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An Efficient One-pot Synthesis of Dialkyl 2,5-Dihydrofuran-2,3-dicarboxylates Mediated by Vinyltriphenylphosphonium Salt

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Abstract: Protonation of the highly reactive 1:1 intermediates produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates by 2-hydroxyketones leads to vinyltriphenylphosphonium salts, which undergo an intramolecular Wittig reaction to produce functionalized dialkyl 2,5-dihydrofuran-2,3-dicarboxylates in fairly high yields.

INTRODUCTION

Dihydrofurans, one of the most fundamental heterocycles, are important intermediates in organic synthesis [1,2], and their synthetic study continues to attract much attention . Although unsubstituted dihydrofurans are relatively easily derived from furan, preparation of polysubstituted dihydrofurans is much more difficult. During the last decades, several methods have been developed for the preparation of dihydrofurans [3-10]. Among the large family of furans, several efforts have been focused on the dihydrofurancarboxylates [7]. Recently, we have described a method for heterocyclic synthesis using a novel approach to vinylphosphonium salts [11,12]. We here report that functionalized 2,5-dihydrofurans **3** are prepared from 2-hydroxyketones by intramolecular Wittig reaction [2-4] using vinyltriphenylphosphonium salts. Thus, reaction of 2-hydroxyketones **2** with dialkyl acetylenedicarboxylates **1** in the presence of triphenylphosphine leads to the corresponding dihydrofurans **3** in fairly good yields.

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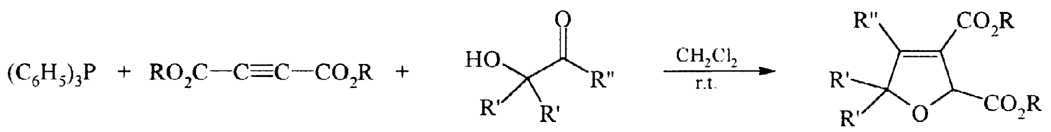


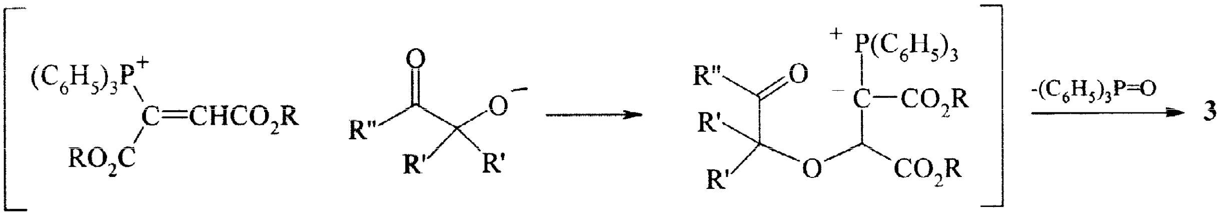
1	R
a	Me
b	Et
c	t-Bu

2	R'	R''
a	Me	Me
b	H	Et
c	Me	Ph

3	R	R'	R''
a	Me	Me	Me
b	Et	Me	Me
c	t-Bu	Me	Me
d	Me	H	Et
e	Et	H	Et
f	t-Bu	H	Et
g	Me	Me	Ph
h	Et	Me	Ph
i	t-Bu	Me	Ph

RESULTS AND DISCUSSION

Many reactions are reported in which a heterocyclic-containing alkene is formed from a phosphorane connected with a carbonyl group by a chain containing a heteroatom [3,4]. Thus, dihydrofuran derivative **3** may be regarded as product of an intramolecular Wittig reaction. Such addition-cyclization products apparently result from initial addition of triphenylphosphine to the acetylenic ester and concomitant protonation of the 1:1 adduct, followed by attack of the anion of **2** to vinyltriphenylphosphonium cation to produce phosphorane **5**, which is converted into the dihydrofurans **3**.



4 **5**

Structure **3** was assigned to the isolated products on the basis of their elemental analyses and IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. Initial fragmentations involved loss of the furan side chains (ROH, HCO_2R, $H_2C{=}CMe_2$) and scission of the ring.

