been established based on precedence and experimental design. Furthermore, the commercial application of this one-pot synthesis has been demonstrated by accomplishing the total synthesis of rofecoxib.

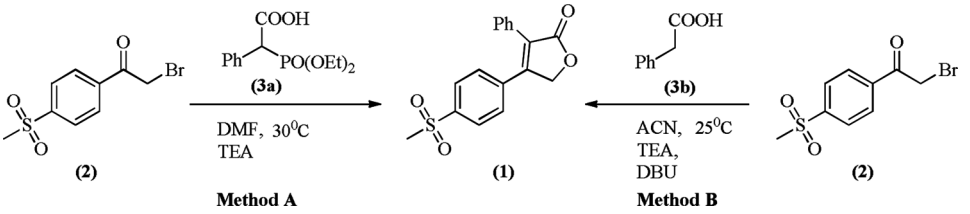


Rofecoxib (1)

In the past two decades, several methods have been disclosed for the synthesis of rofecoxib.[5,11–15] In the original patent published by Merck, rofecoxib was synthesized in three steps, starting from 4-(methylthio)acetophenone, using a cyclocondensation strategy.[11] In another approach, a Suzuki coupling strategy was employed for the introduction of the second aryl group, while regioselective synthesis of rofecoxib was carried out using ruthenium-catalyzed lactonization of diarylacetylene.[12,13] A significant amount of undesired by-product formation is one of the major drawbacks of this process. Desmond et al.[11] and Ducharme et al.[12] disclosed multistep syntheses of rofecoxib, which involve conversion of phenyl acetic acid to its corresponding 3-phenyl-4-(methylthio)phenyl-2-(5*H*)-furanone via intermediate keto ester and 4-methylthio-phenylboric acid formation, which upon oxidation gives the final product. This particular synthetic strategy involves expensive reagents and multistep operations. Black et al.[14] disclosed a multistep synthesis of rofecoxib that involves Friedel–Crafts acylation of thioanisole. Atkinson et al.[15] reported synthesis of 2(5*H*)-furanone derivatives using expensive catalysts (palladium ($PdCl_2$) or rhodium [$Rh_6(CO)_{16}$)], with poor yield and purity.

Earlier, an efficient method for the synthesis of 4-aryl-substituted 2(5*H*)-furanones starting from diethylphosphono acetic acid and phenacyl bromides, using strong base diazabicycloundec-7-ene (DBU), has been reported.[16] However, this method was for the synthesis of only mono-substituted 2(5*H*)-furanones. In continuation, herein we extend the scope of intramolecular Horner–Wadsworth–Emmons-type cyclization reaction under very mild conditions for efficient and one-pot synthesis of 3,4-diaryl substituted 2(5*H*)-furanones.

As shown in Scheme 1 (method A), one-pot synthesis of 4-[4-(methylsulfonyl) phenyl]-3-phenyl-2(5*H*)-furanone (rofecoxib, **1**) was carried out by reacting



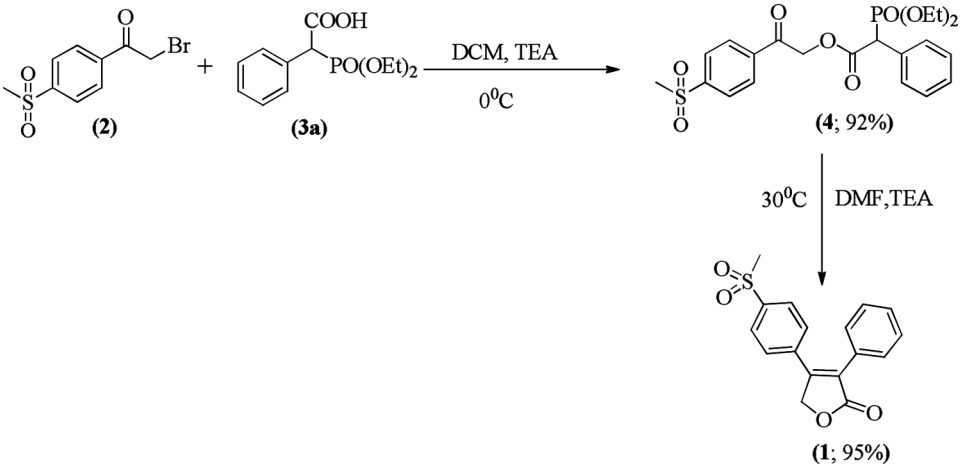
Scheme 1. Synthesis of rofecoxib [method A (new method) and method B (lit. method[5b])].

