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Comparison of amine-induced cyclization of 6-chloro-1-hexynylphosphonate and isobutyl 7-chlorohept-2-ynoate

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ABSTRACT

The reaction of 6-chloro-1-hexynylphosphonate with primary and secondary amines afforded exclusively 2-aminocyclohexenylphosphonates in 62–85% isolated yields. In contrast, reaction of various amines with isobutyl 7-chlorohept-2-ynoate in acetonitrile at 70 °C gave (*E*)-*sec*-butyl 2-(1-alkylpiperidin-2-ylidene)acetates in 65–78% isolated yields. Calculations offer an explanation for the difference in the behavior of the two compounds classes. It is shown that C–C cyclization in the alkyne-phosphonate group occurs via an initial formation of a zwitterionic intermediate, which is stabilized by both an inductive effect of the phosphonate group and a newly formed hydrogen bond. The alkyne-carboxylate group, on the other hand, proceeds via enamine formation as a result of the smaller inductive effect of the carboxylate combined with involvement of an allene-like resonance form. This resonance form both delocalizes the negative charge in the zwitterionic intermediate making it to be less available for attack, and affects the geometry thus preventing formation of the stabilizing hydrogen bond. Hence, the zwitterionic intermediate of the alkyne-carboxylates is less stable leading to formation of an enamine, which is followed by N–C cyclization to give the azaheterocycles.

1. Introduction

Cyclic β-enamino esters[1,2] are useful compounds for preparing various other heterocycles.[3–8] Various methods are known for preparing cyclic β-enamino esters, such as from unsaturated esters possessing a pendent cyano moiety and B-Ar-9-BBNs in the presence of a rhodium(I) catalyst,[9] by iodine-promoted cyclization of enamino esters,[10] from enol lactones, 4-keto amides, and 5-hydroxy lactams,[11] Knovenagel reactions on lactam-derived acetals,[12,13] imino ethers,[14,15] iminium chloride,[16] or (alkylthio) alkylidenium salts followed by decarboxylation.[17,18] Other routes include Eschenmoser's sulfide-contraction procedure via thiolactams[19] and Wittig reaction of *N*-sulfonyl lactams,[20] application of the intramolecular aza-Wittig reaction,[21] from the formal ring transformation reaction of lactones,[22,23] by reaction of Meldrum's acid with chloroimidates,[24] from thiolactams with subsequent conversion to pyrroles,[25] from ω-azido-β-keto esters,[26] from *N*-alkyl lactams.[27,28] Cyclic chiral β-enamine esters have been prepared from ω-halogeno β-keto esters with chiral amines.[9,29,30,31]

The addition of amines to 1-alkynylphosphonates[32] leads to 2-amino-1-alkenylphosphonates.[33] The latter are useful intermediates in organic synthesis for the preparation of other phosphorus-containing compounds. They have been used to prepare various phosphorylated nitrogen heterocycles[34] and the pharmacologically important β-aminophosphonates.[35] (*E*)-2-Diethylaminophosphonate was prepared in 1963 by Saunders and Simpson by addition of diethylamine to ethynylphosphonate.[36] Chatta and Aguiar reported in 1973 that the addition of R_2NH to 1-alkynylphosphonates proceeded in high yields to produce mixtures of (*Z*) and (*E*)-2-aminoalkenylphosphonates, the latter presumably due to the high temperatures employed and also possibly due to the use of a large excess of amine.[37] Acheson et al. in 1986 found that R_2NH added to ethynylphosphonate to form mixtures of (*E*) and (*Z*) products.[38] In 1964, it was further reported that propynylphosphonate adds secondary amines to form 2-dialkylamino-1-propenylphosphonates but in poor yield (10–15%) contaminated with 2,2-bis(dialkylamino)propylphosphonate.[39] Ionin reported that addition of secondary amines to 1-alkylnylphosphonates in the presence of Cu(I) salts in polar solvents gave improved yields and with exclusive (*E*) selectivity.[40] Beletskaya used an Arbuzov reaction of the corresponding

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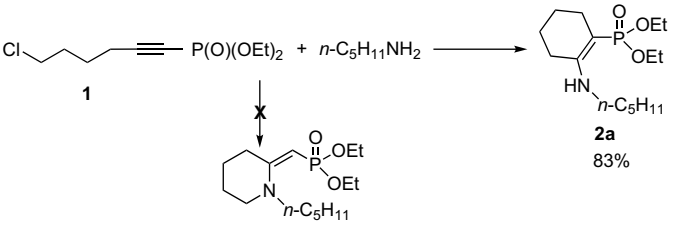
bromo enamine to obtain 2-aminoalkenylphosphonates with retention of stereochemistry.[41] Palacios has prepared 2-amino-1-alkenylphosphonates by the addition of primary amines to allenylphosphonates.[42] He has also prepared them by lithiation of phosphonates and reaction with nitriles.[43] They have also been prepared by reaction of chloroimines with lithiated methylphosphonate; however, mixtures of 2-iminophosphonates and 2-aminoalkynylphosphonates were obtained.[44]

We have recently reported that cyclization of diethyl 5-chloro-1-pentynylphosphonate with various amines leads exclusively to β-aminocyclopentenylphosphonates.[45] The reaction proceeds by a unique mechanism involving a zwitterionic intermediate. Lhommet et al. reported in 2002 that mixtures of β-aminocyclohexenylcarboxylates and 2-(1-alkylpiperidin-2-ylidene)acetates were always obtained from 7-chlorohept-2-ynoates and amines.[46] They interpreted the results on the basis of an intermediate β-enamino ester that either C or N ring closed. These results and our own results prompted us to compare cyclizations of 6-chloro-1-hexynylphosphonate and isobutyl 7-chlorohept-2-ynoate with primary and secondary amines. We here report that diethyl 2-(dialkylamino)cyclohex-1-enylphosphonates **2** (a previously unreported group of compounds) are exclusively obtained from 6-chloro-1-hexynylphosphonate with primary and secondary amines, and (*E*)-*sec*-butyl 2-(1-alkylpiperidin-2-ylidene)acetates **5** are the sole isolated products from the reaction of 7-chlorohept-2-ynoate and primary amines. Calculations give insight into the mechanisms of these cyclizations.

