# Facile Synthesis of Furan Derivatives

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**The enones (II), which were obtained from dimethyl 4,5-isopropylidenedioxy-2-oxopentylphosphonate (Ia) and various aldehydes, were easily converted to 2-alkenylfurans (III) by treatment with *p*-TsOH in MeOH. In a similar manner, the furfuryl phosphonate (IVa) and the 3-methylfurfuryl phosphonate (IVb) were obtained from Ia and its 3-methylated analogue (Ib), respectively.**

**Keywords** 2-substituted furan; 2,3-disubstituted furan; furfuryl derivative; isopropylidenedioxy function; *p*-TsOH; Horner–Wadsworth–Emmons reaction

Many naturally occurring compounds, such as marrubiin, ircinin, cedrelone, longifolin, and plaunol, contain a furan ring.[1] These compounds have been seen as attractive targets for chemical synthesis, because of their unique structure and biological activity. In connection with the synthesis of these natural products, construction of the furan ring system has also been widely investigated. As exemplified by the procedures of Morel and Verkade,[2] Cornforth,[3] Perveev *et al.*,[4] and Scott and Naples,[5] most of the furan syntheses required thermal reaction condition. Recently, Watanabe *et al.*,[6] Baciocchi and Ruzziconi,[7] and Tsuge *et al.*[8] reported substituted furan syntheses under mild reaction conditions. In this note, we wish to report the facile construction of 2-substituted and 2,3-disubstituted furans (Chart 1); this reaction was found during studies on the synthesis of optically active $\alpha,\beta$- and $\beta',\gamma'$-unsaturated alcohols.[9]

Deprotection of the acetonide function in the enone (IIa) with *p*-TsOH in MeOH at room temperature afforded 2-alkenylfuran (IIIa) as the major product (48% yield), and the expected diol was not obtained. Similarly, IIb and IIc gave the corresponding furans (IIIb and IIIc) in 50% and 78% yields, respectively.

The structure of IIIa was determined on the basis of the following spectral data. In the proton nuclear magnetic resonance ($^1$H-NMR) spectrum, the signals of $C_3$-H, $C_4$-H, and $C_5$-H was observed at $\delta$ 6.29 (1H, d, $J=4$ Hz), 6.33 (1H, dd, $J=1.5$, 4 Hz), and 7.29 (1H, d, $J=1.5$ Hz), respectively, and the signal of the olefinic protons of the $C_2$-double bond was observed at $\delta$ 5.82—6.00 (2H, m). In the infrared (IR) spectrum, the absorption (1670 cm$^{-1}$) of the carbonyl function had disappeared, and furan ring and double bond absorptions were observed at 1580, 1500, and 1450 cm$^{-1}$. In the mass spectra (MS), the molecular ion peak was observed at $m/z$ 176 (M$^+$). The above spectral data supported the proposed furan structure. The enones (IIa, b, and c) could be easily prepared, in 72%, 65% and 55% yield, respectively, by a modified[10] Horner–Wadsworth– Emmons (HWE) reaction of the aldehydes with the phosphonate (Ia)[11] prepared from (*dl*)-malic acid.

In a manner similar to that used for the conversion of II into the furan, the phosphonate (Ia) was directly converted, in 60% yield, to the furfuryl phosphonate (IVa).[12] The structure of IVa was supported by the following spectral data. In the $^1$H-NMR spectrum, signals of $C_3$-H, $C_4$-H, and $C_5$-H were observed at $\delta$ 6.29 (1H,

