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Electrosynthesis of α-Arylated β-Substituted Cyclopropylphosphonates. Synthesis of a Phosphonic Analogue of Minalcipran

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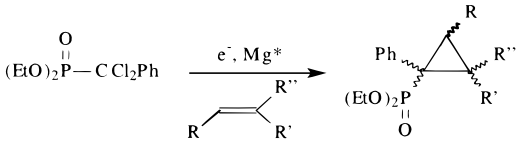
ABSTRACT



The synthesis of α-arylated β-substituted cyclopropylphosphonates was efficiently achieved by electroreduction of diethyl α,α-dichlorobenzylphosphonate in the presence of Michael acceptors in a one-compartment cell equipped with a magnesium sacrificial anode.

Cyclopropane derivatives play an important role in bioorganic[1] and synthetic chemistry.[2] Furthermore, cyclopropyl amino acids function as conformationally constrained amino acid analogues[3] and provide mechanistic probes to determine reaction pathways.[4] Moreover, some phosphonic acids exhibit important biological properties because of their similarity to phosphates.[5] The carbon−phosphorus bond in phosphonates unlike the carbon−oxygen one in phosphates is not susceptible to the hydrolytic action of phosphatases, thereby imparting them higher stability under physiological conditions.

Therefore, it is not surprising that cyclopropylphosphonate derivatives have been a focus of interest for chemists. α-Arylated cyclopropylphosphonates constitute a specific class of such compounds, and several synthetic methods have been investigated for this purpose. The compounds are generally obtained by photochemical decomposition of α-benzyl diazophosphonates to generate the corresponding carbene which was trapped by an alkene,[6] by photoinduced fragmentation and rearrangement of phenyl-substituted epoxyethyl phosphonates,[7] or by the generation of an α-benzyl phosphonate carbanion and reaction with 1,2-dibromoethane.[8]

Finally, a new synthesis of α-benzyl β-hydroxymethyl cyclopropylphosphonates was recently reported by Oh[9] via an epoxide opening reaction of γ,δ-epoxyalkylphosphonates.

Electrochemical techniques are widely used for promoting all kinds of cyclization, and we have recently reported the synthesis of α-chlorinated[10] and α-fluorinated[11] cyclopro-

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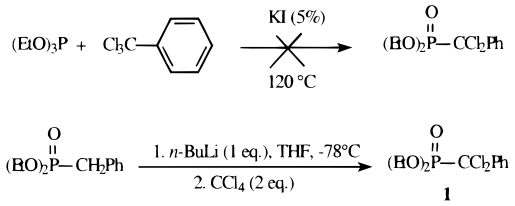
pylphosphonates from α-polyhalogenated phosphonates and Michael acceptors. We therefore became interested in the electrosynthesis of α-arylated *β*-substituted cyclopropylphosphonates from diethyl α,α-dichlorobenzylphosphonate **1**.

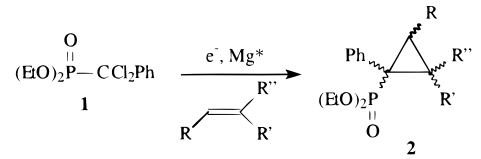
The synthesis of **1** has already been reported by Kukhar[12] via an Arbuzov reaction, but in our hands we were unable to obtain the expected phosphonate. The monochlorination of diethyl benzylphosphonate[13] has been reported; however, using a modified protocol we were able to obtain the dichlorinated phosphonate **1** in 70% yield (Scheme 1).

Scheme 1. Synthesis of Diethyl α,α-Dichlorobenzylphosphonate **1**



Electroreductions[14] of **1**, in a DMF medium, between a carbon−felt cathode and a sacrificial anode in a one-compartment cell at ambient temperature, performed in the presence of 5 equiv of Michael acceptors (Scheme 2),

Scheme 2. Electrosynthesis of Diethyl α-Arylated *β*-Sustituted Cyclopropylphosphonates **2**



2a: R= R'= H, R"= CO_2Me
2b: R= R'= H, R"= $CO_2{}^tBu$
2c: R= R'= H, R"= CN
2d: R= H, R'= CH_3, R"= CO_2Me
2e: R= H, R'= CH_3, R"= CN
2f: R= CH_3, R'= H, R"= CO_2Et

afforded diethyl α-arylated *β*-sustituted cyclopropylphosphonates **2** in moderate to good isolated yields (Table 1). Using less than 5 equiv, we always detected the formation of diethyl α-chlorobenzylphosphonate (^{31}P NMR ($CDCl_3$): δ = 18.5 ppm). In most cases (entries 1, 2, 4, and 5), the cyclopropanation occurred quickly, within 2 h 30 min. With the magnesium anode, the previously described activation phenomenon[10,11] occurred with beneficial consequences. For example, the quantity of electricity consumed was decreased because of a lowering of the electrolysis duration [in this case 2 h 30 min instead of 3 h 10 min (6 mmol of **1**) for the theoretical bielectronic electrochemical reduction of **1**].

Table 1. Diethyl α-Arylated *β*-Substituted Cyclopropylphosphonates **2**

entry	product	yield (%)[a] [evaluated yield (%)[b]]	% de[c]
1	**2a**	55 [80]	40
2	**2b**	60 [100]	70
3	**2c**	− [45]	4
4	**2d**	64 [100]	>98
5	**2e**	73 [100]	40
6	**2f**	− [67]	4

[a] Yield of isolated, purified product. [b] Determined by ^{31}P NMR at the end of the electrolysis. [c] Of the crude product by ^{31}P NMR.