2. Results and discussion

2.1. Synthesis of 2

Diethyl 6-chloro-1-hexynylphosphonate was prepared from 6-chloro-1-hexyne by lithiation with *n*-BuLi followed by reaction with diethyl chlorophosphate as previously described.[45] When diethyl 6-chlorohex-1-ynylphosphonate was reacted with amylamine, one product **2a** was isolated in 83% yield (Eq. 1). No trace of the enamino vinylphosphonates could be detected by NMR spectroscopy or GC/MS.



(1)

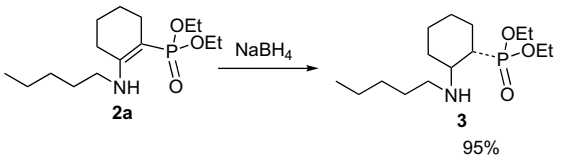
This reaction proved to be general for primary and secondary amines (Table 1). It is carried out under mild conditions at 25 °C without inorganic additives or the need for metal catalysis. No special or glove box techniques are required for this cyclization, which is carried out in screw-capped vials fitted with a magnet. In addition, this reaction tolerates on hydroxyl group (entry 8) and water media (entry 4). Compounds **2** are air, water, and thermally stable, but are sensitive to acid and quickly hydrolyze when exposed to aqueous dilute acid. Thus, the reactions were worked up with aqueous basic solutions. After extraction by CH_2Cl_2 the products are stable to silica gel chromatography, which is the preferred method of purification and isolation. The structures of **2** were confirmed by GC/MS, ^{31}P, ^{13}C, and ^{1}H NMR spectroscopy, and elemental analysis. In the ^{1}H NMR spectra, the broad doublets of triplets in the region 2.64–3.15 ppm, the two neighboring quintets in the region 1.55–1.90 ppm and the triplets in the region 3.00–3.32 ppm due to the hydrogens on C6 and C3, respectively, are consistent with a cyclohexene ring. Further support for the cyclohexene ring was obtained from ^{13}C NMR spectra, which showed two doublets for C1 in the region 69.9–72.9 ppm and for C2 at 160.8–163.1 ppm due to splitting by phosphorus. GC/MS and combustion analysis were consistent with the assigned structures.

Table 1
2-Aminocyclohexenylphosphonates, **2**, from 6-chloro-1-hexynylphosphonates and amines

Entry	Product	Amine	% Isolated yield (conversion)
1	**2a**[a]	Amyl	83(>98)
2	**2b**[b]	*iso*-Propyl	78(>99)
3	**2c**[a]	Propyl	82(>99)
4	**2d**[a]	Methyl	85(>99)
5	**2e**[c]	Benzyl	85(>99)
6	**2f**[c]	Pyrrolidine	62(>98)
7	**2g**[a]	Piperidine	68(>98)
8	**2h**[a]	Ethanolamine	70(>99)

[a] Obtained at 25 °C in about 30 min.
[b] Obtained at 0 °C.
[c] Obtained at 60 °C in 4 h.

In order to obtain an acid-stable product, we reduced the double bond in compound **2a**. The reagent of choice for the reduction was $NaBH_4$ in ethanol at 0 °C, which proceeded to afford the product *trans*-diethyl 2-(pentylamino)cyclohexylphosphate **3** in 95% yield (Eq. 2).



(2)

In addition to its stability to acid, compound **3** is stable to air, water, and was isolated by silica gel chromatography. The structure of **3** and the trans stereochemistry were confirmed by the coupling constant (10 Hz) between the neighboring hydrogens on C1 and C2, which were identified by two-dimensional NMR techniques including HSQC and COSY.

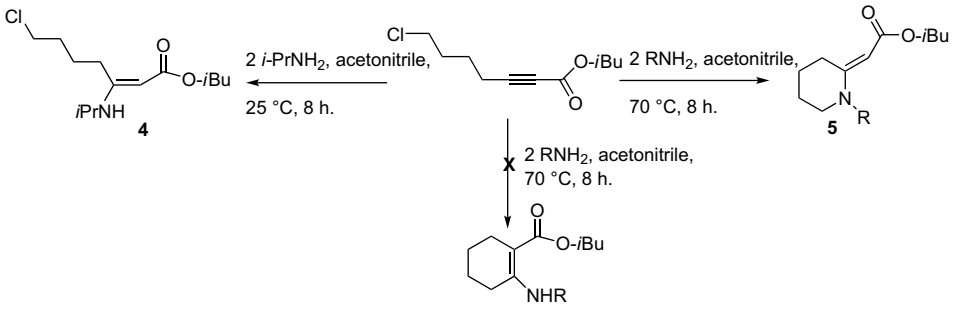
2.2. Synthesis of 5

In contrast, when isobutyl 7-chlorohept-2-ynoate **5**, which was synthesized from isobutyl chloroformate and lithiated 6-chloro-1-hexyne was reacted with 2 equiv of an amine in acetonitrile at 70 °C for 8 h, (*E*)-*sec*-butyl 2-(1-alkylpiperidin-2-ylidene)acetates **5** were produced (Scheme 1). When the reaction was carried out at 25 °C using 2 equiv of *i*-$PrNH_2$, the enamine product **4a** was formed and isolated. Only traces of **5a** were detected in the GC/MS, but were not isolated.

Unlike compound **2**, the presence of a singlet in the region ~4.6 ppm in compounds **5** corresponds to a vinylic hydrogen in the ^{1}H NMR. The ^{13}C NMR spectra and GC/MS are consistent with the heterocycle structure of **5** rather than the cyclohexene ring (compounds **2**). As regards **4a**, the singlet in the region 4.4 ppm in the ^{1}H NMR spectra together with the GC/MS data are indicative of its enamine structure. Under the carboxylate reaction conditions (acetonitrile, 70 °C, 8 h), the chloroalkynylphosphonate also exclusively gave compound **2a**.

2.3. Calculations and mechanisms for formation of 2 and 5

To understand the different behavior of the alkynylphosphonates compared with alkynylcarboxylates, we decided to explore the possible mechanisms of these reactions. Experimentally, an enamine was observed for the isobutyl 7-chlorohept-2-ynoate



Scheme 1. Conditions for the formation of either **4** or **5**.

reaction but was not observed for the diethyl 6-chloro-1-hexynylphosphonate reaction. Furthermore, our earlier study of the ring closure reaction of diethyl 5-chloro-1-pentynylphosphonate suggested that this system proceeds by an initial formation of a zwitterion, which then prefers to cyclize rather than to protonate to give an enamine.[45] The additional CH_2 group in our diethyl 6-chloro-1-hexynylphosphonate is unlikely to cause major changes in the mechanism. We therefore believe that diethyl 6-chloro-1-hexynylphosphonate follows the same mechanism as suggested for diethyl 6-chloro-1-hexynylphosphonate (Scheme 2 mechanism A). Isobutyl 7-chlorohept-2-ynoate, on the other hand, is believed to remain faithful to the traditional reaction course, which involves enamine formation followed by N-cyclization in this case (Scheme 2 mechanism B).