2-bromo-1-(4-methanesulfonyl-phenyl)-ethanone (**2**) and (dialkoxy-phosphonyl)-phenyl-acetic acid (**3a**) in the presence of triethylamine (TEA) in dimethylformamaide (DMF) at room temperature. Typically, using this one-pot synthesis protocol, rofecoxib can be prepared in 2 h, in good yield (90%), and the crude product obtained after filtration was sufficiently pure (99% purity).

Previously, Therien et al.[5b] reported a two-step synthesis of rofecoxib by reacting compound **2** with phenyl acetic acid (**3b**) in the presence of triethylamine (TEA) to get ester intermediate (in situ), followed by 1,8-diazabiyclo[5.4.0]undec-7-ene (DBU)–assisted cyclization (Scheme 1; method B). Despite using a strong base (DBU), the overall yield was 54%, and the pure rofecoxib was obtained after chromatographic purification. One of the plausible explanations for getting poor yields (method B) could be the less acidity of the α-proton in the phenyl acetic acid derivative.

Thus, introduction of diethyl phosphate group at the α-position in phenyl acetic acid (method A) resulted in an increased acidity of α-hydrogen, which makes reaction more facile and together led to a one-pot synthesis of 3,4-diaryl-substituted 2(5*H*)-furanones, even in the presence of a mild base such as TEA.

Further to confirm that one-pot intramolecular Horner–Wadsworth–Emmons-type cyclization reaction proceed via highly reactive phosphonate ester intermediate formation, synthesis of rofecoxib was attempted via an alternate route (Scheme 2).



Scheme 2. Two-step synthesis of rofecoxib.

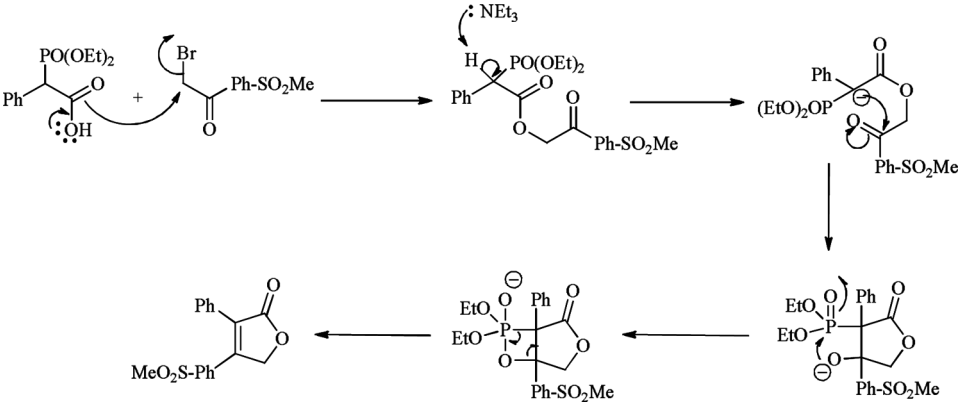
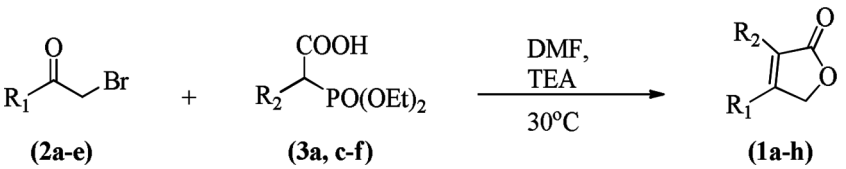


Figure 1. Proposed reaction mechanism for the one-pot synthesis of rofecoxib.

Compounds **2** and **3a** were reacted in the presence of dichloromethane (DCM) in DMF at 0 °C to isolate intermediate phosphonate ester **4** (HPLC purity 98.20%; yield: 92%). Incubation of compound **4**, in TEA and DMF at 30 °C, leads to the formation of rofecoxib (**1**) via intramolecular cyclization (HPLC purity 98.83%; yield: 95%). Thus, formation and isolation of intermediate phosphonate ester (**4**), under mild reaction condition (Scheme 2) confirms that the one-pot intramolecular Horner–Wadsworth–Emmons-type cyclization reaction in Scheme 1, actually proceeds via highly reactive phosphonate ester intermediate formation.

