Synlett N. Jebli et al. Letter

Direct Regio- and Diastereoselective Diphosphonylation of Cyclic Enamines: One-Pot Synthesis of α,α′-Bis(diphenylphosphoryl)- and α,α′-Bis(diphenylphosphorothioyl)cycloalkanones

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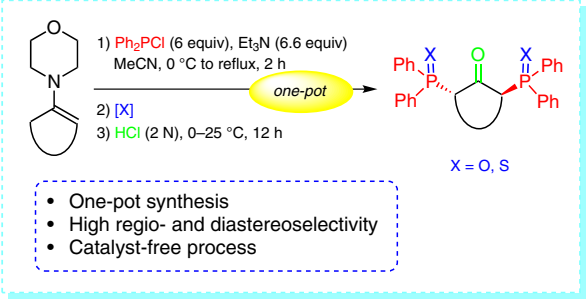


Received: 21.01.2017
Accepted after revision: 20.02.2017
Published online: 08.03.2017
DOI: 10.1055/s-0036-1588970; Art ID: st-2017-b0058-l

Abstract A straightforward regio- and diastereoselective process has been developed for the synthesis of unprecedented symmetrical *trans*-α,α′-bis(diphenylphosphoryl)- and α,α′-bis(diphenylphosphorothioyl)-cycloalkanones, through the reaction of cyclic enamines with excess *P*-chlorodiphenylphosphine in the presence of triethylamine, followed by oxidation or sulfurization and hydrolytic workup.

Key words enamines, *P*-chlorodiphenylphosphine, α,α′-bis(diphenylphosphoryl)cycloalkanones, α,α′-bis(diphenylphosphorothioyl)cycloalkanones, P-ligands

An important area in the chemistry of organophosphorus compounds is the design of new types of P-ligands containing, along with the phosphoryl or thiophosphoryl moieties, one or more other functional groups (keto, amino, hydroxy, etc.). The interest for these compounds is due to their well-known useful applications, such as in the high-performance extraction of various metals including uranium (VI), thorium (IV), and rare earths (III),[1–7] in the preparation of ion-selective electrodes,[8–10] or as ligands for transition-metal-catalyzed cross-coupling reactions and asymmetric synthesis.[11–16] Some of their fluorescent complexes with lanthanum-group metals are also used as light-emitting components in organic light-emitting diodes.[17]

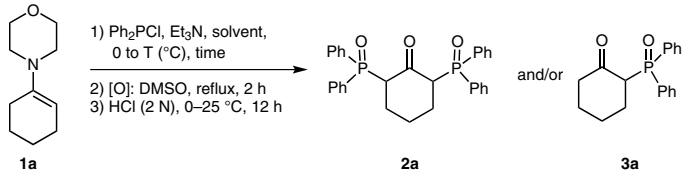
Within our ongoing studies on the reactivity and potential synthetic applications of imines and enamines[18–21] and inspired by the reaction of enamines with chlorophosphines which leads to α-phosphonylcycloalkanones,[22,23] we anticipated that treatment of cyclic enamines with excess *P*-chlorodiphenylphosphine, followed by oxidation or sulfurization and hydrolytic workup, would allow a straightforward approach to unprecedented symmetrical α,α′-bis(diphenylphosphoryl)- and α,α′-bis(diphenylphosphorothioyl)cycloalkanones. Being tridentate ligands, these compounds might show enhanced complexing properties with regard to their α-phosphonylketone homologues.[6,24–26]

To the best of our knowledge, symmetrical α,α′-bis(diphenylphosphoryl)- and α,α′-bis(diphenylphosphorothioyl)cycloalkanones have never been synthesized, but there are only two reports concerning the synthesis of acyclic analogues of α,α′-bis(diphenylphosphoryl)cycloalkanones. This includes (i) the TFAA/TfOH-mediated self-acylation of diphenylphosphorylacetic acid[27] and (ii) the bromination of 3-(diphenylphosphoryl)-3-methylbutanone followed by a Michaelis–Arbuzov phosphonylation.[28] The scope of these reactions is, however, limited and only two acyclic α,α′-bis(diphenylphosphoryl)ketones have been synthesized from these strategies, in lower than 40% overall yield.

