Pergamon

Tetrahedron Letters, Vol. 37, No. 21, pp. 3679-3682, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00597-7

One-Pot and Efficient Electrosynthesis of Cycloalkylphosphonates from Diisopropyl Trichloromethylphosphonate using Magnesium Electrochemical Activation

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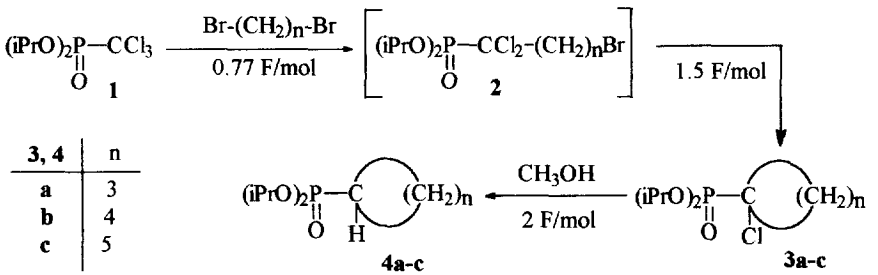
Abstract : Various diisopropyl cycloalkylphosphonates were easily prepared in an one-pot sequence under mild conditions, by electrolysing diisopropyl trichloromethylphosphonate in the presence of ω,ω-dibromoalkanes. The use of an electrochemical activated magnesium anode significantly improved the rate and the yield of the two first steps of the reaction.

Owing to their biological properties, many phosphonate derivatives have found applications in the fields of pharmaceuticals and agrochemicals.[1-3] Unexpectedly, the presence of a cyclic residue within the structure of some of these compounds seems to be related with their specific activity.[4,5] α-Functional cycloalkylphosphonates are easily available either by P-C bond formation between a nucleophilic P^{III} reagent and a suitable cyclic electrophilic substrate[6-9], or by cycloalkylation of an activated α-functional phosphonate.[10-13] By contrast, unsubstituted cycloalkylphosphonates are synthetized with moderate yields[14], under forcing conditions[15] and by time consuming or specific methods.[16-17] We recently developped an efficient two-step synthesis of various diisopropyl and diethyl cycloalkylphosphonates via the corresponding α-trimethylsilylated derivatives.[18]

Although electrochemical technics are widely used for promoting all kinds of cyclization processes[19-20], up to day, no example of such reaction was described in the phosphonate series. In recent papers[21], we described a phenomenon we called "electrochemical activation of magnesium", which improves the electrosynthesis of gem-difluoroalkenes or of diisopropyl 1,1-dichloroalkylphosphonates.
We decided to extend the scope of applicability of this phenomenon and we report now, within this context, an one-pot and efficient electrochemical synthesis of various diisopropyl α-chlorocycloalkylphosphonates **3** and diisopropyl cycloalkylphosphonates **4** from the readily available[22] diisopropyl trichloromethylphosphonate **1** (Scheme).

Results and discussion. Electroreductions of **1**, in DMF medium, between a carbon felt cathode and a magnesium sacrificial anode in a not cooled one-compartment cell, realized in the presence of 1.2 equivalents of ω,ω-dibromoalkanes, afforded phosphonates **2**, which were not isolated and whose formation was monitored by ^{31}P NMR spectroscopy (δ (DMF) varying from 8 to 9 ppm). During this first step of electrosynthesis, the electrochemical magnesium activation process took place as it has been previously described.[21] The autoregulated temperature (≈ 35 °C) was higher than that (≈ 24 °C, with an aluminium anode for example), reached by using others anodes. The exothermicity of the chemical reduction on the magnesium rod activated on its surface by the anodic process (Grignard type reaction) may account for such a difference. The major result was that the complete reduction of **1** was faster than a

bielectronic electrochemical reduction. For instance, for an electrolysis realized with 22 mmol of diisopropyl trichloromethylphosphonate **1**, using a 150 mA imposed current intensity, the theoritical time for the corresponding bielectronic process was about 7h50. In our experiment[23], conversion of phosphonate **1** into phosphonate **2** was complete after 3h (corresponding to 0.77 F/mol of **1**). The cyclization of phosphonate **2** into α-chlorocycloalkylphosphonate **3** was achieved by continuing the electrolysis. During this second step of the electrosynthesis, the magnesium activation took place again but for a moderate part: we engaged about 1.5 F/mol of **1** proving that a small part of phosphonate **2** was chemically reduced by the activated magnesium rod.



Scheme

Diisopropyl α-chlorocycloalkylphosphonates **3** were obtained with very good electrosynthesis yields (≈ 90%) and with good isolated yields (Table 1). Diisopropyl dichloromethylphosphonate (^{31}P NMR : δ(DMF) = 7.2 ppm) and diisopropyl ω-bromo-1-chloroalkylphosphonate (^{31}P NMR : δ(DMF) = 15 to 16 ppm) were detected as impurities in the crude product.

Table 1 : Electrosynthesis of diisopropyl cycloalkylphosphonates **3** and **4**.