The ^{1}H NMR spectrum of **3a** showed four single sharp lines, readily recognizable as arising from geminal methyl (δ 1.35 and 1.42) and methoxy (δ 3.74 and 3.76) protons, along with a doublet at δ 2.11 and a quartet at δ 5.32 for methyl and methine groups, respectively. The four-bond proton-proton coupling constant between the two methine groups is 1.7 Hz, which is significantly high as a result of the rigid skeletal framework of the dihydrofuran moiety.

The ^{13}C NMR spectrum of **3a** displayed eleven distinct resonances in agreement with the 2,5-dihydrofuran structure. Partial assignments of these resonances are given in the Experimental Section.

The ^{1}H and ^{13}C NMR spectra of **3b** and **3c** are similar to those of **3a**, except for the ester moieties, which exhibited characteristic resonances with appropriate chemical shifts (see Experimental).

The NMR spectral data for compounds **3d-f**, as shown in the Experimental section, are consistent with the 2,5-dihydrofuran structure. For these molecules, complex multiplets are observed for the methylene and methine protons of the heterocyclic ring system, as a result of long-range proton-proton couplings.

The procedure has been applied to 2-phenacyl propan-2-ol (**2c**). Compounds **3g** and **3i** are stable crystalline solids, but **3h** is a pale-yellow oil. The structures of **3g**, **3h**, and **3i** are fully supported by NMR and other spectral data (see Experimental).

The structural assignments made on the basis of the NMR spectra of compounds **3a-i** were supported by measurement of their IR spectra. Of special interest is the carbonyl absorption (1701-1749 cm^{-1}) for these compounds. Conjugation with the carbon-carbon double bond appear to be a plausible factor in the reduction of the wavenumbers of the carbonyl absorption bands [13].

Dihydrofurans **3a-i** may be regarded as potentially useful synthetic intermediates [5-10] because they possess the contiguous three carbon unit with different oxidation states. We anticipate that the reactions described herein represent a simple and efficient entry into the synthesis of polyfunctional 2,5-dihydrofuran-2,3-dicarboxylates.

Further investigation of the present method will be required to establish its utility and scope.

EXPERIMENTAL SECTION

Acetylenic esters **1** and 2-hydroxyketones **2** were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. ^{1}H and ^{13}C NMR spectra were measured with JEOL EX-90A spectrometer at 90 and 22.6 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer.

Preparation of dimethyl 2,5-dihydro-4,5,5-trimethylfuran-2,3-dicarboxylate (3a)

General procedure.

To a magnetically stirred solution of triphenylphosphine (0.524 g, 2 mmol) and 3-hydroxy-3-methylbutane-2-one **2a** (0.204 g, 2 mmol) in dichloromethane (4 ml) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.284 g, 2 mmol) in dichloromethane (4 ml) at -5° C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 24 hr. The solvent was removed mixture was then allowed to warm up to room temperature and stirred for 24 hr. The solvent was removed under reduced pressure and the residue was purified by silica gel (Merck silica gel 60, 230-400 mesh) column chromatography using hexane-ethyl acetate (4:1) as eluent. The solvent was removed under reduced pressure and product (0.36 g, light-yellow oil, 78%) was obtained. IR (neat) (ν_{max}, cm^{-1}) : 1749 and 1714 (C=O), 1661 (C=C). ^1H NMR (90 MHz, $CDCl_3$): δ = 1.35 and 1.42 (6H, 2s, Me_2C), 2.11 (3H, d, J=1.7 Hz, CH_3), 3.74 and 3.76 (6H, 2s, $2CH_3O$), 5.32 (1H, q, J=1.7 Hz, CH); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ = 11.85 ($^{13}CH_3$-C=), 26.39 and 26.45 [($^{13}CH_3)_2C$], 51.43 and 52.29 ($2CH_3O$), 82.50 (CH), 92.52 ($^{13}CMe_2$), 121.27 (=^{13}C-C=O), 159.30 (CH_3-^{13}C), 163.62 (=C-^{13}C=O), 171.39 (CH-^{13}C=O). MS (m/z, %) : 228 (M^+, 2), 169 (M^+-CO_2Me, 100), 154 (169-Me, 48), 109 (169-HCO_2Me, 80). Anal. Calcd. for $C_{11}H_{16}O_5$ (228.24) : C, 57.89; H, 7.07%. Found: C, 58.2; H, 7.1%.

