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Cyclopropanation of 1,2-dibromoethylphosphonate: a synthesis of β-aminocyclopropylphosphonic acid and derivatives

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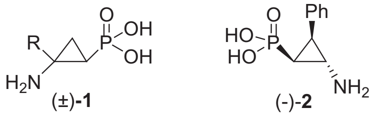
ABSTRACT

Diethyl (1,2-dibromoethyl)phosphonate was found to undergo cyclopropanation with nitromethane in good yield. The resulting *trans* β-nitrocyclopropylphosphonate was converted to the *trans* N-protected aminocyclopropylphosphonate through a reduction–protection sequence. Subsequent hydrolysis gave the free β-aminocyclopropylphosphonic acid without any formation of ring-opening byproduct. Cyclopropanation of 1,2-dibromoethylphosphonates with nitroalkanes and their reduction are also discussed.

Introduction

Aminocyclopropylphosphonic acids and their derivatives have attracted considerable attention due to their interesting synthetic studies and their useful biological activities.[1–3] These molecular structures combine several interesting features: (i) the cyclopropane motif is found in many naturally occurring and biologically active compounds.[4] In addition the cyclopropane ring often acts as a molecular subunit inducing particular biological activities.[5] (ii) There is a long standing interest in phosphonic acids and derivatives as analogs of natural organo-phosphates.[6]

Aminophosphonic acids display promising antibacterial[7] and anti-cancer properties.[8] They are also potent neuromodulators, plant growth regulators, and herbicides.[9] Although, α-aminocyclopropylphosphonic acids (α-ACPPs) have been extensively studied as analogs of natural and non-natural amino acids,[10] β-aminocyclopropylphosphonic acids (β-ACPPs) **1** and derivatives have received less attention. Hanessian and co-workers have reported the first and unique synthesis of the enantiopure β-amino-3-phenylcyclopropylphosphonic acid (−)-**2**, a constrained analog of the GABA$_B$ antagonist (Fig. 1).[11]



(±)-**1** (-)-**2**

Figure 1. β-Aminocyclopropylphosphonic acids.

Their approach is based on a conjugate addition of the chiral chlorophosphonamide anion to α,β-unsaturated esters, followed by a Curtius rearrangement (*path* a). Later, Mikolajczyk and Midura reported the preparation of the other enantiomer (+)-**2** by cyclopropanation of vinylphosphonates with sulfoxonium ylides (*path* b), as key-step, and a subsequent Curtius rearrangement (Fig. 2).[12] Very recently, Charette and co-workers[13] reported a stereoselective synthesis of β-phthalimidocyclopropylphosphonate by rhodium-catalyzed cyclopropanation of alkenes with a diazo compound (*path* c). However, in the latter case no conversion to the free β-aminocyclopropylphosphonic acid **1** is reported. Moreover, synthesis of racemic β-aminocyclopropylbisphosphonate **1** (R = P(O)(OEt)$_2$) was reported by Couthon and co-workers[14] involving a Michael type addition of ethyl 2-bromoacetate on vinylidene-1,1-bisphosphonate (*path* d), followed by an intramolecular cyclization and a Curtius rearrangement (Fig. 2).

This context prompted us to search for an efficient and concise synthesis of β-aminocyclopropylphosphonic acids **1** for which the amino group would be introduced without the use of a Curtius rearrangement. Indeed, to date, most of the reported procedures to access such compounds involve the use of this rearrangement.

Few years ago we reported a short and efficient synthesis of α-ACPPs from cyclopropanone acetals through a Kabachnik–Fields reaction.[15–18] The biological evaluation of these compounds showed some interesting activities as ACC-Oxidase inhibitor.[3]

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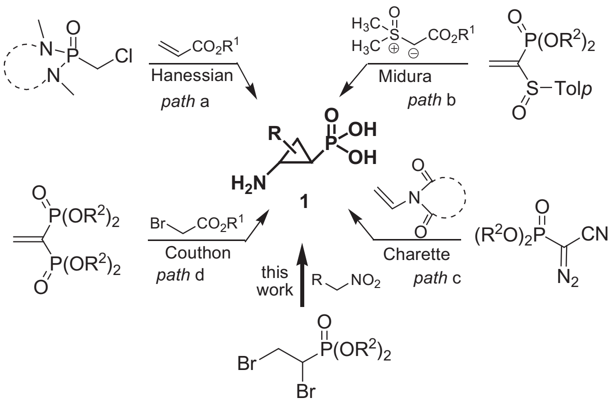
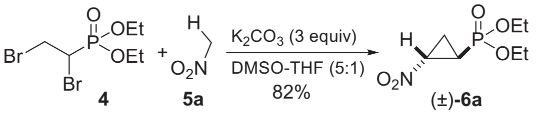


Figure 2. Synthetic routes toward β-aminocyclopropylphosphonic acids.