As shown in Fig. 1, the one-pot synthesis of rofecoxib (Scheme 1) begins with the nucleophilic substitution reaction to give intermediate phosphonate ester. After phosphonate formation, it is postulated that this one-pot reaction proceeds via an intramolecular Horner–Wadsworth–Emmons-type cyclization pathway, which involves deprotonation of the phosphonate ester to get phosphonate carbanion. Intramolecular nucleophilic addition of this carbanion to ketone gives oxaphosphetane (via C-C bond rotation and betaine formation) and finally, elimination of the phosphonate group leads to the formation of the desired alkene (rofecoxib). Overall, an electron-withdrawing group (EWG; phenyl ring) at the α-position to the phosphonate group is essential for the final elimination of the phosphonate group.

Finally, to broaden the commercial application and scope of this one-pot reaction with respect to diversified aryl substitutions, eight derivatives of 3,4-diaryl-substituted 2(5*H*)-furanones were prepared as depicted in Scheme 3 and Table 1. Two sets of compounds were prepared either by introducing electron-donating groups (EDG), such as



Scheme 3. General scheme for the synthesis of 3,4-diaryl-substituted 2(5*H*)-furanones.

Table 1. Reactivity comparison of various substituents at 3,4-positions of 2(5*H*)-furanones (**1a**–**h**)

Compounds	R_1	R_2	Time (h)[a]	Purity (%)[b]	Yield (%)
1a	*4*-Me-Ph-	Ph-	2	97.61	90.02
1b	*4*-OMe-Ph-	Ph-	2	97.33	91.11
1c	4-F-Ph-	Ph-	2	98.01	90.07
1d	4-NO_2-Ph-	Ph-	2	97.96	91.5
1e	Ph-	4-Me-Ph-	4	97.15	90.96
1f	Ph-	4-OMe-Ph-	4	98.09	90.03
1g	Ph-	4-F-Ph-	1	97.99	91.01
1h	Ph-	4-NO_2-Ph-	1	97.08	91.18

[a]Reaction completion time monitored with TLC.
[b]Purity of compounds analyzed by HPLC at λ_{max} 220 nm using column ODS C-18, 150 cm × 4.6 mm × 4 μm on AGILENT 1100.

methyl and methoxy groups at the *para*-position of either of the phenyl rings (compounds **1a, 1b, 1e** and **1f**), or electron-withdrawing groups (EWG), such as fluoro and nitro groups at the *para*-position of either of the phenyl rings (compounds **1c, 1d, 1g** and **1h**), and all the eight compounds were isolated with purity >97% and yield >90% (Table 1). However, it was interesting to observe that compounds **1e** and **1f** (EDG at R_2 position) took relatively longer reaction time (4 h) than compounds **1g** and **1h** (EWG at R_2 position, with 1 h reaction time). Similar substitutions at R_1 showed no difference the reactivity (reaction time same as rofecoxib, 2 h), which confirms that an increase in the electronegativity at the α-position to the phosphonate group facilitates one-pot intramolecular Horner–Wadsworth–Emmons-type cyclization reaction and overall elimination of the phosphonate group as the rate-limiting step. Thus, the flexibility in the usage of different starting materials (substituted phenacyl bromides (**2a**–**e**) and diethylphosphono phenyl acetic acids (**3a, c–f**; Scheme 3) broaden the scope of this one-pot reaction toward the synthesis of 3,4-diaryl substituted 2(5*H*)-furanones.

In summary, this novel one-pot synthetic procedure overcomes numerous drawbacks of earlier reported procedures and possesses several advantages: (a) It involves operational simplicity and fewer steps, thereby the time cycle required for the synthesis of substituted 3,4-diaryl substituted 2(5*H*)-furanones has been drastically reduced, which makes the process commercially viable. (b) It involves high-yielding solution-phase chemistry, flexibility in the usage of substituted starting materials, and mild reaction conditions, which facilitate its commercial scalability and overall cost-effectiveness.

CONCLUSION

In conclusion, we demonstrated a novel and highly efficient one-pot synthesis of 3,4-diaryl-substituted 2(5*H*)-furanones, accomplished with the total synthesis of rofecoxib (**1**), which overcomes several drawbacks and operational difficulties of earlier reported procedures and establishes sufficient evidence to confirm our observations that this proposed one-pot reaction proceeds via intramolecular Horner–Wadsworth–Emmons-type cyclization pathway.