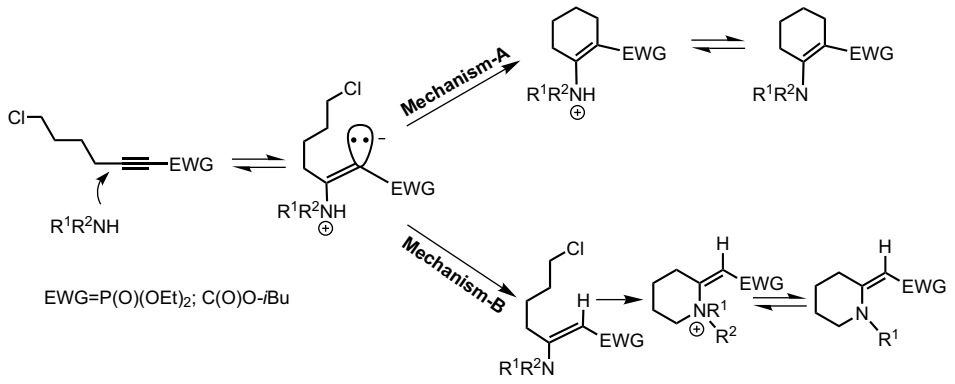
To test these proposed mechanisms and understand the grounds for the difference in the behavior of the two systems, we turned to calculations (see Experimental section for details). Compounds **2d** and **5b** obtained from diethyl 6-chloro-1-hexynylphosphonate and methylamine or isobutyl 7-chlorohept-2-ynoate and methylamine, respectively, were considered as model systems.

Figure 1 depicts reaction profiles obtained for the two systems when mechanism A is assumed, namely formation of a zwitterion intermediate followed by direct cyclization. Figure 1a and b corresponds to the reaction with diethyl 6-chloro-1-hexynylphosphonate and isobutyl 7-chlorohept-2-ynoate, respectively. Additional results at various calculation levels are given as Supplementary data.

Looking at the results it is clearly seen that the overall barrier for diethyl 6-chloro-1-hexynylphosphonate cyclization is lower than that for isobutyl 7-chlorohept-2-ynoate. This trend is consistent and does not depend on the calculation level. The stabilization of the phosphonate system is apparent in both steps of the reaction. Namely, both in the formation of the zwitterion and in the following alkylation step. The phosphonate group is a better electron withdrawing group than the carboxylate (e.g., σ_m (phosphonate)=0.55 whereas σ_m (carboxylate)=0.37).[47] Thus, part of the stabilization of the zwitterion intermediate in the phosphonate system compared to that of the carboxylate system may result from the differential inductive effect caused by these groups. Yet, while certainly being responsible for part of the stabilization, it is unlikely to account for all the effect.

To gain more insight and understand the root cause for the difference, Figure 2 compares the respective geometries of the zwitterionic intermediates (Int-A1 in Fig. 1) for the two systems. Figure 2a and b present the intermediate obtained from the alkyne-phosphonate and the alkyne-carboxylate groups, respectively. Only parts of the molecule, where major differences have been observed, are illustrated. Two major differences are apparent when looking at Figure 2. The first difference relates to the distance between the amine hydrogen and the oxygen of either the P=O and the carbonyl groups, being 1.84 Å and 2.68 Å, respectively. This distance indicates that the zwitterionic intermediate in the phosphonate system enjoys additional stabilization of a hydrogen bonding, which is absent in the case of the carboxylate system. Together with the larger inductive effect of the phosphonate group, the relative stability of the zwitterionic intermediates is clear.

The second difference observed in Figure 2 and further highlighted in Scheme 3a relates to the dihedral angles ∠CCPO compared with ∠CCCO, which describe the angles between the plain of the alkene-anion group and the plain of the P=O or carbonyl groups, respectively. This angle, which is around 0° in the case of the alkene-phosphonate becomes around 80° in the case of alkene-carboxylate. We note that this large difference does not appear in the reactants implying that it is a consequence of the zwitterion formation. In fact, this dihedral angle in the case of the carboxylate



Scheme 2. Two possible mechanisms of amine-induced ring closure.

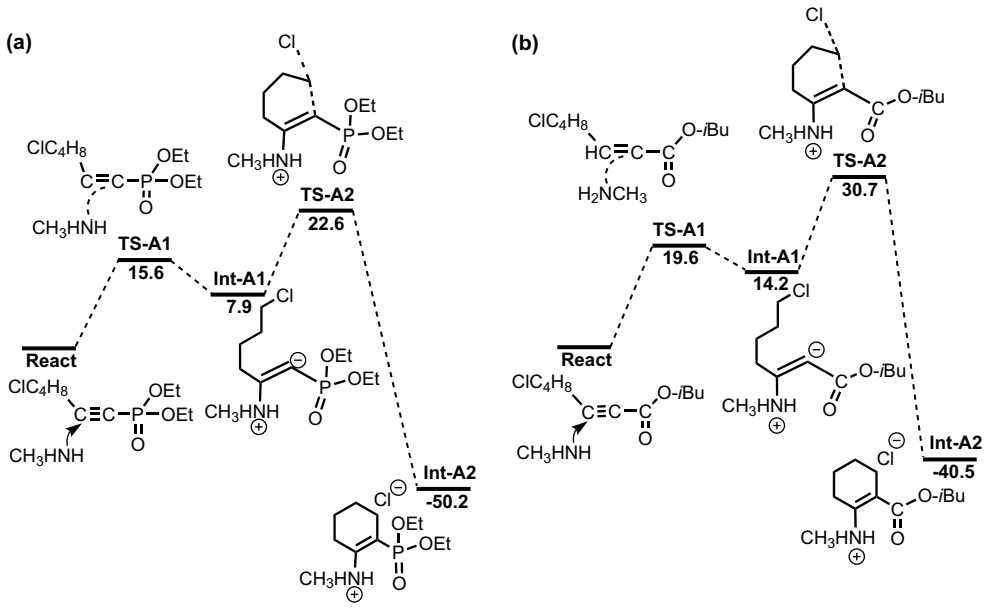


Figure 1. Calculated energy profile of methylamine addition to (a) diethyl 6-chloro-1-hexynylphosphonate and (b) isobutyl 7-chlorohept-2-ynoate, followed by alkylation according to mechanism. A. Energies (in kcal/mol) are obtained at the MP4(SDQ)/6-311G*//HF/6-31G* level of calculation with PCM.

system can be explained if one considers resonance between the two forms **6** and **7** as depicted in Scheme 3b.

