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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]

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).

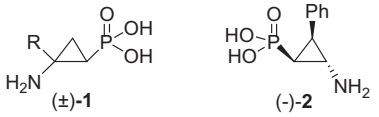

Figure 1. β-Aminocyclopropylphosphonic acids.

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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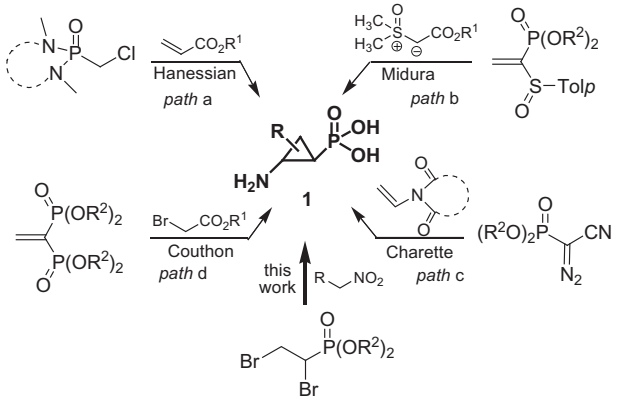
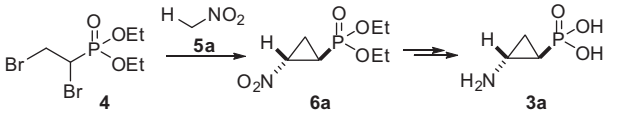


Figure 2. Synthetic routes toward β-aminocyclopropylphosphonic acids.



Scheme 1. Synthetic sequence of β-aminocyclopropylphosphonic acid.

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).

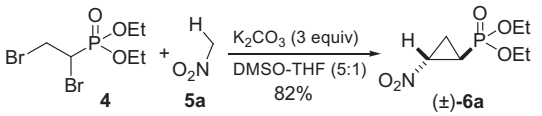
Results and discussion

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.

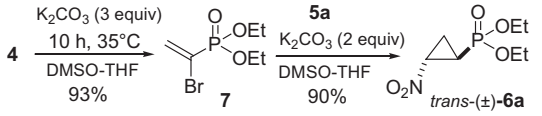
It is noteworthy that in this reaction the formation of a small amount of diethyl 1-bromovinylphosphonate **7** resulting from the dehydrobromination of dibromophosphonate **4** was always

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

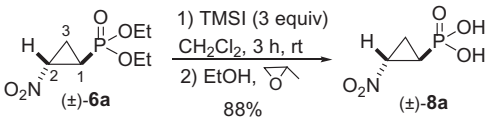


Entry	Time (h)	[c] mol/L	**6a** (yield %)
1	24	1.00	30
2	24	0.20	73
3	20	0.14	81[b]
4	24	0.10	81
5	5	0.14	82[c]

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

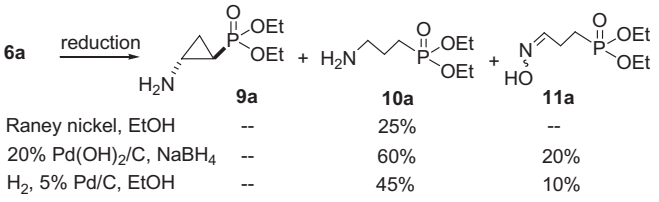


Scheme 3. Synthesis of nitrocyclopropylphosphonic acid **8a**.

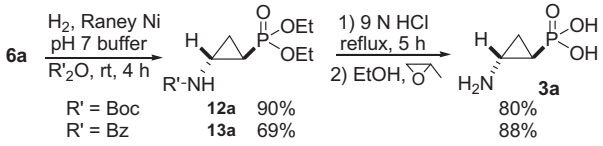
observed. Indeed, treatment of dibromophosphonate **4**, with K_2CO_3 in DMSO–THF in the absence of nitromethane, furnished the bromovinylphosphonate **7** in excellent yield (93%). Then, the latter underwent an attack by nitromethane **5a** through a sequence involving a Michael addition, followed by 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,



Scheme 4. Attempts to reduce the nitro group into free amine.



Scheme 5. Preparation of the free β-aminocyclopropylphosphonic acid **3a**.

reduction over an excess of T-1 Raney nickel in EtOH only afforded 25% of the undesired ring-opening product **10a**.[31–33]

However, reduction over $Pd(OH)_2/C$ with $NaBH_4$[34] furnished 60% yield of ring opening product **10a**, along with a 20% of a mixture of *cis*/*trans* oxime **11a**.[35] Reduction of **6a** under hydrogen with a catalytic amount of 5% Pd/C in EtOH gave roughly the same results. All attempts to prepare the free amine **9a** were unsuccessful (Scheme 4).

On the other hand, to overcome this problem, the nitrophosphonate **6a** was subjected to a one-pot reduction–protection sequence with a catalytic amount of Raney nickel in ethanol under hydrogen atmosphere in the presence of a pH 7 phosphate buffer solution.[36] The free amine hence formed, is in situ protected as a carbamate with the use of 3 equiv of Boc_2O or as an amide with Bz_2O to give *N*-Boc aminophosphonate **12a** or *N*-Bz **13a** in 90% or 69% yields, respectively (Scheme 5). Finally, the acidic hydrolysis of the protected aminophosphonates **12a** and **13a** with 9 N HCl at reflux for 5 h followed by propylene oxide treatment gave the same desired aminophosphonic acid **3a** in good yield. It is noteworthy that, in comparison to their carboxylate counterparts,[27–29] the β-aminocyclopropylphosphonates can be hydrolyzed without any formation of ring-opening products (Scheme 5).

