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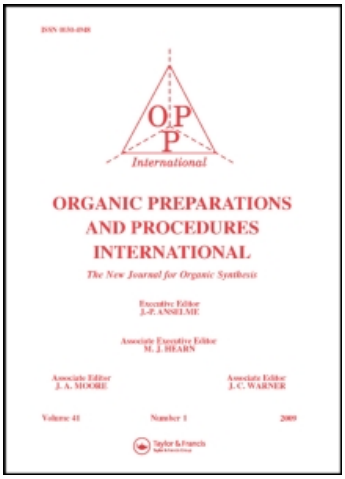


**Organic Preparations and Procedures International**
Publication details, including instructions for authors and subscription information:
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# SYNTHESIS OF DIETHYL 3-ARYL-3-OXOPROPYLPHOSPHONATES

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**To cite this Article** Yu, Jen-Wen and Huang, Steve K.(1997) 'SYNTHESIS OF DIETHYL 3-ARYL-3-OXOPROPYLPHOSPHONATES', Organic Preparations and Procedures International, 29: 2, 214 — 218
**To link to this Article: DOI:** 10.1080/00304949709355187
**URL:** http://dx.doi.org/10.1080/00304949709355187

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## SYNTHESIS OF DIETHYL 3-ARYL-3-OXOPROPYLPHOSPHONATES

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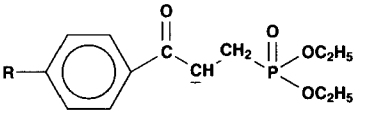
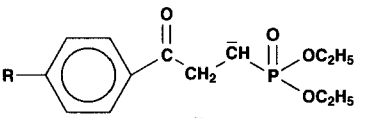
γ-Ketophosphonate **2** provides dual sites[1] for reaction with base, either with the formation of **A** or **B**.[2] Since *p*-substituents on the phenyl group may affect the stability of the enolate ion and thus




**A**

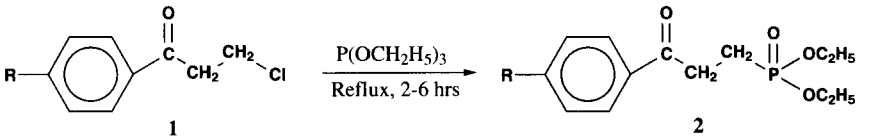



**B**

be important with the formation of **B** in competitive reactions, we sought a better route to prepare some of γ-ketophosphonates. A series of γ-ketophosphonates **2** containing some phenyl derivatives has been prepared in low to moderate yields from the Mannich reaction of the 1-diethylamino-3-aryl-propan-3-one hydrochloride or methiodide with triethyl phosphite (TEP).[3] Previous procedures require multiple steps with expensive reagents. For example, the addition of methyl iodide to form the quaternary salt of a Mannich intermediate and followed by reaction with TEP gave γ-ketophosphonates **2** in low yields.[3a] Furthermore the crude product required further purification. The parent compound (**2a**, R = H) was prepared (73%) by the reaction of **1a** with TEP in diglyme after prolonged reflux (15 hrs).[4] Other procedures for the related alkyl γ-ketophosphonates utilized the Michael addition of TEP to the α,β-unsaturated ketones in alcohol[5] or with a dialkylphosphite in alkoxide solution.[6] Another route involved the condensation of the haloethyl ketones with sodium dialkylphosphite.[7] One alkylation of α-copper(I) alkanephosphonates with dihalopropenes for γ-ketophosphonates was also reported.[8]

We now report the formation of *p*-substituted phenyl γ-ketophosphonates **2** *via* the Arbuzov reaction in excellent yields by simple reflux in TEP as reagent and solvent with the corresponding β-chloroethyl ketones **1** (Tables 1 and 2). The progress of the reaction was monitored by g.l.c. and the

reaction was complete as shown by the disappearance of **1**.




1 2

The phosphonates **2** were identified by $^{1}H$-, $^{13}C$-, $^{31}P$-NMR, IR, MS and elemental analyses. The characteristic peak of the -$C\underline{H}_2$-P(=O) group of **2** shows a chemical shift at 1.95-2.10 ppm with a coupling constant ($J_{PCH}$) of 17-18 Hz in the $^{1}H$ NMR spectrum (Table 3). A $^{13}C$ signal at 19.3-19.7 ppm had a large coupling constant ($J_{PC}$) of 144-145 Hz (Table 4). These data were matched in the

**TABLE 1.** Preparation of β-Chloroethyl Ketones 1

| R | Yield (%) | mp (°C) | | Recrystallization solvent |
|---|---|---|---|---|
| | | Found | Lit. | |
| H- | 85 | 49-50 | 48[a] | hexane |
| $CH_3$- | 91 | 77-78 | 77[a] | EtOH/$H_2O$ |
| $C_2H_5$- | 84 | 63-64 | 63-64[b] | hexane |
| *n*-$C_3H_7$- | 83 | 52-53 | —— | hexane |
| $CH_3O$- | 88 | 58-59 | —— | EtOH/$H_2O$ |
| Cl- | 89 | 51-52 | 45-47[b] | hexane |
| Br- | 87 | 60-62 | 59-61[c] | hexane |

(a) From ref. 10b. b) From ref. 11a. c) From ref. 11b.