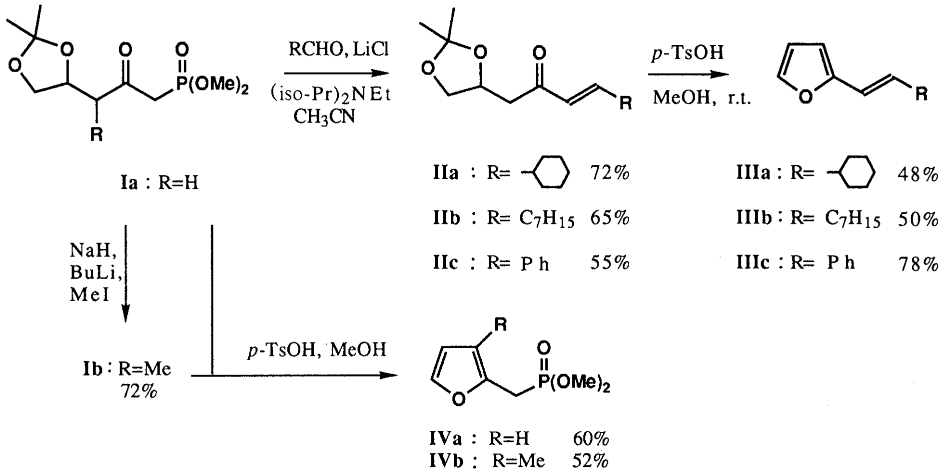

Chart 1

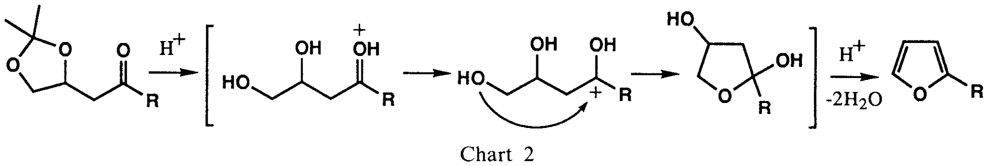

Chart 2

d, $J=4$ Hz), 6.33 (1H, dd, $J=1.5$, 4 Hz), and 7.36 (1H, d, $J=1.5$ Hz), respectively, and signals of the methylene protons and $O$-methyl protons were observed at $\delta$ 3.26 (2H, d, $J=21$ Hz) and 3.73 (6H, d, $J=11$ Hz), respectively. In the IR spectrum, the absorption of the carbonyl group (1715 cm$^{-1}$) had disappeared, and the furan ring (C=C) absorptions were observed at 1600 and 1500 cm$^{-1}$. The MS also supported the proposed structure. The HWE reaction of IVa with various aldehydes seems to offer a convenient method for synthesis of 2-substituted furans.[8)]

2,3-Disubstituted furan derivatives could also be prepared using 3-substituted I. 3-Methyl phosphonate (Ib) was easily obtained, in 72% yield, by methylation of the dianion generated by successive treatments of Ia with NaH and BuLi at $-15$ °C. Treatment of Ib with $p$-TsOH in yielded the expected 3-methylfurfuryl phosphonate (IVb) in 52% yield. The structure of IVb was consistent with the spectroscopic data.

This furan formation seems to proceed through the following 3 steps (Chart 2); i) deprotection with acid, ii) cyclization reaction as shown in parenthesis (*via* the favored 5-*exo*-trigonal process (Baldwin's role),[13)] iii) dehydration reaction.

## Experimental

IR spectra were measured on a JASCO A-202 spectrometer. $^1$H-NMR spectra were measured on JEOL JNM-PS-100 and JNM-GX-270 spectrometers. Mass spectra were taken a JEOL JMS-D-300 spectrometer. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. Thin layer chromatography (TLC) was performed on Merck Silica gel 60 F$_{254}$ plates. All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate.

**General Procedure for the Synthesis of the Enones (IIa, b, and c)** The aldehyde (1.01 mmol) in $CH_3CN$ (5 ml) was added to a stirred solution of LiCl (42 mg, 1.0 mmol), the phosphonate (Ia, 226 mg, 1.0 mmol), and diisopropylethylamine (129 mg, 1.0 mmol) in $CH_3CN$ (2 ml) at room temperature. After being stirred for 40 h, the reaction mixture was diluted with ether (50 ml), and the organic layer was washed, and then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 3% AcOEt in hexane (v/v) afforded IIa (72 % yield) as a colorless oil.