Intermediate **7** contains an allene group. It is well known that since the π-bonds of allenes are orthogonal, the planes defined by their end substituents are also orthogonal. Hence, contribution of **7** to the overall wavefunction of the system is expected to affect the angle around these carbons. Hence, the angle being ~80° suggests that the carbon system involves some allene character, which results from a resonance with **7**. On the other hand, the fact that the corresponding angle in the phosphonate system is around zero implies that this resonance form does not play an important role in this case. This in turn leads to an additional explanation for the higher barrier for the reaction with alkyne-carboxylate compared to that of the alkyne-phosphonate via mechanism A. In the phosphonate system, the negative charge on the alkene-anion remains relatively localized and ready to complete alkylation. In the carboxylate system, on the other hand, this lone pair undergoes delocalization as a result of the resonance with **7**. Therefore, its availability for the C–Cl attack is reduced resulting in an increased barrier for the alkylation within mechanism A.

Finally, in order to complete the description one has to consider the enamine path, which appears to be the choice of isobutyl 7-chlorohept-2-ynoate. This path may lead to either N- or C-cyclization. Hence, we calculated both C- and N-cyclization of the corresponding enamine (Fig. 3). Additional results at various levels of calculations are given in Supplementary data.

The reaction barrier for N-cyclization is found to be slightly lower than that for the C-cyclization suggesting agreement with the experimental results that this will be the preferred product. These results are consistent at most of the computational levels tested. Yet, the difference in the calculated barriers is usually very small. Thus, in contrast to the experimental observation, being 100% azaheterocycle, based on the calculations one would expect a mixture of both C- and N-cyclization with a strong preference toward the azaheterocycle product. In fact, Lhommet et al. performed this reaction in the presence of different solvents and observed mixtures of the corresponding azaheterocycle and cyclohexenylcarboxylate. Their results suggest that the products largely depend on the system's environment.[46] Thus, in general, one would expect small differences in the barrier of the two mechanisms. It is important to note that still, although Lhommet et al. used the acetylenic methyl esters, azaheterocycles were the major products when the reaction was carried out in acetonitrile,[46] which is consistent with our results. We believe, therefore, that our results are satisfactory, and in this specific case the too small differences are merely an outcome of deficiency in the description of the solvent effect.

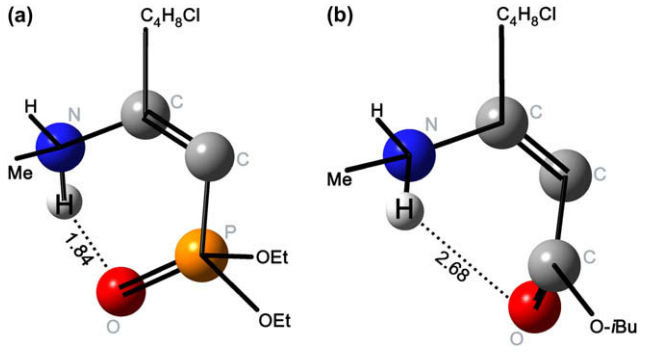
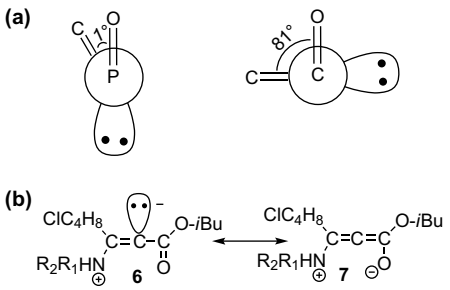


Figure 2. Calculated structures of the zwitterionic intermediates resulting from methylamine addition to (a) diethyl 6-chloro-1-hexynylphosphonate and (b) isobutyl 7-chlorohept-2-ynoate. Only key atoms are shown.



Scheme 3. (a) Comparison of the dihedral angles ∠CCPO and ∠CCCO in the zwitterionic form of the phosphonate versus the carboxylate systems, respectively. (b) Two possible resonance forms of the zwitterionic intermediate of the carboxylate system.

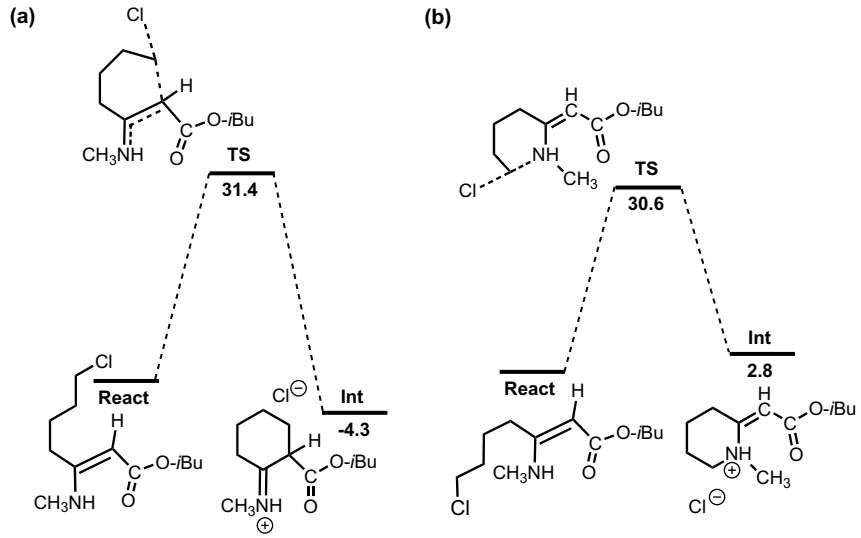


Figure 3. Calculated energy profiles of (a) C-cyclization and (b) N-cyclization of enamine that resulted from methylamine addition to isobutyl 7-chlorohept-2-ynoate. Energies (in kcal/mol) are obtained at the MP4(SDQ)/6-311G*//HF/6-31G* level of calculation with PCM.