Diethyl 2,5-dihydro-4,5,5-trimethylfuran-2,3-dicarboxylate (3b)

Light-yellow oil, 0.40 g, 77%. IR (neat) (ν_{max}, cm^{-1}) : 1735 and 1711 (C=O), 1663 (C=C). ^1H NMR (90 MHz, $CDCl_3$): δ = 1.26 and 1.33 (6H, 2t, J=7.1 Hz, $2CH_3$), 1.34 and 1.42 (6H, 2s, Me_2C), 2.16 (3H, d, J=1.7 Hz, CH_3), 4.18 and 4.20 (4H, 2q, J=7.1 Hz, $2CH_2O$), 5.30 (1H, q, J=1.7 Hz, CH); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ = 11.73 ($^{13}CH_3$-C=), 14.13 and 14.18 (2 $^{13}CH_3CH_2$), 26.43 and 26.50 [($^{13}CH_3)_2C$], 60.31 and 61.08 ($2OCH_2$), 82.83 (CH), 92.44 ($^{13}CMe_2$), 121.63 (=^{13}C-C=O), 158.93 (CH_3-^{13}C=), 163.21 (=C-^{13}C=O), 171.03 (CH-^{13}C=O). MS (m/z, %) : 257 (MH^+, 4), 183 (M^+-CO_2Et, 100), 137 (183-EtOH, 26), 109 (183-HCO_2Et, 70). Anal. Calcd. for $C_{13}H_{20}O_5$ (256.30) : C, 60.92; H, 7.87 %. Found: C, 61.4; H, 7.6%.

Di-t-butyl 2,5-dihydro-4,5,5-trimethylfuran-2,3-dicarboxylate (3c)

Light-yellow oil, 0.44 g, 70%. IR (neat) (ν_{max}, cm^{-1}) : 1736 and 1705 (C=O), 1664(C=C). ^1H NMR (90 MHz, $CDCl_3$): δ = 1.33 and 1.40 (6H, 2s, Me_2C), 1.47 and 1.49 (18H, 2s, $2CMe_3$), 2.16 (3H, d, J=1.7 Hz, CH_3), 5.30 (1H, q, J=1.7 Hz, CH); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ = 11.52 ($^{13}CH_3$-C=), 26.47 and 28.06 [($^{13}CH_3)_2C$], 27.89 and 28.18 ($6CH_3$ of $2CMe_3$), 80.99 and 81.08 (2 $^{13}CMe_3$), 84.21 (CH), 92.11 ($^{13}CMe_2$), 123.02 (=^{13}C-C=O), 157.51 (CH_3-^{13}C=), 162.64 (=C-^{13}C=O), 170.13 (CH-^{13}C=O). MS (m/z, %) : 313 (MH^+, 3), 211 (M^+-HCO_2CMe_3, 90), 155 (211-H_2C=CMe_2, 100), 109 (211-HCO_2CMe_3, 40). Anal. Calcd. for $C_{17}H_{28}O_5$ (312.41) : C, 65.36; H, 9.03%. Found: C, 66.0; H, 8.9%.

Dimethyl 2,5-dihydro-4-ethylfuran-2,3-dicarboxylate (3d)