IIa: IR (neat): 1670, 1615, 1380, 1260, 1160 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.20—2.23 (11H, m, cyclohexyl), 1.36, 1.43 (3H each, s, $C(CH_3)_2$), 2.63 (1H, dd, $J=8$, 16 Hz, $C\underline{H}_aH_bCO$), 3.11 (1H, dd, $J=6$, 16 Hz, $CH_a\underline{H}_bCO$), 3.56 (1H, dd, $J=7$, 9 Hz, $OC\underline{H}_aH_b$), 4.20 (1H, dd, $J=6$, 7 Hz, $OCH_a\underline{H}_b$), 4.36—4.63 (1H, m, OCH), 6.06 (1H, d, $J=16$ Hz, COCH=), 6.79 (1H, dd, $J=6$, 16 Hz, =CH). MS $m/z$: 252 (M$^+$), 237, 194, 177. High-MS for $C_{15}H_{24}O_3$ (M$^+$): Calcd $m/z$ 252.17252; Found 252.17118.

IIb: 65% yield, a colorless oil. IR (neat): 1670, 1620, 1380, 1250, 1150 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.88 (3H, t, $J=7$ Hz, $CH_3$), 1.36, 1.41 (3H each, s, $C(CH_3)_2$), 1.28—1.54 (10H, m, $(CH_2)_5$), 2.13—2.26 (2H, m, $C=CCH_2$), 2.68 (1H, dd, $J=8$, 16 Hz, $C\underline{H}_aH_bCO$), 3.11 (1H, dd, $J=6$, 16 Hz, $CH_aC\underline{H}_bCO$), 3.56 (1H, dd, $J=7$, 9 Hz, $OC\underline{H}_aH_b$), 4.21 (1H, dd, $J=6$, 7 Hz, $OCH_a\underline{H}_b$), 4.38—4.64 (1H, m, OCH), 6.08 (1H, d, $J=16$ Hz, =CHCO), 6.87 (1H, dd, $J=7$, 16 Hz, =CH). MS $m/z$: 268 (M$^+$), 253, 148. High-MS for $C_{16}H_{28}O_3$ (M$^+$): Calcd $m/z$ 268.20381; Found 268.20335.

IIc: 55% yield, a colorless oil. IR (neat): 1660, 1600, 1500, 1380, 1250, 1160 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.36, 1.42 (3H each, s, $C(CH_3)_2$), 2.65 (1H, dd, $J=8$, 16 Hz, $C\underline{H}_aH_bCO$), 3.23 (1H, dd, $J=6$, 16 Hz, $CH_a\underline{H}_bCO$), 3.60 (1H, dd, $J=7$, 9 Hz, $OC\underline{H}_aH_b$), 4.25 (1H, dd, $J=6$, 7 Hz, $OCH_a\underline{H}_b$), 4.35—4.62 (1H, m, OCH), 6.73 (1H, d, $J=16$ Hz, COCH=), 7.29—7.66 (6H, m, =CH, aromatic H). MS $m/z$: 246 (M$^+$), 231, 188, 170, 131. High-MS for $C_{15}H_{18}O_3$ (M$^+$): Calcd $m/z$ 246.12557; Found 246.12488.

**Dimethyl 3-Methyl-4,5-isopropylidenedioxy-2-oxopentylphosphonate (Ib)** A solution of *dl*-Ia (400 mg, 1.5 mmol) in tetrahydrofuran (THF) (1 ml) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 67.5 mg, 1.69 mmol) in THF (5 ml) under an Ar atmosphere at $-15$ °C. The mixture was stirred for 0.5 h, then BuLi (1.5 M in hexane, 1.58 mmol) was added dropwise over 0.5 h, and then MeI (213 mg, 1.5 mmol) was added dropwise. After 6 h, $NH_4Cl$ (398 mg, 7.4 mmol) was added portionwise, and the reaction mixture was diluted with ether (50 ml). The organic layer was washed, dried, and evaporated *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 50% AcOEt in hexane (v/v) afforded Ib (302 mg, 72%) as a colorless oil. IR (neat): 1710, 1630, 1380, 1250, 1220 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.19 (3H, d, $J=7$ Hz, $CH_3$), 1.36, 1.40 (3H each, s, $C(CH_3)_2$), 2.90—3.30 (1H, m, CHCO), 3.32 (2H, d, $J=18$ Hz, $CH_2P$), 3.57—3.70 (1H, m, $OC\underline{H}_aH_b$), 3.72 (6H, d, $J=5$ Hz, $(OCH_3)_2$), 4.06—4.17 (1H, m, $OCH_a\underline{H}_b$), 4.30—4.48 (1H, m, OCH). MS $m/z$: 265 ($M^+-CH_3$), 151, 124, 109.