EXPERIMENTAL

Melting points were recorded on open glass capillaries, using a scientific melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu Fourier transform (FT)–IR 8300 spectrophotometer (Vmax in cm^{-1}, using KBr pellets). The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker Avance-400 spectrometer (400 and 100 MHz respectively). The chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS), either in acetone-d_6, $CDCl_3$, or dimethylsulfoxide (DMSO-d_6) solution. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), bs (broad singlet), and m (multiplet). Mass spectra (ESI-MS) were obtained on Shimadzu LC-MS 2010-A spectrometer. Elemental analyses were carried out using a Perkin-Elmer 2400 CHN analyzer, and values within limit of ±0.4% of the theoretical values were taken into consideration. High-performance liquid chromatographic (HPLC) analysis were carried out at λ_{max} 220 nm using column ODS C-18, 150 cm × 4.6 mm × 4 μm on an Agilent 1100 series instrument. All the chemicals used for the synthesis were purchased from Aldrich Company Limited, Dorset (UK).

Preparation of 4-(4-(Methylsulfonyl)phenyl)-3-phenylfuran-2(5*H*)-one (1)

2-(Diethoxyphosphino)-2-phenylacetic acid (5 g, 18.3 mmol; **3a**) was added to a mixture of 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (5.09 g, 18.3 mmol; **2**) in DMF (50 mL) under a nitrogen atmosphere. The reaction mixture was cooled to 0°C, and TEA (7.94 mL, 55.0 mmol) was added. Further, the mixture was stirred at 30°C for 2 h and quenched in ice-cold water (200 mL). The precipitated compound was filtered, washed with acetone, and dried under reduced pressure to afford the title compound as a yellow solid (4.5 g, 92%), mp 203–204 °C, lit mp 204.7 °C[5b] HPLC purity: 98.83%; IR (KBr, cm^{-1}): 3481, 3018, 1745, 1747, 1446, 1340; ESI (m/z) 315.06 (M + H); ^{1}H NMR (acetone-d_6): δ = 3.15 (s, 3H), 5.37 (s, 2H), 7.32 (m, 2H), 7.42 (m, 3H), 7.68 (d, 2H, J = 8.46 Hz), 7.96 (d, 2H, J = 8.47 Hz); ^{13}C (DMSO-d_6): δ = 43.1, 70.9, 126.9, 127.4, 128.7, 128.8, 128.9, 129.1, 129.8, 135.8, 142.0, 156.0, 172.4 ppm. Elemental analyses found (calcd.): C, 64.95 (64.92); H, 4.49 (4.52); O, 20.36 (20.37); S, 10.20 (10.18).

Preparation of 2-(4-(Methylsulfonyl)phenyl)-2-oxoethyl 2-(Diethoxyphosphoryl)-2-phenylacetate (4)

Compound **3a** (5 g, 18.3 mmol) was added to a mixture of compound **2** (5.09 g, 18.3 mmol) in DCM (50 mL) under a nitrogen atmosphere. The reaction mixture was cooled to 0°C, and TEA (3.97 mL, 27.5 mmol) was added to the reaction mixture at 0 °C and stirred for 1h. The reaction mixture was quenched in water (100 mL) and extracted with ethyl acetate (100 mL × 3), the organic layer was dried over sodium sulfate (15 g), and the solvent was removed under reduced pressure to afford the intermediate compound **4**, as a thick oil (7.9 g, 92%). HPLC purity: 98.20%; IR (KBr, cm^{-1}): 3018, 2410, 1747, 1761, 1321, 1153; ESI (m/z) 469.19 (M+H);

^{1}H NMR (acetone-d_6): δ 1.16 (t, 3H, $J = 7.02$ Hz), 1.28 (t, 3H, $J = 7.05$ Hz), 3.07 (s, 3H), 3.95 (m, 1H), 4.06 (m, 3H), 4.39–4.47 (d, 1H, $J = 23.64$ Hz), 5.36 (d, 2H, $J = 4.02$ Hz), 7.35 (d, 3H, $J = 6.21$ Hz), 7.52 (d, 2H, $J = 6.93$ Hz), 8.04 (s, 4H); ^{13}C NMR (DMSO-d_6): δ = 14.2, 40.6, 41.1, 62.3, 75.7, 126.5 127.2, 128.9, 129.6, 135.0, 142.3, 196.6 ppm. Elemental analyses found (calcd.): C, 53.84 (53.87); H, 5.38 (5.41); O, 27.32 (27.35); P, 6.61 (6.59); S, 6.85 (6.88).