**TABLE 2.** Preparation of γ-Ketophosphonates **2** from β-Chloroethyl Ketones **1** [a]

| R | Reaction time (hrs) | Yield (%) | bp (°C/mmHg) | Mannich reaction[b] | |
|---|---|---|---|---|---|
| | | | | Yield (%) | bp (°/mmHg) |
| H- | 6 | 95[c] | 125-126, 0.003 | 60 | 161-164, 0.04 |
| $CH_3$- | 6 | 96 | 131-132, 0.003 | 43 | 160-165, 0.04 |
| $C_2H_5$- | 6 | 93 | 139-140, 0.005 | —— | —— |
| *n*-$C_3H_7$- | 6 | 90 | 138-139, 0.001 | —— | —— |
| $CH_3O$- | 6 | 89 | 145-146, 0.001 | 50 | 220, 0.04 |
| Cl- | 2 | 92 | 137-139, 0.003 | 32 | 179, 0.03 |
| Br- | 2 | 87 | 142-143, 0.003 | 70 | 180, 0.03 |

a) The reaction was carried out at reflux temperature. b) From ref. 3. c) From ref. 4, yield 73%, $bp_{0.1}$ 172°.

HETCOR spectrum. The $^{31}P$ chemical shift of the phosphonate was in the range of 32.0-32.5 ppm in the $^{31}P$-NMR spectrum. The infrared absorption of the phosphonate **2** shows a very strong peak at 1235 $cm^{-1}$ for P=O stretching and a band at 960-1050 $cm^{-1}$ for P-O-C stretching. The carbonyl group stretching is at 1670-1685 $cm^{-1}$.



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**TABLE 3.** $^1$H NMR Chemical Shifts of γ-Ketophosphonates **2**[a]

| R | P(O)C$\underline{H}_2$- δ, ppm (Hz[b]) | -C$\underline{H}_2$-C(O)- δ, ppm (Hz[c]) | Aromatic Signals | R |
|---|---|---|---|---|
| H- | 2.07 (17.7) | 3.17 (10.7) | 7.32-7.85 (m) | ——— |
| $CH_3$- | 1.95 (17.5) | 3.02 (7.7) | 7.02 (m), 7.63 (m) | 2.16 (d) |
| $C_2H_5$- | 2.02 (17.7) | 3.09 (7.4) | 7.12 (m), 7.73 (m) | 2.53 (q), 1.09 (t) |
| *n*-$C_3H_7$- | 2.10 (17.7) | 3.18 (9.0) | 7.17 (m), 7.80 (m) | 2.55 (t), 1.57 (sex) 0.85 (t) |
| $CH_3O$- | 2.04 (17.7) | 3.10 (9.3) | 6.80 (m), 7.82 (m) | 3.72(s) |
| Cl- | 2.08 (17.8) | 3.16 (10.9) | 7.34 (m), 7.81 (m) | ——— |
| Br- | 2.10 (17.8) | 3.17 (11.9) | 7.52 (m), 7.75 (m) | ——— |

a) Spectra were registered in $CDCl_3$ at room temperature TMS δ, ppm = 0. b) Coupling constant of $J_{PCH}$. c) Coupling constant of $J_{PCCH}$.

## EXPERIMENTAL SECTION

Commercially available chemicals of reagent grade were used. The triethyl phosphite was distilled from sodium before use.[9] 3-Chloropropionyl chloride was purchased from Janssen Chemical Co. All solvents and aromatic compounds were purified and checked by g.l.c. before use. G.l.c. analyses were performed with a Varian 3700 chromatograph with a flame ionization detector using a capillary column, Supelco SPB-5. A column temperature of 80-200° was programmed with nitrogen as the carrier gas. Melting points were determined on MEL-TEMP and were uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AM-300WB spectrometer in deuteriochloroform using tetramethylsilane as the standard for proton spectra and the solvent signals as the standard for carbon spectra. $^{31}$P NMR spectra were also recorded on a Bruker AM-300WB spectrometer using 85% $H_3PO_4$ as the standard. Infrared spectra were measured with a Jasco IR-700 Spectrometer. Mass spectra were obtained from a VG Trio-2000 instrument with EI mode at 70 ev. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer.

**General Procedure for Preparation of β-Chloropropiophenone Derivatives (1)**[10].- In a 100-mL, two-necked flask fitted with a magnetic stirrer were placed 7.8 g (0.1 mole) of benzene (or monosubstituted aromatic compounds) and 16 g (0.12 mole) of $AlCl_3$ in 50 mL of dry $CS_2$ (CAUTION! Hood). While the mixture was stirred at 5-35°, depending on the aromatic compounds, 12.7 g (0.1 mole) of 3-chloropropionyl chloride in 25 mL of $CS_2$ was added dropwise. After stirring for 3 hrs, the mixture was decomposed with an ice-cold 10% HCl solution and the mixture was extracted with ether. The ethereal extract was washed with water, 10% sodium carbonate solution, again with water and then dried over anhydrous magnesium sulfate. The ether and $CS_2$ were removed at reduced pressure on a rotary evaporator. The solid residue was recrystallized from hexane and/or EtOH/$H_2O$ to give the products listed in Table 1.