By comparison with these existing strategies, our method, which uses easily prepared enamines and commercially available *P*-chlorodiphenylphosphine as starting materials, has the advantages of brevity (one-pot protocol), generality, satisfactory yields, and mild reaction conditions. Furthermore, it is applicable for the production of both bisphosphine oxide and bisphosphine sulfide derivatives.

In order to establish the optimum reaction conditions for the formation of the target compounds, we used 1-morpholinocyclohexene (**1a**) and *P*-chlorodiphenylphosphine as model substrates, in the presence of triethylamine. The reaction was studied by varying several conditions (sol-

Table 1 Optimization of the Reaction Conditions



1a **2a** **3a**

Entry	Ph_2PCl (equiv)[a]	Solvent	Temp (°C)	Time (h)	Yield of **2a** (%)[b]	Yield of **3a** (%)[b]
1	1	Et_2O	25	2	2	64
2	1	Et_2O	reflux	2	3	63
3	1	THF	25	2	2	61
4	1	THF	reflux	2	3	58
5	1	MeCN	25	2	6	75
6	1	MeCN	reflux	2	5	67
7	2	MeCN	25	2	10	72
8	2	MeCN	reflux	2	15	63
9	2	MeCN	reflux	12	13	57
10	3	MeCN	25	2	28	49
11	3	MeCN	reflux	2	35	40
12	3	MeCN	reflux	12	33	36
13	4	MeCN	reflux	2	39	28
14	5	MeCN	reflux	2	43	21
15	6	MeCN	reflux	2	51	13
16	7	MeCN	reflux	2	51	15

[a] 1.1 equiv of Et_3N for each equiv of Ph_2PCl.
[b] Isolated yield.

vents, molar equivalents of Ph_2PCl, temperature, reaction time). The results of these comparative experiments are summarized in Table 1.

Initially, the reaction was tested with one equivalent Ph_2PCl and 1.1 equivalents Et_3N in different solvents, in order to improve the experimental protocol for the formation of the monophosphonylated products[22,23] and to ascertain if the desired diphosphonylated compounds could be detected in these conditions. The reaction provided mainly the monophosphonylated product **3a** with trace amounts of the α,α′-bis(diphenylphosphoryl)cyclohexanone (**2a**, Table 1, entries 1–6). The best results were recorded with MeCN as solvent, which gave 75% and 6% yields of **3a** and **2a**, respectively (Table 1, entry 5). On the basis of these observations, it could be concluded that the formation of the first C–P bond seems to be quite faster than that of the second, which explains the sufficiency of one equivalent of Ph_2PCl for the completion of the monophosphonylation step.

With these preliminary results in hand, we next focused on how to enhance the yield of the desired diphosphonylated product **2a** by increasing the molar ratio of Ph_2PCl. As shown in Table 1, when the reaction was conducted with two equivalents of the phosphorus electrophile in MeCN at room temperature, the desired product **2a** was isolated in only 10% yield (Table 1, entry 7). The yield in **2a** was enhanced to 15% by heating in refluxing MeCN, for two hours (Table 1, entry 8). Further improvement of the yield to 35% was observed when using three equivalents of Ph_2PCl in refluxing MeCN (Table 1, entry 11). Under the same reaction conditions, it was gratifying to observe that 51% yield of the desired product **2a** was obtained when the amount of Ph_2PCl was increased to six molar equivalents (Table 1, entry 15). Switching to seven equivalents of Ph_2PCl brought no improvement to the yield of **2a** (Table 1, entry 16).

Based on these results, the optimized conditions were established as follows: The enamine reacts in the presence of six equivalents of Ph_2PCl and 6.6 equivalents of Et_3N in MeCN at 0 °C to reflux temperature for two hours. The oxidation or sulfurization of the obtained bisphosphine intermediate was performed in a one-pot protocol by treating, respectively, with dimethyl sulfoxide (DMSO) under reflux for two hours or with elemental sulfur at room temperature, for the same time. Finally, the acidic hydrolysis leading

to the desired diphosphonylketone was accomplished by treatment with HCl (2N) at 0 °C to room temperature for 12 hours.