Preparation of 4-(4-(Methylsulfonyl)phenyl)-3-phenylfuran-2(*5H*)-one (1)

Compound **4** (5 g, 10.7 mmol) was dissolved in DMF (50 mL) under a nitrogen atmosphere. The reaction mixture was cooled to 0°C, and TEA (4.45 mL, 32.1 mmol) was added. Further, the mixture was stirred at 30°C for 2 h and quenched in ice-cold water (200 mL). The precipitated compound was filtered, washed with acetone, and dried under reduced pressure to afford the title compound **1** as a yellow solid (3.2 g, 95%), mp 203–204 °C. HPLC Purity: 98.83%. Spectral data of compound **1** were found to be identical as obtained using Scheme 1.

Preparation of Compounds 1a–h

A mixture of compound **2** (18.3 mmol; **2a**–**e**) and compound **3** (18.3 mmol; **3a, c**–**f**) in DMF (5 vol.) was stirred at 0 °C, and TEA (3.97 mL, 36.6 mmol) was added. Further, the mixture was stirred at 30 °C for 1–4 h (monitored by thin-layer chromatogrpahy, TLC). The reaction mixture was quenched in ice-cold water (10 vol.). The precipitated compound was filtered, washed with acetone, and dried under reduced pressure to afford the title compounds **1a**–**h**.

3-Phenyl-4-(p-tolyl)furan-2(*5H*)-one (1a). Yellow solid (yield 90.02%), mp. 212–213 °C; HPLC purity: 97.61%; IR (KBr, cm^{-1}): 3481, 3018, 1745, 1742, 1446, 1375; ESI (m/z) 251.29 (M+H); ^{1}H NMR (acetone-d_6): δ = 2.34 (s, 3H), 5.37 (s, 2H), 7.23 (m, 2H), 7.34 (m, 3H), 7.42 (d, 2H, $J = 8.46$ Hz), 7.68 (d, 2H, $J = 8.47$ Hz); ^{13}C (DMSO-d_6): δ = 25.3, 70.9, 126.9, 127.4, 128.7, 128.8, 128.9, 129.1, 129.8, 135.8, 142.0, 156.0, 172.4 ppm. Elemental analyses found (calcd.): C, 81.58 (81.56); H, 5.64 (5.62); O, 12.78 (12.80).

4-(4-Methoxyphenyl)-3-phenylfuran-2(*5H*)-one (1b). Yellow solid (yield = 91.11%), mp 188–189 °C. HPLC purity: 97.33%; IR (KBr, cm^{-1}): 3478, 3015, 1755, 1738, 1450, 1375; ESI (m/z) 267.29 (M+H); ^{1}H NMR (acetone-d_6): δ = 3.83 (s, 3H), 5.37 (s, 2H), 7.23 (m, 2H), 7.32 (m, 3H), 7.42 (d, 2H, $J = 8.46$ Hz), 7.62 (d, 2H, $J = 8.47$ Hz); ^{13}C (DMSO-d_6): δ = 57.8, 70.9, 116.9, 117.4, 128.7, 128.8, 128.9, 129.1, 129.8, 135.8, 142.0, 156.0, 172.4 ppm. Elemental analyses found (calcd.): C, 76.68 (76.65); H, 5.30 (5.32); O, 18.02 (18.04).

4-(4-Fluorophenyl)-3-phenylfuran-2(*5H*)-one (1c). Yellow solid (yield = 90.07%), mp 223–224 °C. HPLC purity: 98.01%; IR (KBr, cm^{-1}): 3484, 3010, 1745, 1742, 1446, 1342; ESI (m/z) 255.26 (M+H); ^{1}H NMR (acetone-d_6): δ = 5.37 (s, 2H), 7.23 (m, 2H), 7.32 (m, 3H), 7.44 (d, 2H, $J = 8.46$ Hz), 7.64 (d, 2H, $J = 8.47$ Hz); ^{13}C (DMSO-d_6): δ = 70.9, 115.9, 116.4, 128.7, 128.8, 128.9, 129.1,

129.8, 135.8, 142.0, 162.0, 172.4 ppm. Elemental analyses found (calcd.): C, 75.58 (75.56); H, 4.36 (4.38); F, 7.47 (7.49), O, 12.59 (12.57).

