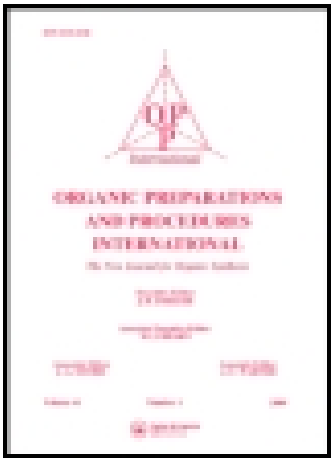

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SYNTHESIS OF DIETHYL 3-ARYL-3-OXOPROPYLPHOSPHONATES

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SYNTHESIS OF DIETHYL 3-ARYL-3-OXOPROPYLPHOSPHONATES

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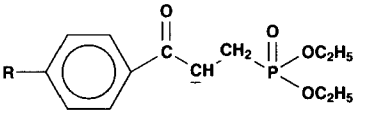
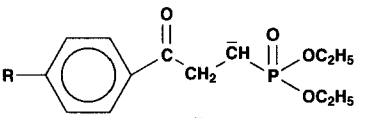
γ-Ketophosphonate **2** provides dual sites[1] for reaction with base, either with the formation of **A** or **B**.[2] Since *p*-substituents on the phenyl group may affect the stability of the enolate ion and thus



A

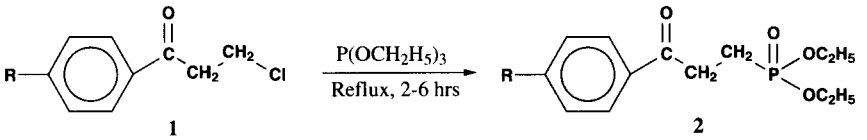


B

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}.

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

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.

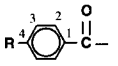


TABLE 5. Elemental Analyses and Mass Data of γ-Ketophosphonates **2**

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) Angelo Pecunioso*, Damiano Papini, Bruno Tamburini, Francesco Tinazzi

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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