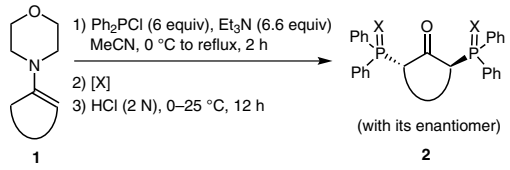
With the optimized conditions in hand,[29] we next studied the scope of this methodology. A variety of structurally diverse enamines derived from cyclic ketones and morpholine were investigated and a series of α,α′-bis(diphenylphosphoryl)- and α,α′-bis(diphenylphosphorothioyl)cycloalkanones of type **2** were obtained in satisfactory yields (Table 2). One can notice that the yield slightly increased when enamines derived from substituted cyclohexanones were used as starting materials. The method also proved to work for 1-morpholinocyclopentene.

The reaction was found to be highly diastereoselective. Although, for compounds **2**, a mixture of *cis* and *trans* isomers is possible, the *trans* configuration is obtained exclusively, except for the five-membered cyclic compounds **2d** and **2g** (*cis* isomer present in 30% and 13% ratio, respectively, see Table 2). The *trans* configuration was assigned on the basis of the single-crystal X-ray diffraction data of compounds **2a**, **2b** and **2g** which indicated that the relative stereochemistry of the two phosphonyl groups is *trans* (Figure 1). It should be noted that in case of compound **2b**, the 4-methylcyclohexan-1-one ring is mainly observed in the chair conformation. However, a small fraction was observed adopting a boat conformation. The ratio was properly defined in two parts with final occupancy factors of 0.94 and 0.06, for the chair and boat conformations, respectively (Figure 1, b).

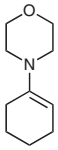
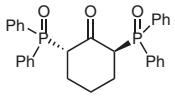
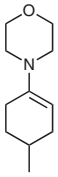
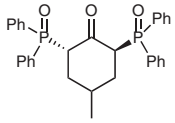
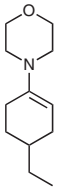
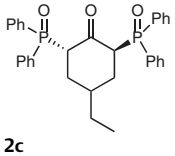
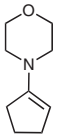
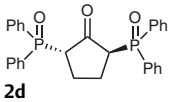
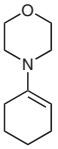
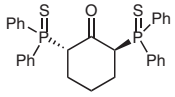
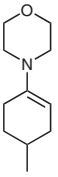
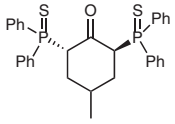
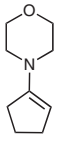
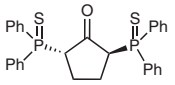
A mechanistic rationalization for the formation of the target compounds **2a–g** is provided in Scheme 1. This proposed mechanism involves, first of all, a nucleophilic attack by enamine on the phosphorus electrophile, giving rise to a (diphenylphosphinyl)enamine intermediate $\mathbf{I_1}$ in equilibrium with its regioisomer $\mathbf{I_2}$. The less-substituted (less-hindered) and less-conjugated enamine $\mathbf{I_2}$ was assumed to be more reactive than $\mathbf{I_1}$, what explains the regioselectivity in the second phosphinylation step and the formation of the second C–P bond from the less-hindered side, giving rise to the α,α′-bis(diphenylphosphinyl)enamine intermediate $\mathbf{I_3}$, rather than its α,α-regioisomer. The $\mathbf{I_3}$ intermediates were not stable enough to be isolated or hydrolyzed directly to obtain the corresponding α,α′-bis(diphenylphosphinyl)ketones. They were thus subjected, in situ, to oxidation or sulfurization followed by acid hydrolysis, to give the final α,α′-bis(diphenylphosphoryl)- or α,α′-bis(diphenylphosphorothioyl)cycloalkanones **2**, predominately in their *trans* form.