4-(4-Nitrophenyl)-3-phenylfuran-2(*5H*)-one (1d). Yellow solid (yield = 91.50%), mp 238–239 °C. HPLC purity: 97.96%; IR (KBr, cm^{-1}): 3488, 3014, 1745, 1742, 1446, 1342; ESI (*m/z*) 282.26 (M+H); ^{1}H NMR (acetone-d_6): δ = 5.37 (s, 2H), 7.23 (m, 2H), 7.32 (m, 3H), 7.64 (d, 2H, J = 8.46 Hz), 7.86 (d, 2H, J = 8.47 Hz); ^{13}C (DMSO-d_6): δ = 70.9, 116.9, 117.4, 124.7, 124.8, 128.9, 129.1, 129.8, 135.8, 142.0, 156.0, 172.4 ppm. Elemental analyses found (calcd.): C, 68.32 (68.34); H, 3.94 (3.92); N, 4.98 (4.96); O, 22.75 (22.77).

4-Phenyl-3-(p-tolyl)furan-2(*5H*)-one (1e). Yellow solid (yield = 90.96%), mp 217–218 °C; HPLC purity: 97.15%; IR (KBr, cm^{-1}): 3481, 3018, 1745, 1742, 1446, 1375; ESI (*m/z*) 251.29 (M+H); ^{1}H NMR (acetone-d_6): δ = 2.34 (s, 3H), 5.37 (s, 2H), 7.23 (m, 2H), 7.34 (m, 3H), 7.42 (d, 2H, J = 8.46 Hz), 7.68 (d, 2H, J = 8.47 Hz); ^{13}C (DMSO-d_6): δ = 24.3, 70.9, 126.9, 127.4, 128.7, 128.8, 128.9, 129.1, 129.8, 135.8, 142.0, 156.0, 172.4 ppm. Elemental analyses found (calcd.): C, 81.58 (81.56); H, 5.64 (5.62); O, 12.78 (12.80).

3-(4-Methoxyphenyl)-4-phenylfuran-2(*5H*)-one (1f). Yellow solid (yield = 90.03%), mp 192–193 °C. HPLC purity: 98.09%; IR (KBr, cm^{-1}): 3484, 3018, 1745, 1742, 1448, 1375; ESI (*m/z*) 267.29 (M+H); ^{1}H NMR (acetone-d_6): δ = 3.83 (s, 3H), 5.37 (s, 2H), 7.23 (m, 2H), 7.32 (m, 3H), 7.42 (d, 2H, J = 8.46 Hz), 7.62 (d, 2H, J = 8.47 Hz); ^{13}C (DMSO-d_6): δ = 57.8, 70.9, 116.9, 117.4, 128.7, 128.8, 128.9, 129.1, 129.8, 135.8, 142.0, 156.0, 172.4 ppm. Elemental analyses found (calcd.): C, 76.68 (76.65); H, 5.30 (5.32); O, 18.02 (18.04).

3-(4-Fluorophenyl)-4-phenylfuran-2(*5H*)-one (1g). Yellow solid (yield = 91.01%), mp 226–227 °C. HPLC purity: 97.99%; IR (KBr, cm^{-1}): 3484, 3010, 1745, 1742, 1446, 1342; ESI (*m/z*) 255.26 (M+H); ^{1}H NMR (acetone-d_6): δ = 5.37 (s, 2H), 7.23 (m, 2H), 7.32 (m, 3H), 7.44 (d, 2H, J = 8.46 Hz), 7.64 (d, 2H, J = 8.47 Hz); ^{13}C (DMSO-d_6): δ = 70.9, 115.9, 116.4, 128.7, 128.8, 128.9, 129.1, 129.8, 135.8, 142.0, 162.0, 172.4 ppm. Elemental analyses found (calcd.): C, 75.58 (75.56); H, 4.36 (4.38); F, 7.47 (7.49); O, 12.59 (12.57).

3-(4-Nitrophenyl)-4-phenylfuran-2(*5H*)-one (1h). Yellow solid (yield = 91.18%), mp 234–236 °C. HPLC purity: 97.08%; IR (KBr, cm^{-1}): 3484, 3010, 1745, 1742, 1446, 1342; ESI (*m/z*) 282.26 (M+H); ^{1}H NMR (acetone-d_6): δ = 5.37 (s, 2H), 7.23 (m, 2H), 7.32 (m, 3H), 7.64 (d, 2H, J = 8.46 Hz), 7.86 (d, 2H, J = 8.47 Hz); ^{13}C (DMSO-d_6): δ = 70.9, 116.9, 117.4, 124.7, 124.8, 128.9, 129.1, 129.8, 135.8, 142.0, 156.0, 172.4 ppm. Elemental analyses found (calcd.): C, 68.32 (68.34); H, 3.94 (3.92); N, 4.98 (4.96); O, 22.75 (22.77).