The diastereoselectivity observed during the reaction was largely dependent on the Michael acceptor used (Table 1). For example, electrolysis with *tert*-butyl acrylate (entry 2) instead of methyl acrylate (entry 1) enhanced the diastereoselection while methyl methacrylate (entry 4) provided a single diastereoisomer.

When acrylonitrile was used as Michael acceptor (entry 3), we were unable to obtain pure cyclopropylphosphonate **2c**. Even after we have engaged 2 F·mol^{-1} of **1**, we still observed in the ^{31}P NMR spectrum the presence of **1**. This phenomenon is probably due to the concomitant reduction of acrylonitile. Using a 1,2-disubstituted olefinic acceptor (entry 6), the cyclopropanation occurred, but several byproducts were detected and we were unable to obtain the pure compound **2f**.

The relative configuration of α-arylated *β*-substituted cyclopropylphosphonates **2** was elucidated by measuring $^3J_{CP}$ coupling constants in the ^{13}C NMR spectra of stereoisomers as mixtures. As has been previously reported,[15] $^3J_{CP}$(*cis)* coupling constants are higher than $^3J_{CP}$(*trans)* in cyclopropylphosphonates (Figure 1).

In each case, the major diastereoisomer obtained was the *cis* one. The preferred relative configuration might be explained by considering the mechanistic scheme usually accepted for such cyclopropanation process,[16] which involves a Michael addition followed by a ring closure.

We next turned our attention toward the synthesis of a phosphonic analogue of Minalcipran. (±)-(*Z*)-2-Aminomethyl-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide **3** [Minalcipran, Ixel], used in the racemic form, is a clinically efficient antidepressant due to competitive inhibition of the re-uptake of serotonin (5-HT) and noradrenaline in the

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(14) **Typical Procedure for the Electrosynthesis of 2e**: In a one-compartment cell, equipped with a carbon felt cathode (S = 16 cm^2) and a magnesium anode, a solution of diethyl α,α-dichlorobenzylphosphonate **1** (1.8 g, 6 mmol) and methacrylonitrile (2 g, 30 mmol, 5 equiv) in DMF (35 mL) containing Et_4NBr (0.02 mol·L^{-1}) was introduced. A 100 mA constant current was applied. The electrolysis was continued until **1** was completely consumed (monitored by ^{31}P NMR spectroscopy). The reaction mixture was poured into THF (80 mL) and then acidified with 1 N HCl (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with 1 N HCl (2 × 50 mL) and dried. The solvents were evaporated in vacuo to give **2e**. Further purification on silica gel (CH_2Cl_2/CH_3OH 98/2) gave pure **2e** (1.28 g, yield 73%).
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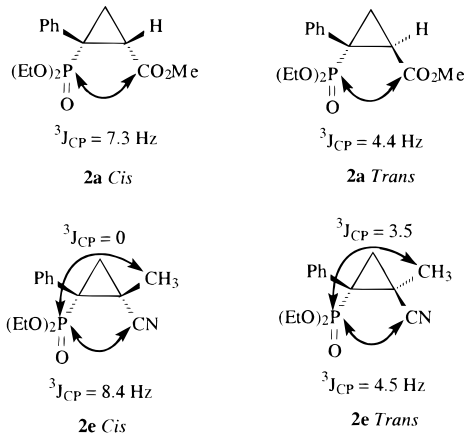
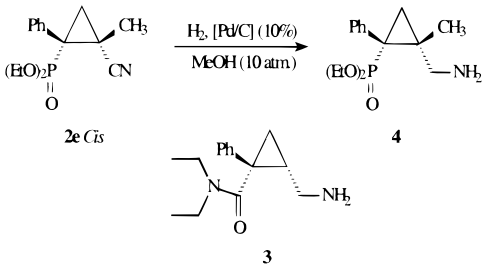


Figure 1. $^3J_{CP}$(*cis*) and $^3J_{CP}$(*trans*) coupling constants for **2a** and **2e**.

CNS.[17] This compound, after slight structural modifications, has also been recently reported as a new class of noncompetitive NMDA receptor antagonist.[18] As cyclopropylphosphonate **2c** could not be obtained in a pure form, we have developed a synthesis of compound **4** from **2e** *cis*, structurally related to the phosphonic analogue of Minalcipran. The **2e** isomers were separated after purification by silica gel column chromatography (eluent: CH_2Cl_2/CH_3OH 98/2), and we obtained the pure *cis* isomer of cyclopropylphosphonate **2e**. Several agents for the reduction of the nitrile moiety were investigated: using lithium aluminum hydride we mainly observed the dephosphonylation process while a solution of borane in THF gave the expected product in low yield (27%). Finally, reduction with dihydrogen under pressure led to the (±) γ-amino cyclopropylphosphonate **4** in good yield (70%) (Scheme 3).

Scheme 3. Synthesis of Phosphonic Analogue of Minalcipran **4**



In conclusion, we have developed a new and efficient synthesis of α-arylated β-substituted cyclopropylphosphonates from diethyl α,α-dichlorobenzylphosphonate.

Using methacrylonitrile during the electrosynthesis, we could obtain the phosphonic analogue **4** of Minalcipran in good yield. Synthetic transformations of such α-arylated β-substituted cyclopropylphosphonates and asymmetric electrosynthesis of such compounds are under study within our laboratory and will be reported in due course.

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Supporting Information Available: Characterization data and NMR for **1**, **2**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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