Table 1
Preparation of nitrocyclopropylphosphonate **6a** from dibromophosphonate **4**[a]

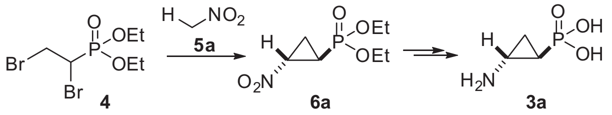


Entry	Time (h)	[c] mol/L	**6a** (yield %)
1	24	1.00	30
2	24	0.20	73
3	20	0.14	81[b]
4	24	0.10	81
5	5	0.14	82[c]

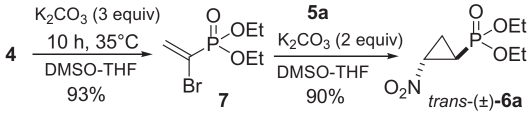
[a] Reaction conditions: dibromo **4**, methane **5a** (1.2 equiv) K_2CO_3 (3 equiv), DMSO–THF (5:1), rt.

[b] Isolated yield for reaction in DMSO.

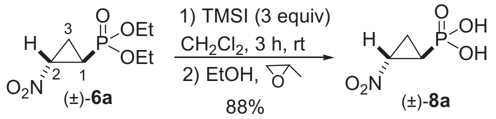
[c] Reaction carried out under sonication.



Scheme 1. Synthetic sequence of β-aminocyclopropylphosphonic acid.



Scheme 2. Formation of **6a** from bromovinylphosphonate **7**.



Scheme 3. Synthesis of nitrocyclopropylphosphonic acid **8a**.

Continuing our efforts in this field we extended our interest to the preparation of heterocyclic α-aminophosphonic acids[19–22] and their incorporation into peptides.[23] In the present work, we now turn our attention to the synthesis of non-substituted β-aminophosphonic acid **1**, which to date remains unknown. Extension to β-alkylated counterparts is also reported. Our approach for the synthesis of the racemic ACPP **3a** is depicted in Scheme 1. The ACPP **3a** would be prepared from the nitrophosphonate **6a** through reduction and hydrolysis. The latter would be obtained from the cyclopropanation[24] of the (1,2-dibromoethyl)phosphonate **4** with nitromethane **5a** (Scheme 1).

Results and discussion

The (1,2-dibromoethyl)phosphonate **4** was easily prepared from the bromination of the commercially available diethyl vinylphosphonate according to the procedure reported by Sainz-Diaz and co-workers.[25]

The one-pot double alkylation was performed at room temperature by a slow addition of nitromethane **5a** to a stirred solution of dibromophosphonate **4** and 3 equiv of potassium carbonate in a mixture of DMSO and THF (5:1), to give the desired nitrocyclopropylphosphonate **6a** in good yields (Table 1, entries 1–4). We observed that when the concentration of the reaction medium was ranging from 0.14 M to 0.10 M, the yield of the reaction was deeply increased (compare entries 3 and 4 to entry 1). In addition under the same conditions, the use of sonication decreased the reaction time from 24 h to 5 h (entry 5, 82% yield). By comparison, similar double alkylation was already reported, under basic conditions starting from 1,2-dibromoethylcarbzoxylate, yielding nitrocyclopropylcarboxylate in only 59% after 48 h.[26] On the other hand, in order to facilitate the work-up procedure for this reaction, we tried to lower the amount of DMSO used, by introducing a co-solvent. We found that in DMSO or in a mixture of DMSO/THF (5:1) the reaction occurred in comparable yields. However, in THF only the vinylphosphonate intermediate **7** was formed.

It is noteworthy that in this reaction the formation of a small amount of diethyl 1-bromovinylphosphonate **7** resulting from the dehydrobromination of dibromophosphonate **4** was always observed. Indeed, treatment of dibromophosphonate **4**, with K_2CO_3 in DMSO–THF in the absence of nitromethane, furnished the bromovinylphosphonate **7** in excellent yield (93%). Then, the latter underwent an attack by nitromethane **5a** through a sequence involving a Michael addition, followed by an intramolecular S_N2 alkylation to form the expected aminophosphonate **6a** in 90% yield (Scheme 2). As a consequence, we postulate that the formation of the vinylphosphonate **7** precedes the possible competitive nucleophilic reaction of nitromethane on the dibromophosphonate **4**. Then the Michael addition of nitromethane to the vinylphosphonate **7** gives the intermediate 1-bromo-3-nitropropylphosphonate, which is not observed. The latter undergoes a fast intramolecular cyclization to provide the nitrocyclopropylphosphonate **6a**.

Next, the hydrolysis of phosphonates **6a** was accomplished by treatment with 3 equiv of a freshly opened bottle of trimethylsilyl iodide in dichloromethane at room temperature,[16] followed by the addition of propylene oxide in ethanol to provide the β-nitrocyclopropylphosphonic acid **8a** in 88% (Scheme 3). It is noteworthy that lowering the amount of TMSI for the reaction, or using instead TMSBr, resulted in the formation of about 10–30% of the monophosphonate intermediate.

Next, we investigated the reduction of the nitro group to the free amine. Precedents in the literature highlighted, during reduction of nitrocyclopropylcarboxylate, the ability of the resulting aminocyclopropylcarboxylate to undergo a ring opening, due to the push–pull effect, leading to γ-aminobutyric acid (GABA).[27–29] Taking into account this phenomena, several mild methods for the reduction of the nitro group to the free amine were investigated. Known reagents such as Zn/AcOH, Zn/HCl_{aq},[30] or $NiCl_2$/$NaBH_4$ did not give satisfactory results: no reaction, many TLC spots, or 5% yield of undesired product **10a** were obtained, respectively. Moreover,