Entry	Yield (%)[(a)] in **3** (Electrolysis yield (%) in **3**)[(b)]	Yield (%)[(c)] in **4** (Electrolysis yield (%) in **4**)[(d)]	^{31}P NMR ($CDCl_3$) δ in ppm	
			3	**4**
a	64 (87)	52 (73)	17.0	28.1
b	72 (90)	58 (78)	18.3	31.5
c	65 (85)	50 (73)	17.8	28.9

(a) Isolated yield. Product characterized by ^{1}H, ^{13}C, ^{31}P NMR and mass spectroscopies. (b) Determined by ^{31}P NMR spectroscopy on the crude product obtained at the end of electrolysis.[23] (c) Overall isolated yield starting from **1**. Product characterized by ^{1}H, ^{13}C, ^{31}P NMR and mass spectroscopies. (d) Overall electrolysis yield starting from **1** determined by ^{31}P NMR spectroscopy on the crude product obtained at the end of the electrolysis.[24]

Moreover an electrolysis performed with 1,4-dichlorobutane allowed us to synthetize phosphonate **3b** in 54 % yield. On the other hand, electrolysis realized with 1,2-dichloroethane or 1,6-dibromohexane failed. In these cases, diisopropyl dichloromethylphosphonate (^{31}P NMR : δ (DMF) = 7.2 ppm) and phosphates (^{31}P NMR : δ(DMF) = 0 to 2 ppm) were obtained as the sole products of the reaction.

For the electrosynthesis of diisopropyl cycloalkylphosphonates **4**[24], the two first steps are the same as above. When the electrosynthesis of the phosphonate **3** was completed, 3 mL of methanol were introduced in the reaction mixture and the electrolysis was pursued until the complete consumption of **3**. During this third step, we did not observe any direct chemical reduction of **3** by the magnesium rod, and the duration (≈ 7h under our conditions) agrees with a bielectronic reduction process (2 F/mol); we noted, on the magnesium anode, an hydrogen evolution resulting from the reaction of methanol with activated magnesium sites of the surface of the anode. The overall electrolysis yield in **4** from **1** (73% to 78%) (Table 1) indicates an electrolysis yield for the third step of the reduction in the order of 90%. Finally the diisopropyl cycloalkylphosphonates **4**, isolated after acidic treatement and purified by distillation, were obtained from **1**, in a one-pot operation, with an overall good yield (Table 1).

In conclusion, we describe an efficient one-pot electrosynthesis of diisopropyl α-chlorocycloalkylphosphonates as well as diisopropyl cycloalkylphosphonates from readily available disopropyl trichloromethylphosphonate, under mild conditions and with benefit of the magnesium electrochemical activation phenomenon.

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23. *Electrosynthesis of Diisopropyl α-chlorocyclopentylphosphonate 3b:* In a one-compartment cell, equiped with a carbon felt cathode (S = 25 cm^2) and a magnesium rod as anode (immersion height 5 cm), a solution of diisopropyl trichloromethylphosphonate **1** (6.24 g, 22 mmol) and of 1,4-dibromobutane (25 mmol) in DMF (70 mL) containing Et_4NBr (0.02 $mol.L^{-1}$) was intoduced. A 150 mA constant current was applied. The complete formation of phosphonate **2** was reached after 3h (monitored by ^{31}P NMR spectroscopy). The electrolysis was pursued until the complete consumption of phosphonate **2**. The reaction mixture was poured in THF (80 mL), then hydrolyzed by 1N HCl (100 mL) and extracted with ether (3 x 50 mL). The organic layers were washed with 1N HCl (2 x 50 mL) and dried. The solvents were evaporated in vacuo to give **3b**. Further purification by bulb-to-bulb distillation led to the pure cyclopentylphosphonate **3b** ($bp_{0.6}$ = 118 °C, 72 % yield). ^{31}P NMR ($CDCl_3$) [δppm] : 18.3, s; ^1H NMR ($CDCl_3$, 200 MHz) [δppm, (JHz)]:1.2, t(6), 12H, $(CH_3)_2CHO$; 1.4-2.2, m, 8H, H-ring; 4.7, m, 2H, $(CH_3)_2CHO$; $^{13}C\{^1H\}$ NMR ($CDCl_3$) [δppm, (JHz)] : 23.2, d(12.2), C3 & C4; 23.5, d(5.4), $(CH_3)_2CHO$; 23.8, d(3.7), $(CH_3)_2CHO$; 38.7, d (2.95), C2 & C5; 70.3, d(169.2), C1; 71.5, d(7.2), $(CH_3)_2CHO$).
24. *Electrosynthesis of Diisopropyl cyclopentylphosphonate 4b :* The process is the same as described above for **3b** (except that we introduced only 1.0 eq. of 1,4-dibromobutane), until the complete consumption of **2**, then we introduced 3 mL of methanol in the reaction mixture and the electrolysis was pursued until the complete consumption of **3b**. Usual work-up gave the crude phosphonate **4b**, which was purified by bulb-to-bulb distillation ($bp_{0.4}$ = 100 °C, 58 % yield).
^{31}P NMR ($CDCl_3$) [δppm] : 31.5, s; ^1H NMR ($CDCl_3$, 200 MHz) [δppm, (JHz)] : 1.2,d(6), 12H; $(CH_3)_2CHO$; 1.3-2, m, 9H, H-ring; 4.7, m, 2H, $(CH_3)_2CHO$. $^{13}C\{^1H\}$ NMR ($CDCl_3$) [δppm, (JHz)] : 23.5, 2d(4.7 & 3.2), $(CH_3)_2CHO$; 25.9, d(12), C3 & C4; 26.6, d(2.4), C2 & C5; 35.2, d(148), C1); 69.3, d(6.9), $(CH_3)_2CHO$).

(*Received in France* 11 *March* 1996; *accepted* 27 *March* 1996)