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REFERENCES

1. (a) Wang, Y.; Gloer, J. B.; Scott, J. A.; Malloch, D. Appenolides A-C: Three new antifungal furanones from the coprophilous Fungus Podospora appendiculata. *J. Nat. Prod.* **1993**, *56*, 341; (b) Tamai, Y.; Torihara, M.; Kido, Y.; Yamahara, J.; Motizuki, M.; Ito, M.; Katsuta, Y. Synthesis and antiulcer effects of 5-hydroxy-4-[2-substituted-(E)-ethenyl]-2(5*H*)-furanone. *Yakugaku Zasshi.* **1993**, *113*, 655; (c) Baveja, J. K.; Li, G.; Nordon, R. E.; Hume, E. B.; Kumar, N.; Willcox, M. D.; Poole-Warren, L. A. Biological performance of a novel synthetic furanone-based antimicrobial. *Biomaterials* **2004**, *25*, 5013.
2. (a) Weber, V.; Coudert, P.; Rubat, C.; Duroux, E.; Vallée-Goyet, D.; Gardette, D.; Bria, M.; Albuisson, E.; Leal, F.; Gramain, J. C.; Couquelet, J.; Madesclaire, M. Novel 4,5-diaryl-3-hydroxy-2(5*H*)-furanones as anti-oxidants and anti-inflammatory agents. *Bioorg Med Chem.* **2002**, *10*, 1647; (b) Lattmann, E.; Ayuko, W. O.; Kinchinaton, D.; Langley, C. A.; Singh, H.; Karimi, L.; Tisdale, M. J. Synthesis and evaluation of 5-arylated 2(5*H*)-furanones and 2-arylated pyridazin-3(2H)-ones as anti-cancer agents. *J. Pharm. Pharmacol.* **2003**, *55*, 1259.
3. Sindhuramachandran, C. V.; Sreekumar, P. K.; Synthesis, characterization, and antibacterial evaluation of 2(5*H*)furanone Derivatives from highly functionalized mucobromic acid. *Int. J. Pharm. Pharm. Sci.* **2011**, *3*, 225.
4. Sorbera, L. A.; Rabasseda, X.; Castaner, J. Rofecoxib. *Drugs Fut.* **1998**, *23* (12), 1287.
5. (a) Prasit, P.; Wang, Z.; Brideau, C.; Chan, C. C.; Charlson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Gresser, M.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, J. O.; Neil, G. P.; Quellet, M.; Percival, M. D.; Perrier, H.; Riendeau, D.; Rodger, I.; Tagari, P.; Therien, M.; Vikers, P.; Wong, E.; Xu, L.; Young, R. N.; Zamboni, R.; Boyce, S.; Rupniak, N.; Forrest, M.; Visco, D.; Patrick, D. The discovery of rofecoxib [MK 966, Vioxx, 4-(4′-methylsulfonylphenyl)-3-phenyl-2(5*H*)-furanone], an orally active cyclooxygenase-2-inhibitor. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773; (b) Thérien, M.; Gauthier, J. Y.; Leblanc, Y.; Léger, S. P.; Hélène, P. P.; Wang, Z. Synthesis of rofecoxib (MK 0966, Vioxx® 4-(4′-methylsulfonylphenyl)-3-phenyl-2(5*H*)-furanone), a selective and orally active inhibitor of cyclooxygenase-2. *Synthesis* **2001**, 1778; (c) Black, C.; Grimm, E.; Wang, Z.; Leger, S. Diaryl-5-oxygenated 2-(5*H*)-furanones as COX-2 inhibitors. U.S. Patent 5691374, 1997.
6. (a) Yao, M.-N.; Deng, M.-Z. Facile approach to 4-substituted 2(5*H*)-furanones. *J. Org. Chem.* **2000**, *65*, 5034; (b). Wu, J.; Zhu, Q.; Wang, L.; Fathi, R.; Yang, Z. Palladium-catalyzed cross-coupling reactions of 4-tosyl-2-(5*H*)-furanone with boronic acid: A facile and efficient route to generate 4-substited 2(5*H*)-furanones. *J. Org. Chem.* **2003**, *68*, 670; (c). Eabio, B.; Chiara, A.; Renzo, R. Synthesis of 4-alkyl-3-bromo-2(5*H*)-furanones and unsymmetrically disubtituted 3,4-dialkyl-2(5*H*)-furanones by palladium-catalysed cross-coupling reactions. *Tetrahedron Lett.* **2001**, *42*, 3851; (d) Boukouvalas, J.; Lachance, N.; Ouellet, M.; Trudeau, M. Facile access to 4-aryl-2(5-*H*)-furanones by Suzuki cross coupling: Efficient synthesis of rubrolides C and E. *Tetrahedron Lett.* **1998**, *39*, 7665; (e) Lee, G. C. M.; Garst, M. E. 2(5*H*)-Furanones substituted in the 5 and/or in the 4 position, as anti-inflammatory agents. WO Patent 9116,055, 1991; *Chem. Abstr.* **1992**, *116*, 59197m.
7. (a) Still, J. K. The Palladium-catalysed cross-coupling reaction of organoboron reagents. *Angew. Chem. Int. Ed.* **1986**, *25*, 508; (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. The Stille reactions. *Org. React.* **1998**, *50*, 1; (c) Bellina, F.; Falchi, E.; Rossi, R. Regioselective synthesis of cytotoxic 4-(1-alkynyl)-substituted 2-(5*H*)-furanones. *Tetrahedron* **2003**, *59*, 9091; (d) Bellina, F.; Anselmi, C.; Viel, S.; Maunina, L.; Rossi, R. Selective synthesis of (Z)-4-aryl-5-[1-(aryl) methylidene]-3-bromo-2(5*H*)-furanones. *Tetrahedron* **2001**, *57*,