**General Procedure for the Synthesis of Furan Derivatives (IIIa—c, and IVa, b)** A mixture of the enone (0.24 mmol) and $p$-TsOH (6 mg, 0.032 mmol) in MeOH (1 ml) was stirred for 4 h at room temperature. The reaction mixture was diluted with $CH_2Cl_2$ (20 ml), and the organic layer was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue which was purified by column chromatography on silica gel using 3—5% AcOEt in hexane (v/v) as the eluent.

IIIa: 48% yield, a colorless oil. IR (neat); 1650, 1580, 1500, 1450, 1260, 1010 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.18—2.05 (11H, m, cyclohexyl), 5.82—6.00 (2H, m, CH=CH), 6.16 (1H, d, $J=4$ Hz, $C_3$-H), 6.33 (1H, dd, $J=1.5$, 4 Hz, $C_4$-H), 7.29 (1H, d, $J=1.5$ Hz, $C_5$-H). MS $m/z$: 176 (M$^+$), 93, 83, 67.

IIIb: 50% yield, a colorless oil. IR (neat): 1650, 1600, 1500, 1450, 1250, 1000 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.88 (3H, t, $J=6$ Hz, $CH_3$), 1.27—1.48 (10H, m, $(CH_2)_5$), 2.04—2.24 (2H, m, $=-CH_2$), 6.02—6.13 (2H, m, CH=CH), 6.14 (1H, $J=4$ Hz, $C_3$-H), 6.33 (1H, dd, $J=1.5$, 4 Hz, $C_4$-H), 7.29 (1H, d, $J=1.5$ Hz, $C_5$-H). MS $m/z$: 192 (M$^+$), 163, 107, 94.

IIIc: 78% yield, a colorless oil. IR (neat): 1630, 1600, 1500, 1450, 1250, 1000 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 6.33 (1H, dd, $J=1.5$, 4 Hz, $C_4$-H), 6.87 (1H, $J=16$ Hz, =CH), 7.05 (1H, $J=16$ Hz, CH=), 7.21—7.51 (7H, m, $C_3$-H, $C_5$-H, aromatic-5H). MS $m/z$: 170 (M$^+$), 141, 115, 102, 91, 77.

In a similar manner, IVa, b were synthesized from Ia and Ib, respectively. In these cases, the reaction time required was over 24 h.

IVa: 60% yield, a colorless oil. IR (neat): 1600, 1500, 1230, 1030 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.26 (2H, d, $J=21$ Hz, $CH_2P$), 3.73 (6H, d, $J=11$ Hz, $(OCH_3)_2$), 6.29 (1H, d, $J=4$ Hz, $C_3$-H), 6.33 (1H, dd, $J=1.5$, 4Hz, $C_4$-H), 7.36 (1H, d, $J=1.5$ Hz, $C_5$H). MS $m/z$: 190 (M$^+$), 109, 81, 68.

IVb: 52% yield, a colorless oil. IR (neat): 1600, 1500, 1240, 1020 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.67 (3H, s, $CH_3$), 3.26 (2H, d, $J=21$ Hz, $CH_2P$), 3.74 (6H, d, $J=11$ Hz, $(OCH_3)_2$), 6.32 (1H, d, $J=1.5$ Hz, $C_4$-H), 7.32 (1H, d, $J=1.5$ Hz, $C_5$-H). MS $m/z$: 204 (M$^+$), 109, 95, 81.

## References and Notes

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