3. Conclusion

We have developed a simple but effective procedure for preparing 2-aminocyclohexenylphosphonates, **2**, from amines (primary and secondary) and diethyl 6-chloro-1-hexynylphosphonate. In one case, **2a** was reduced to the corresponding *trans*-2-aminocyclohexylphosphonate, **3**, a previously unreported class of compounds. In contrast, azaheterocycles **5** are the only compounds obtained by cyclization of 7-chlorohept-2-ynoate with primary amines. Calculations suggest formation of **2** directly via a zwitterionic intermediate while the formation of **5** is through enamines **4**, which can be isolated. It is shown that a combination of induction effects, hydrogen bonding and resonance, leads the systems to choose the mechanism.

4. Experimental

4.1. General

All reactions were carried out under N_2 unless otherwise noted. All solvents were purified according to standard methods prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded in chloroform-d_3 on a Bruker 300 MHz.

4.2. Representative procedure for the synthesis of 2

4.2.1. Preparation of 4 diethyl 2-(pentylamino)cyclohex-1-enylphosphonate ***2a*** *(Table 1, entry 1)*

To 0.252 g (1 mmol) of diethyl 6-chlorohex-1-ynylphosphonate was added to 2 mmol of the amine in a 9 mL vial. After stirring for 3 h at ambient temperature, the reaction mixture was washed with 0.1 N NaOH solution, extracted with (2×20 mL CH_2Cl_2), and separated on silica gel column (10% methanol/90% ethyl acetate), and was analyzed by GC/MS, elemental analysis, and NMR spectroscopy.

Yield 0.25 g, 83%, yellow oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.90 (t, 3H, J_{HH}=7.2 Hz), 1.31 (t, 6H, J_{HH}=7.2 Hz), 1.20–1.38 (overlap, 4H), 1.52–1.66 (overlap, 4H), 1.74 (qn, 2H, J_{HH}=6.3 Hz), 2.75 (dt, 2H, J_{HH}=6.3 Hz, $^3J_{PH}$=1.8 Hz), 3.10 (t, 2H, J_{HH}=8.1 Hz), 3.16 (t, 2H, J_{HH}=6.0 Hz), 4.02 (qn, 4H, J_{HH}=7.2 Hz); ^{31}P NMR (121.4 MHz, $CDCl_3$): δ=29.49; ^{13}C NMR (75.5 MHz, $CDCl_3$): 13.7, 16.1 (d, $^3J_{PC}$=6.9 Hz), 19.5, 22.1, 23.3, 24.5, 27.1 (d, $^2J_{PC}$=4.5 Hz), 29.0, 49.0, 51.7, 60.3 (d, $^2J_{PC}$=5.1 Hz), 69.9 (d, $^1J_{PC}$=216.4 Hz), 160.8 (d, $^2J_{PC}$=21.5 Hz); MS (EI): *m*/*z* (%) 303 (10.3), 274 (10.2), 260 (13.0), 246 (34.1), 166 (70.1), 97 (95.4), 95 (100), 82 (19.2), 55 (26.1), 41 (35.5), 29 (48.6). Anal. Calcd for $C_{15}H_{30}NO_3P$: C, 59.38; H, 9.97; N, 4.62; P, 10.21. Found: C, 59.45; H, 10.07; N, 4.53; P, 10.13.

4.2.2. Diethyl 2-(iso-propylamino)cyclohex-1-enylphosphonate ***2b*** *(Table 1, entry 2)*

Yield 0.22 g, 78%, yellow oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.11, (d, 6H, J_{HH}=6.3 Hz), 1.30 (t, 6H, J_{HH}=7.2 Hz), 1.63 (qn, 2H, J_{HH}=6.6 Hz), 1.71 (qn, 2H, J_{HH}=6.3 Hz), 2.76 (dt, 2H, J_{HH}=6.3 Hz, $^3J_{PH}$=1.5 Hz), 3.05 (t, 2H, J_{HH}=6.3 Hz), 3.62 (m, 1H), 4.02 (qn, 4H, J_{HH}=7.2 Hz); ^{31}P NMR (121.4 MHz, $CDCl_3$): δ=30.06; ^{13}C NMR (75.5 MHz, $CDCl_3$): 16.2 (d, $^3J_{PC}$=6.9 Hz), 18.7, 19.4, 23.3, 27.6 (d, $^2J_{PC}$=5.6 Hz), 39.4, 47.6, 60.5 (d, $^2J_{PC}$=5.4 Hz), 70.4 (d, $^1J_{PC}$=216.6 Hz), 162.1 (d, $^2J_{PC}$=21.5 Hz); MS (EI): *m*/*z* (%) 275 (10.0), 260 (8.7), 232 (12.1), 138 (100), 97 (48.7), 96 (25.8), 82 (17.1), 55 (21.4), 41 (26.6). Anal. Calcd for $C_{13}H_{26}NO_3P$: C, 56.71; H, 9.52; N, 5.09; P, 11.25. Found: C, 56.68; H, 9.58; N, 5.05; P, 11.35.

4.2.3. Diethyl 2-(propylamino)cyclohex-1-enylphosphonate ***2c*** *(Table 1, entry 3)*

Yield 0.23 g, 82%, yellow oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (t, 3H, J_{HH}=7.5 Hz), 1.58 (t, 6H, J_{HH}=7.2 Hz), 1.64 (qn, 2H, J_{HH}=6.9 Hz), 1.75 (qn, 2H, J_{HH}=6.9 Hz), 1.96 (m, 2H), 2.83 (dt, 2H, J_{HH}=7.5 Hz, $^3J_{PH}$=2.1 Hz), 3.16 (t, 2H, J_{HH}=7.2 Hz), 3.82 (t, 2H, J_{HH}=6.6 Hz), 3.95 (qn, 4H, J_{HH}=7.2 Hz); ^{31}P NMR (121.4 MHz, $CDCl_3$): δ=31.78; ^{13}C NMR (75.5 MHz, $CDCl_3$): 13.8, 15.1 (d, $^3J_{PC}$=6.8 Hz), 20.1, 21.0, 22.3, 23.4, 27.0, 39.0, 51.0, 60.2 (d, $^2J_{PC}$=5.4 Hz), 72.2 (d, $^1J_{PC}$=215.1 Hz), 161.8 (d, $^2J_{PC}$=20.9 Hz); MS (EI): *m*/*z* (%) 275 (14.7), 244 (27.7), 230 (8.7), 218 (8.7), 160 (17.6), 138 (100), 110 (42.2), 97 (68.6), 83 (68.6), 55 (29.9), 41 (55.9). Anal. Calcd for $C_{13}H_{26}NO_3P$: C, C, 56.71; H, 9.52; N, 5.09; P, 11.25. Found: C, 56.63; H, 9.61; N, 4.97; P, 11.36.