Light-yellow oil, 0.35 g, 81 %. IR (neat) (ν_{max}, cm^{-1}) : 1744 and 1713 (C=O), 1653 (C=C). ^1H NMR (90 MHz, $CDCl_3$): δ = 1.13 (3H, t, J=7.8 Hz, CH_3), 2.70 (2H, q, J=7.8 Hz, CH_2), 3.74 and 3.75 (6H, 2s, $2OCH_3$), 4.87 (2H, m , CH_2O), 5.37 (1H, m, CH); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ = 12.26 (CH_3), 19.83 (CH_2), 51.47 and 52.20 ($2OCH_3$), 79.08 (CH_2O), 85.55 (CH), 122.28 (=^{13}C-C=O), 159.50 (^{13}C=C-C=O), 162.96 (CH-^{13}C=O), 171.11 (=C-^{13}C=O). **MS (*m/z*, %)** : 214 (M^{+}, 3), 155 (M^{+}-CO_2Me, 100), 123 (155-MeOH, 22), 95 (155-HCO_2Me, 28). **Anal. Calcd. for $C_{10}H_{14}O_5$** (214.22) : C, 56.07; H, 6.59%. Found: C, 55.4; H, 6.3%.

Diethyl 2,5-dihydro-4-ethylfuran-2,3-dicarboxylate (3e)

Light-yellow oil, 0.38 g, 78%. IR (neat) ($\nu_{max,}$ cm^{-1}) : 1741 and 1708 (C=O), 1655 (C=C). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.15 (3H, t, *J*=7.8 Hz, CH_3), 1.30 and 1.35 (6H, 2t, *J*=7.2 Hz, 2CH_3), 2.72 (2H, q, *J*=7.8 Hz, CH_2), 4.22 and 4.25 (4H, 2q, *J*=7.2 Hz, 2CH_2O), 4.88 (2H, m, CH_2O), 5.35 (1H, m, CH); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ = 11.16 (CH_3), 13.07 and 13.10 (2CH_3 ester), 18.65 (CH_2), 59.25 and 59.98 (2OCH_2 ester), 77.98 (OCH_2)- 84.56 (CH), 121.50 (=^{13}C-C=O), 157.87 (^{13}C=C-C=O), 161.38 (CH-^{13}C=O), 169.60 (C=C-^{13}C=O). MS (*m/z*, %) : 242 (M^{+}, 2), 169 (M^{+}-CO_2Et, 100), 155 (169-CH_2, 32), 141 (155-CH_2, 55), 95 (169-HCO_2Et, 32). Anal. Calcd. for $C_{12}H_{18}O_5$ (242.27) : C, 59.49; H, 7.49%. Found: C, 59.2; H, 7.1%.

Di-t-butyl 2,5-dihydro-4-ethylfuran-2,3-dicarboxylate (3f)

Light yellow oil, 0.45 g, 76%. IR (neat) ($\nu_{max,}$ cm^{-1}) : 1736 and 1708 (C=O), 1655 (C=C). ^{1}H NMR (90 Mhz, $CDCl_3$): δ = 1.16 (3H, t, *J*=7.8 Hz, CH_3), 1.47 and 1.49 (18H, 2s, 2CMe_3), 2.72 (2H, q, *J*=7.8 Hz, CH_2), 4.84 (2H, m, CH_2O), 5.18 (1H, m, CH); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ = 12.30 (CH_3), 19.51 (CH_2), 27.93 and 28.14 (6CH_3 of 2CMe_3), 78.96 (CH_2O), 81.12 and 81.20 (2C of 2CMe_3), 86.82 (CH), 124.08 (=^{13}C-C=O), 157.35 (^{13}C=C-C=O), 161.91 (CH-^{13}C=O), 169.93 (=C-^{13}C=O). MS (*m/z*, %) : 298 (M^{+}, 2), 197 (M^{+}-CO_2CMe_3, 40), 183 (197-CH_2, 30), 141 (197-H_2C=CMe_2, 100), 95 (197-HCO_2CMe_3, 20). Anal. Calcd. for $C_{16}H_{26}O_5$ (298.38) : C, 64.41; H, 8.78%. Found: C, 63.8; H, 8.5%.