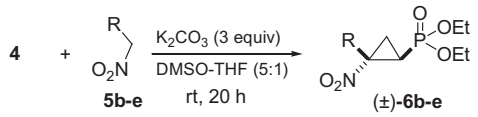
Scope and limitations: The double alkylation of dibromophosphonate **4** was then applied to other nitroalkanes **5b–d** and provided *trans*-nitrophosphonates **6b–d** in good yields (Table 2, entries 1–3). However, it has to be noted that the presence of a free alcohol **5e** inhibits the double alkylation reaction, and does not give the desired product **6e** (entry 4).

Next, the hydrolysis of phosphonates **6b–c** was accomplished by treatment with 3 equiv of trimethylsilyl iodide in dichloromethane at room temperature,[16] followed by the addition of propylene oxide in ethanol to provide the β-nitrocyclopropylphosphonic acids **8b**, and **8c** in 83% and 79%, respectively (Scheme 6).

In contrast, the reduction–protection sequence of **6b** ($R \neq H$) under the same conditions used above (Raney Ni/H_2, Boc_2O, pH 7 phosphate buffer solution) did not yield the expected product **12**, only ketone **14b**[37] was isolated in 75% yield. The latter resulted from the reduction of the nitro group, followed by a cyclopropane ring-opening into an imine intermediate, which is then hydrolyzed. Moreover, the reduction–protection sequence of **6b** with $NiCl_2/NaBH_4$ in EtOH, in the presence of Boc_2O (3 equiv) gave only the protected ring-opening product **15b**[38] in 78% yield (Scheme 6).

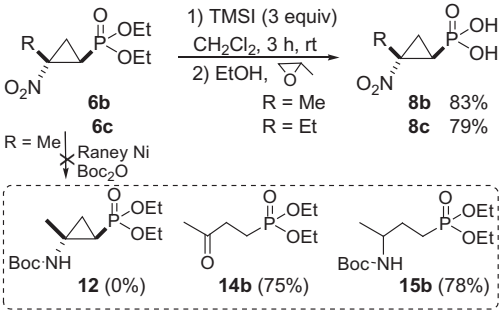
Finally, the stereochemical study showed that all these nitrocyclopropylphosphonates **6a–d** and derivatives have the complete *trans* configuration. This stereochemistry was determined by the analysis of the $^3J_{P-C} = 2.0–3.0$ Hz coupling constants as observed

Table 2
Preparation of nitrocyclopropylphosphonates **6b–d** from dibromophosphonate **4**[a]



Entry	R	[c] mol/L	Product **6**	Yield
1	Me	0.12	**6b**	72 (67)[b]
2	Et	0.14	**6c**	71
3	CH_2OTBS	0.14	**6d**	68
4	CH_2OH	0.14	**6e**	NR[c]

[a] Reaction conditions: dibromo **4**, nitroalkane **5** (1.2 equiv) K_2CO_3 (3 equiv), DMSO–THF (5:1), rt.
[b] Value in parentheses, isolated yield for reaction in DMSO.
[c] NR: no reaction.



Scheme 6. Reduction and hydrolysis of substituted nitrophosphonates **6b–c**.

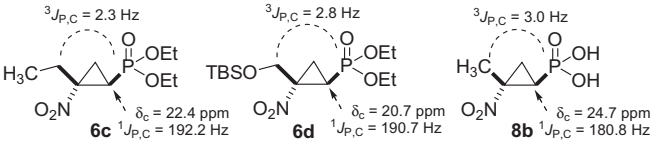


Figure 3. NMR data for cyclopropanes *trans*-**6** and *trans*-**8** (δ_C values [ppm] and $^3J_{C,P}$ *cis* coupling constants [Hz]).

in ^{13}C NMR spectroscopy between the phosphorus atom and the carbon atom bound to the β-position (Fig. 3). The classical range of values is $^3J_{P-C\ cis} = 2.0–4.5$ Hz for the *trans* isomers and $^3J_{P-C\ trans} = 0–1.2$ Hz for the *cis* isomers, as reported in the literature.[12,16,39] The analysis of the ^1H NMR spectra of compounds **6a** and **8a** showed that the H-2 proton has a *trans* relationship to H-1 and H-3 ($J_{2,1} = 3.6–3.8$ and $J_{2,3} = 3.6–3.8$ Hz). Moreover, the magnitude of the coupling constants observed for $J_{1,3}$ is ca. 11–12 Hz for the *cis* and 7–8 Hz for the *trans* relationship, respectively (see Supplementary material). These characteristic values are in agreement with those reported for *trans* nitrocyclopropane isomers.[40]

This *trans* selectivity is in agreement with the results reported by de Meijere et co-workers for the formation of β-nitrocyclopropane-carboxylates.[26] This selectivity is probably not the result of simple steric repulsions as illustrated by compounds **6c** and **6d** and comes almost probably for stereoelectronic factor.

Conclusion

In conclusion, we have developed an efficient cyclopropanation reaction of dibromoethylphosphonate with nitroalkanes. This procedure affords β-nitrocyclopropylphosphonates with exclusive *trans* selectivity. The hydrolysis of the phosphonate moiety leads

easily to the corresponding β-nitrocyclopropylphosphonic acids. Our efforts for the synthesis of β-aminocyclopropylphosphonates led us to investigate the catalytic reduction of β-nitrophosphonates. This reduction, conducted with Raney nickel catalyst under hydrogen atmosphere, must be done with a concomitant protection of the free amine as an amide or a carbamate, to prevent the known competitive ring-opening reaction. Application of this methodology to other brominated vinylphosphonates and asymmetric synthesis of β-nitrocyclopropylphosphonates is under way and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (experimental part of news compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.035.

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