4.2.4. Diethyl 2-(methylamino)cyclohex-1-enylphosphonate ***2d*** *(Table 1, entry 4)*

Yield 0.21 g, 85%, yellow oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.30 (t, 6H, J_{HH}=7.2 Hz), 1.62 (qn, 2H, J_{HH}=6.3 Hz), 1.77 (qn, 2H, J_{HH}=6.3 Hz), 2.75 (s, 3H), 2.74 (dt, 2H, J_{HH}=7.8 Hz, $^3J_{PH}$=2.1 Hz), 3.14 (t, 2H, J_{HH}=6.0 Hz), 4.02 (qn, 4H, J_{HH}=7.2 Hz); ^{31}P NMR (121.4 MHz, $CDCl_3$): δ=29.48; ^{13}C NMR (75.5 MHz, $CDCl_3$): 15.8 (d, $^3J_{PC}$=7.2 Hz), 19.9, 23.3, 26.9 (d, $^2J_{PC}$=4.6 Hz), 39.1, 51.0, 60.1 (d, $^2J_{PC}$=5.4 Hz), 72.0

(d, $^{1}J_{PC}$=214.9 Hz), 161.5 (d, $^{2}J_{PC}$=21.2 Hz); MS (EI): *m*/*z* (%) 247 (19.3), 232 (3.9), 218 (4.0), 202 (5.2), 172 (6.9), 126 (4.9), 112 (7.7), 111 (100), 110 (81.4), 109 (89.2), 108 (18.3), 96 (10.1), 82 (21.4), 68 (12.6), 55 (21.1), 42 (30.1), 28 (40.6). Anal. Calcd for $C_{11}H_{22}NO_3P$: C, 53.43; H, 8.97; N, 5.66; P, 12.53. Found: C, 53.51; H, 9.04; N, 5.57; P, 12.59.

4.2.5. Diethyl 2-(benzylamino)cyclohex-1-enylphosphonate **2e** (Table 1, entry 5)

Yield 0.28 g, 85%, yellow oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.26 (t, 6H, J_{HH}=6.9 Hz), 1.71 (qn, 2H, J_{HH}=6.0 Hz), 1.81 (qn, 2H, J_{HH}=6.6 Hz), 2.88 (dt, 2H, J_{HH}=6.6 Hz, $^{3}J_{PH}$=2.4 Hz), 3.24 (t, 2H, J_{HH}=6.0 Hz), 3.94 (qn, 4H, J_{HH}=6.0 Hz), 4.35 (s, 2H), 7.15–7.38 (overlap, 5H); ^{31}P NMR (121.4 MHz, $CDCl_3$): δ=28.40; ^{13}C NMR (75.5 MHz, $CDCl_3$): 16.2 (d, $^{3}J_{PC}$=6.9 Hz), 19.9, 23.5, 27.5 (d, $^{2}J_{PC}$=4.6 Hz), 49.6, 55.0, 60.5 (d, $^{2}J_{PC}$=5.4 Hz), 72.9 (d, $^{1}J_{PC}$=214.3 Hz), 126.5, 126.9, 128.4, 136.2, 161.5 (d, $^{2}J_{PC}$=21.5 Hz); MS (EI): *m*/*z* (%) 323 (14.1), 294 (1.2), 278 (2.8), 232 (14.7), 207 (1.6), 186 (87.1), 104 (8.2), 91 (77.9), 82 (29.0), 65 (23.0), 55 (15.4), 28 (67.1). Anal. Calcd for $C_{17}H_{26}NO_3P$: C, 63.14; H, 8.10; N, 4.33; P, 9.58. Found: C, 63.08; H, 8.05; N, 4.25; P, 9.55.

4.2.6. Diethyl 2-(pyrrolidin-1-yl)cyclohex-1-enylphosphonate **2f** (Table 1, entry 6)

Yield 0.18 g, 62%, yellow oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.30 (t, 6H, J_{HH}=7.2 Hz), 1.55–1.72 (overlap, 2H), 1.90 (m, 4H), 2.63 (overlap, 4H), 3.05 (br t, 2H, J_{HH}=7.2 Hz), 3.25 (br t, 2H, J_{HH}=5.4 Hz), 4.00 (qn, 4H, J_{HH}=6.9 Hz); ^{31}P NMR (121.4 MHz, $CDCl_3$): δ=28.92; ^{13}C NMR (75.5 MHz, $CDCl_3$): 16.3 (d, $^{3}J_{PC}$=6.9 Hz), 23.2, 26.6, 28.0, 31.3 (d, $^{2}J_{PC}$=4.3 Hz), 53.8, 55.5, 60.5 (d, $^{2}J_{PC}$=5.5 Hz), 71.9 (d, $^{1}J_{PC}$=216.9 Hz), 162.8 (d, $^{2}J_{PC}$=21.1 Hz); MS (EI): *m*/*z* (%) 287 (1.5), 235 (2.5), 168 (3.4), 152 (1.8), 110 (4.1), 84 (100), 70 (6.6), 55 (5.9), 42 (10.6). Anal. Calcd for $C_{14}H_{26}NO_3P$: C, 58.52; H, 9.12; N, 4.87; P, 10.78. Found: C, 58.41; H, 9.20; N, 4.95; P, 10.72.