9997; (e) Forgione, P.; Wilson, P. D.; Fallis, A. G. Magnesium-mediated carbometallation of propargyl alcohols: Direct routes to furans and furanones. *Tetrahedron Lett.* **2000**, *41*, 17.

8. (a) Suzuki, A.; Reacent advances in the cross-coupling reaction of organoboron derivatives with organic electrophile, 1995–1998. *J. Orgmet. Chem.* **1999**, *576*, 147; (b) Huang, X.; Sheng, S. R. A facile solid-phase synthesis of substituted 2(5*H*)-furanones from polymer-supported α-selenocarboxylic acids. *J. Comb. Chem.* **2003**, *5*, 273; (c) Craig, D.; Etheridge, C. J.; Smith, A. M. (Alkoxyallyl)sulfones as enal β-anion equivalents: Synthesis of 5-substituted 2(5*H*)-furanones. *Tetrahedron* **1996**, *52*, 5267.
9. (a) Miyaura, N.; Suzuki, A. Palladium cross-coupling reaction of organoboron compounds. *Chem. Rev.* **1995**, *95*, 2457; (b) Barder, T. E.; Walkar, S. D.; Martineli, J. R.; Buchwald, S. L. Catalysts for Suzuki–Miyaura cross-coupling processes: Scope and studies of the effect of ligand structure. *J. Am. Chem. Soc.* **2005**, *127*, 4685.
10. Ghosh, A. K.; Leshchenko, S.; Noetzel, M. Stereoselective photochemical 1,3-dioxolane addition to 5-alkoxymethyl-2(5*H*)-furanones: Synthesis of bis-tetrahydronfuranyl ligand for HIV protease inhibitor UIC-94017 (TMC-114). *J. Org. Chem.* **2004**, *69*, 7822.
11. Desmond, R.; Dolling, U.; Marcune, B.; Tillyer, R.; Tschaen, D. Process for making phenyl hetrocycles useful as COX-2 inhibitors. WO Patent 08482, 1996.
12. Ducharme, Y.; Gauthier, J. Y.; Prasit, P.; Leblane, Y.; Wang, Z.; Leger, S.; Therien, M. Phenyl hetrocycles useful as COX-2 inhibitors. WO Patent 18799, 1995.
13. Hancock, B.; Winters, C.; Gertz, B.; Ehrich, E. Compsitions for once a day treatment of Cyclooxygenase-2 mediated diseases. WO Patent 44028, 1997.
14. Black, C.; Grimm, E.; Leger, S.; Prasit, P. Diaryl-2-(5*H*)-furanones as COX-2 inhibitors. WO Patent 19469, 1996.
15. Atkinson, J. G.; Wang, Z. Stilbene derivatives useful as cyclooxygenase-2 inhibitors. WO Patent 13483 1996.
16. Thombare, P.; Desai, J.; Argade, A.; Gite, S.; Shah, K.; Pavase, L.; Patel, P. Novel and efficient route for the synthesis of 4-aryl substituted 2(5*H*)-furanones. *Synth. Commun.* **2009**, *39*, 2423.