**Preparation of γ-Ketophosphonates (2).**- A mixture of 0.025 mole of a substituted phenyl β-chloroethyl ketone **1** and 20 mL (excess) of triethyl phosphite (TEP) in a 50-mL, round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was refluxed for 2-6 hrs. After the



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excess TEP was distilled off, the brown residue was then subjected to fractional distillation *in vacuo* to afford an oil. The yields and spectral data of the products are summarized in Tables 2-5.

**TABLE 4.** $^{13}C$ NMR Spectra [a] of γ-Ketophosphonates **2**

| R | P<u>C</u>H$_2$ (Hz)[b] | -<u>C</u>H$_2$- (Hz)[c] | <u>C</u>O (Hz)[d] | Aromatic Signals[e] C1 | C2 | C3 | C4 | R |
|---|---|---|---|---|---|---|---|---|
| H- | 19.5 (145) | 31.5 (3) | 197.1 (15) | 136.1 | 128.4 | 127.8 | 133.1 | —— |
| $CH_3$- | 19.3 (145) | 31.0 (-) | 196.3 (15) | 133.4 | 128.8 | 127.6 | 143.5 | 21.0 |
| $C_2H_5$- | 19.5 (144) | 31.2 (3) | 196.6 (15) | 133.7 | 127.8 | 127.9 | 149.9 | 28.5, 14.8 |
| *n*-$C_3H_7$- | 19.7 (144) | 31.3 (3) | 196.8 (15) | 133.9 | 128.6 | 128.0 | 148.6 | 37.8, 24.0, 13.5 |
| $CH_3O$- | 19.6 (145) | 30.9 (-) | 195.4 (16) | 129.2 | 129.9 | 113.5 | 163.4 | 55.1 |
| Cl- | 19.6 (145) | 31.6 (3) | 196.0 (15) | 134.5 | 129.3 | 128.8 | 139.6 | —— |
| Br- | 19.6 (145) | 31.6 (3) | 196.3 (16) | 134.9 | 129.4 | 131.9 | 128.4 | —— |

a) Spectra were registered in $CDCl_3$ at room temperature. b) $J_{P\text{-}C}$. c) $J_{P\text{-}C\text{-}C}$. d) $J_{P\text{-}C\text{-}C\text{-}C}$. e) Aromatic signals are given as structure indicated below.

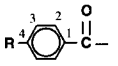


**TABLE 5.** Elemental Analyses and Mass Data of γ-Ketophosphonates **2**

| R | Elemental Analysis (Found) C | H | Mass spectrum (m/e) $M^+$ | Base peak |
|---|---|---|---|---|
| H- | 57.77 (57.54) | 7.09 (7.04) | 270 | 105 |
| $CH_3$- | 59.19 (59.18) | 7.45 (7.19) | 284 | 119 |
| $C_2H_5$- | 60.39 (60.10) | 7.77 (7.85) | 298 | 133 |
| *n*-$C_3H_7$- | 61.53 (61.30) | 8.07 (8.22) | 312 | 147 |
| $CH_3O$- | 56.00 (55.83) | 7.05 (7.15) | 300 | 135 |
| Cl- | 51.24 (51.42) | 5.95 (5.81) | 304 | 139 |
| Br- | 44.72 (44.39) | 5.20 (5.06) | 348 | 183 |

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## ASYMMETRIC SYNTHESIS OF (R)-N-(*t*-BUTOXYCARBONYL)-4-CYANOPHENYLALANINE METHYL ESTER

*Submitted by* (04/23/96)

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The unnatural amino acid (R)-4-cyanophenylalanine is an important precursor of a number of pharmacologically active substances.[1] Recently, detailed procedures have been reported for the preparation of both the (R)-4-cyanophenylalanine and its N-benzoyl derivative using either an enantioselective enzymatic hydrolysis of the racemic 4-cyanophenylalanine ethyl ester[1a] or the enantioselective catalytic hydrogenation of the corresponding N-benzoyl dehydro amino acid respectively.[2] We report here an alternative procedure for the preparation of the (R)-N-(*t*-butoxycarbonyl)-4-cyanophenylalanine methyl ester (**4**) *via* the asymmetric synthesis using the commercially available[3] chiral auxyliary **1**. Full spectroscopic and analytical characterizations for both compound **4** and the heterocyclic intermediates **2** are also reported.

Alkylation of the *bis*-lactim ether **1** with 4-cyanobenzyl bromide, under the conditions reported by Schollkopf *et al.*,[4] gave intermediate **2** in 62% yield as a single diastereoisomer. Hydrolysis