4.2.7. Diethyl 2-(piperidin-1-yl)cyclohex-1-enylphosphonate **2g** (Table 1, entry 7)

Yield 0.21 g, 68%, yellow oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.30 (t, 6H, J_{HH}=6.9 Hz), 1.27–1.62 (overlap, 10H), 2.25–2.40 (overlap, 4H), 2.64 (br t, 2H, J_{HH}=7.5 Hz), 3.16 (br t, 2H, J_{HH}=5.4 Hz), 4.02 (qn, 4H, J_{HH}=7.2 Hz); ^{31}P NMR (121.4 MHZ, $CDCl_3$): δ=29.55; ^{13}C NMR (75.5 MHz, $CDCl_3$): 15.8 (d, $^{3}J_{PC}$=6.9 Hz), 22.3, 22.8, 27.8, 29.3 (d, $^{2}J_{PC}$=4.3 Hz), 53.5, 54.7, 60.0 (d, $^{2}J_{PC}$=5.4 Hz), 71.7 (d, $^{1}J_{PC}$=217.4 Hz), 162.3 (d, $^{2}J_{PC}$=20.9 Hz); MS (EI): *m*/*z* (%) 301 (1.2), 154 (2.6), 136 (2.2), 123 (2.8), 97 (24.5), 84 (100), 70 (9.4), 42 (13.5). Anal. Calcd for $C_{15}H_{28}NO_3P$: C, 59.78; H, 9.36; N, 4.65; P, 10.28. Found: C, 59.91; H, 9.27; N, 4.70; P, 10.19.

4.2.8. Diethyl 2-(2-hydroxyethylamino)cyclohex-1-enylphosphonate **2h** (Table 1, entry 8)

Yield 0.19 g, 70%, yellow oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.31 (d, 6H, J_{HH}=7.2 Hz), 1.71 (qn, 2H, J_{HH}=7.2 Hz), 1.83 (qn, 2H, J_{HH}=7.2 Hz), 2.92 (dt, 2H, J_{HH}=7.5 Hz, $^{3}J_{PH}$=1.8 Hz), 3.30 (t, 2H, J_{HH}=7.2 Hz), 3.47 (t, 2H, J_{HH}=7.2 Hz), 3.76 (t, 2H, J_{HH}=5.7 Hz), 3.98 (qn, 4H, J_{HH}=7.2 Hz); ^{31}P NMR (121.4 MHz, $CDCl_3$): δ=28.44; ^{13}C NMR (75.5 MHz, $CDCl_3$): 15.7 (d, $^{3}J_{PC}$=6.9 Hz), 21.1, 22.5, 32.1, 43.3, 58.6, 61.0 (d, $^{2}J_{PC}$=5.5 Hz), 62.4, 165.9 (d, $^{2}J_{PC}$=21.6 Hz); MS (EI): *m*/*z* (%) 277 (12.7), 260 (3.9), 246 (13.7), 234 (94.0), 206 (25.9), 164 (40.2), 146 (46.1), 108 (100), 97 (45.1), 83 (27.5), 65 (14.7), 41 (17.6). Anal. Calcd for $C_{12}H_{24}NO_4P$: C, 51.98; H, 8.72; N, 5.05; P, 11.17. Found: C, 52.07; H, 8.81; N, 4.95; P, 11.09.

4.3. (*rac*) Diethyl *trans*-2-(pentylamino)cyclohexylphosphonate 3

To the reaction mixture of **2a**, 4 mL of ethanol and 2 equiv of $NaBH_4$ were added to the reaction mixture at 0 °C. The mixture was stirred for 1 h at 0 °C and then it was heated gradually to room temperature and stirred for additional 2 h. The product was extracted with (2×20 mL CH_2Cl_2), and separated on silica gel column (10% methanol/90% ethyl acetate), and was analyzed by GC/MS, elemental analysis, and NMR spectroscopy.

Yield 0.29 g, 95%, yellow oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, 3H, J_{HH}=7.2 Hz), 1.34 (t, 6H, J_{HH}=6.9 Hz), 1.20–1.38 (overlap, 4H), 1.39–1.66 (overlap, 6H), 1.76–2.04 (overlap, 3H), 2.28–2.53 (overlap, 2H), 2.90–3.10 (m, 1H, J_{HH}=10.1 Hz), 4.11 (m, 4H); ^{31}P NMR (121.4 MHz, $CDCl_3$): δ=32.38; ^{13}C NMR (75.5 MHz, $CDCl_3$): 13.6, 16.0 (d, $^{3}J_{PC}$=6.3 Hz), 20.6, 22.2, 23.4 (d, $^{1}J_{PC}$=161.4 Hz), 24.7, 25.7, 29.3, 30.1 (d, $^{2}J_{PC}$=1.7 Hz), 49.0, 53.5, 53.7, 61.1 (d, $^{2}J_{PC}$=6.9 Hz), MS (EI): *m*/*z* (%) 305 (4.9), 276 (2.8), 248 (40.6), 234 (19.2), 168 (11.8), 154 (100), 97 (14.3), 84 (10.6), 41 (8.1). Anal. Calcd for $C_{15}H_{32}NO_3P$: C, 58.99; H, 10.56; N, 4.59; P, 10.14. Found: C, 59.08; H, 10.64; N, 4.49; P, 10.07.

4.4. (*E*)-Isobutyl 7-chloro-3-(*iso*-propylamino)hept-2-enoate 4a

To 0.216 g (1 mmol) of isobutyl 7-chlorohept-2-ynoate dissolved in 5 mL of dry acetonitrile was added 2 equiv of *iso*-propyl amine in a screw-capped vial at room temperature. The mixture was stirred for 8 h at room temperature and then the product was separated on silica gel column (90% petroleum ether/10% ethyl acetate), and analyzed by GC/MS, elemental analysis, and NMR spectroscopy.

Yield 0.24 g, 87%, yellow oily liquid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ=0.90 (d, 6H, J_{HH}=6.6 Hz), 1.18 (d, 6H, J_{HH}=6.3 Hz), 1.64–1.76 (m, 2H), 1.80–1.92 (overlap, 3H), 2.19 (t, 2H, J_{HH}=7.5 Hz), 3.54 (t, 2H, J_{HH}=6.3 Hz), 3.77 (d, 2H, J_{HH}=6.9 Hz), 4.40 (s, 1H); ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ=19.2, 24.3, 25.6, 27.9, 31.4, 31.9, 44.2, 44.5, 68.7, 81.1, 163.8, 170.9; MS (EI): *m*/*z* (%) 277 (3.8), 275 (6.8), 260 (2.0), 240 (100), 220 (5.7), 202 (32.2), 184 (38.0), 166 (12.2), 160 (29.5), 138 (18.5), 124 (20.5), 96 (27.0), 82 (29.9), 68 (15.5), 57 (24.7). Anal. Calcd for $C_{14}H_{26}ClNO_2$: C, 60.96; H, 9.50; Cl, 12.85; N, 5.08. Found: C, 61.06; H, 9.57; Cl, 12.69; N, 4.97.