Dimethyl 2,5-dihydro-5,5-dimethyl-4-phenylfuran-2,3-dicarboxylate (3g)

Colorless crystals, 0.46 g, 79%. Mp 89-90° C (ether). IR (KBr) ($\nu_{max,}$ cm^{-1}) : 1738 and 1708 (C=O), 1668 (C=C). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.38 and 1.46 (6H, 2s, 2CH_3), 3.55 and 3.80 (6H, 2s, 2OCH_3), 5.52 (1H, s, CH), 7.1-7.7 (5H, m, C_6H_5); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ = 26.96 and 27.10 (2CH_3), 51.47 and 52.37 (2OCH_3), 82.50 (CH), 92.93 (^{13}CMe_2), 124.44 (=^{13}C-C=O), 127.62 and 128.07 (*ortho-* and *meta-* CH), 128.31 (*para-* CH), 133.03 (*ipso-* C), 159.58 (=^{13}C-Ph), 162.39 (=C-^{13}C=O), 171.11 (CH-^{13}C=O). MS (*m/z*, %) : 290 (M^{+}, 6), 231 (M^{+}-CO_2Me, 100), 199 (231-MeOH, 62), 171 (231-HCO_2Me, 68). Anal. Calcd. for $C_{16}H_{18}O_5$ (290.30) : C, 66.19; H, 6.25%. Found: C, 66.1; H, 6.2%.

Diethyl 2,5-dihydro-5,5-dimethyl-4-phenylfuran-2,3-dicarboxylate (3h)

Light-yellow oil, 0.49 g, 77%. IR (neat) ($\nu_{max,}$ cm^{-1}) : 1738 and 1707 (C=O), 1663 (C=C). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.00 and 1.31 (6H, 2t, *J*=7.2 Hz, 2CH_3), 1.39 and 1.48 (6H, 2s, 2CH_3), 4.00 (2H, ABX_3 system, OCH_2), 4.26 (2H, q, *J*=7.2 Hz, OCH_2), 5.51 (1H, s, CH), 7.1-7.6 (5H, m, C_6H_5); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ = 13.64 and 14.09 (2CH_3), 26.88 and 27.04 (2CH_3), 60.31 and 61.20 (2OCH_2), 82.74 (CH), 92.80 (^{13}CMe_2), 125.01 (=^{13}C-C=O), 127.70 and 127.94 (*ortho-* and *meta-* CH), 128.19 (*para-* CH), 133.32 (*ipso-*

C), 159.14 (=^{13}C-Ph), 162.27 (=C-^{13}C=O), 170.58 (CH-^{13}C=O). MS (*m/z*, %) : 318 (M^+, 3), 245 (M^+-CO_2Et, 100), 199 (245-EtOH, 82), 171 (245-HCO_2Et, 86). Anal. Calcd. for $C_{18}H_{22}O_5$ (318.36) : C, 67.90; H,6.97%. Found: C, 67.7; H, 6.8%.

Di-t-butyl 2,5-dihydro-5,5-dimethyl-4-phenylfuran-2,3-dicarboxylate (3i)

Light-yellow solid, 0.56 g, 75%. Mp 41° C (ether). IR (KBr) (ν_{max}, cm^{-1}) : 1734 and 1701 (C=O), 1659 (C=C). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.20 (9H, s, CMe_3), 1.36 and 1.44 (6H, 2s, $2CH_3$), 1.51 (9H, s, CMe_3), 5.32 (1H, s, CH), 7.0-7.5 (5H, m, C_6H_5); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ = 27.00 (CH_3), 27.65 ($3CH_3$ of CMe_3) , 27.89 (CH_3), 28.00 ($3CH_3$ of CMe_3), 80.87 and 81.20 (2^{13}CMe$_3$), 83.93 (CH), 92.48 (^{13}CMe$_2$), 126.76 (=^{13}C-C=O), 127.70 and 127.86 (*ortho-* and *meta-* CH), 127.95 (*para-* CH), 133.93 (*ipso-* C), 157.22 (=^{13}C-Ph), 161.70 (=C-^{13}C=O), 169.72 (CH-^{13}C=O). MS (*m/z*, %) : 375 (MH^+,1), 273 (M^+-CO_2CMe_3, 76), 217 (273-H_2C=CMe_2, 100), 199 (273-Me_3COH, 55), 171 (273-HCO_2CMe_3, 62). Anal. Calcd. for $C_{22}H_{30}O_5$ (374.46) : C, 70.56; H, 8.08%. Found: C, 70.4; H, 8.0%.

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