4.4.1. (*E*)-Isobutyl 2-(1-iso-propylpiperidin-2-ylidene)acetate **5a** (Table 2, entry 1)

To 0.216 g (1 mmol) of isobutyl 7-chlorohept-2-ynoate dissolved in 5 mL of dry acetonitrile was added 2 equiv of an amine in a screw-capped vial at room temperature. The mixture was heated at 70 °C for 8 h, then it was cooled to room temperature and the product was separated on silica gel column (90% petroleum ether/10% ethyl acetate), and analyzed by GC/MS, elemental analysis, and NMR spectroscopy.

Yield 0.19 g, 78%, yellow oily liquid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ=0.91 (d, 6H, J_{HH}=6.6 Hz), 1.20 (d, 6H, J_{HH}=6.9 Hz), 1.59–1.78 (overlap, 4H), 1.83–1.96 (m, 1H), 3.08 (t, 2H, J_{HH}=6.3 Hz), 3.12 (t, 2H, J_{HH}=6.9 Hz), 3.77 (d, 2H, J_{HH}=6.6 Hz), 3.98–4.08 (m, 1H), 4.68 (s, 1H); ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ=18.9, 19.2, 19.3, 23.1, 26.4, 28.1, 39.9, 48.1, 68.6, 81.0, 163.0, 169.6; MS (EI): *m*/*z* (%) 239 (30.0), 224 (20.6), 210 (4.8), 197 (6.2), 182 (14.4), 166 (77.5), 138 (100), 124

Table 2
(*E*)-*sec*-Butyl 2-(1-alkylpiperidin-2-ylidene)acetates **5**

Entry	Product	Amine	% Isolated yield[a] (conversion[b])
1	**5a**	*iso*-Propyl	78(>98)
2	**5b**	Methyl	73(>98)
3	**5c**	Benzyl	75(>98)
4	**5d**	Ethanolamine	65(>98)

[a] After silica gel chromatography.
[b] Estimated by GC/MS.

(69.6), 97 (76.5), 82 (34.3), 55 (37.3). Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.13; H, 10.49; N, 5.98.

4.4.2. (E)-Isobutyl 2-(1-methylpiperidin-2-ylidene)acetate ***5b*** *(Table 2, entry 2)*

Yield 0.15 g, 73%, yellow oily liquid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ=0.92 (d, 6H, J_{HH}=6.9 Hz), 1.57–1.63 (m, 2H), 1.70–1.73 (m, 2H), 1.85–1.90 (m, 1H), 2.80 (s, 3H), 3.06 (t, 2H, J_{HH}=6.6 Hz), 3.20 (t, 2H, J_{HH}=5.7 Hz), 3.79 (d, 2H, J_{HH}=6.6 Hz), 4.53 (s, 1H); ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ=19.3, 19.9, 23.5, 26.7, 28.1, 39.9, 51.8, 68.7, 82.5, 162.6, 169.0; MS (EI): *m*/*z* (%) 211 (17.0), 169 (4.5), 156 (15.0), 138 (100), 111 (99.9), 96 (6.0), 82 (13.0), 68 (9.0), 55 (9.9). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.33; H, 9.97; N, 6.70.

4.4.3. (E)-Isobutyl 2-(1-benzylpiperidin-2-ylidene)acetate ***5c*** *(Table 2, entry 3)*

Yield 0.22 g, 75%, yellow oily liquid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ=0.89 (d, 6H, J_{HH}=6.6 Hz), 1.60–1.89 (overlap, 4H), 1.87–1.93 (m, 5H), 3.20 (t, 2H, J_{HH}=6.6 Hz), 3.25 (t, 2H, J_{HH}=6.0 Hz), 3.76 (d, 2H, J_{HH}=6.6 Hz), 4.41 (s, 2H), 4.70 (s, 1H), 7.16–7.37 (m, 5H); ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ=19.3, 19.7, 23.3, 26.8, 28.0, 49.7, 55.1, 68.7, 82.7, 126.6, 127.1, 128.7, 136.2, 162.5, 169.3; MS (EI): *m*/*z* (%) 287 (35.6), 272 (1.5), 232 (8.5), 214 (42.3), 186 (92.2), 171 (23.2), 91 (100), 82 (22.9). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.35; H, 8.90; N, 4.68.

4.4.4. (E)-Isobutyl 2-(1-(2-hydroxyethyl)piperidin-2-ylidene)acetate ***5d*** *(Table 2, entry 4)*

Yield 0.16 g, 65%, yellow oily liquid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ=0.92 (d, 6H, J_{HH}=6.6 Hz), 1.57–1.74 (overlap, 4H), 1.85–1.90 (m, 1H), 2.45 (t, 2H, J_{HH}=7.2 Hz), 3.12 (t, 2H, J_{HH}=6.6 Hz), 3.33 (t, 2H, J_{HH}=6.6 Hz), 3.56 (t, 2H, J_{HH}=6.6 Hz), 3.87 (d, 2H, J_{HH}=6.6 Hz), 4.52 (s, 1H); ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ=19.1, 19.2, 20.2, 23.4, 26.5, 31.8, 61.7, 70.6, 95.0, 164.8, 170.9; MS (EI): *m*/*z* (%) 241 (6.8), 226 (3.5), 210 (16.5), 198 (41.2), 168 (53.5), 142 (45.1), 127 (87.5), 126 (100), 111 (42.3), 97 (59.2), 82 (54.6), 55 (69.5). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.83; H, 9.67; N, 5.65.

4.5. Computational details

All calculations were perfomed with the Gaussian 03 program package.[48] Geometries were gradient-optimized and characterized by frequency analysis at the HF/6-31G* level. Profiles were ascertained by following the reaction path using the intrinsic reaction coordinate (IRC) technique with mass weighted coordinates.[49] The effect of the solvent on the reaction profiles was calculated with the use of the PCM Model.[50,51] Profiles for the reactions with diethyl 6-chloro-1-hexynylphosphonate were calculated assuming a water environment whereas those of isobutyl 7-chlorohept-2-ynoate were calculated in an acetonitrile environment, in agreement with the experimental conditions.

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Supplementary data

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