The observed diastereoselectivity is actually only set in the final hydrolysis step. The obtained results indicate that C-protonation of the C=C double bond in intermediate $\mathbf{I_4}$ occurs predominately from the side of the $Ph_2P{=}X$ group on the sp^3 carbon, giving rise to the *trans* isomer. This strongly suggests that the diphenylphosphoryl, or diphenylthiophosphoryl group $Ph_2P{=}X$ on the sp^3 carbon, specifically di-

Table 2 Substrate-Scope Studies



1 2

Entry	Enamine	[X][a]	Product	*trans*/*cis* (%)[b]	Yield (%)[c]
1		[O]	 **2a**	100/0	51
2		[O]	 **2b**	100/0	60
3		[O]	 **2c**	100/0	65
4		[O]	 **2d**	70/30	58
5		[S]	 **2e**	100/0	53
6		[S]	 **2f**	100/0	61
7		[S]	 **2g**	87/13	55

[a] [X], [O]: DMSO, reflux, 2 h; [S]: 1/8 S_8, 25 °C, 2 h.
[b] Determined from the ^{31}P NMR spectra.
[c] Isolated yield.

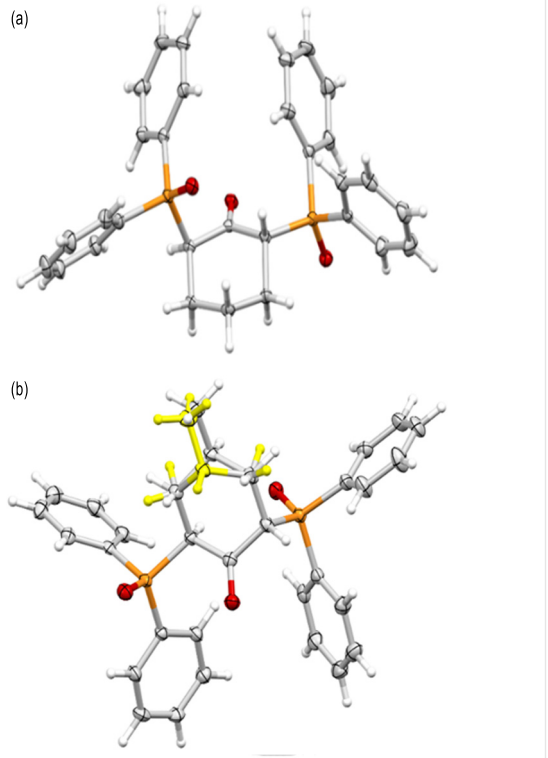


Figure 1 (a) X-ray molecular structure of compound **2a**. (b) X-ray molecular structure of compound **2b** showing both chair and boat (in yellow) conformations. Thermal displacements ellipsoids are drawn at the 50% probability level.

rects the C-protonation of the double bond in $\mathbf{I_4}$, but whether it is only sterically mediated to obtain the less hindered *trans* isomer, whether the $Ph_2P{=}X$ group induces a strong stereoelectronic control or whether this group is first protonated and then, in a specific conformation, transfers the proton to the C=C double bond, is not clear at this time; further work will be undertaken to clarify this situation.

In summary, we have successfully developed a straightforward regio- and diastereoselective approach to unprecedented symmetrical *trans*-α,α′-bis(diphenylphosphoryl)- and α,α′-bis(diphenylphosphorothioyl)cycloalkanones, through the reaction of cyclic enamines with excess *P*-chlorodiphenylphosphine in the presence of triethylamine, followed by oxidation or sulfurization and hydrolytic workup. The synthesized compounds could have promising applications as tridentate ligands for the complexation of various metals including rare earths (III). These studies are ongoing in our laboratory and will be reported in due course.

Acknowledgment

We gratefully acknowledge the Tunisian Ministry of Higher Education and Scientific Research and the Belgium Research Foundation Flanders (FWO) for financial support. K. V. Hecke thanks the Hercules Foundation (project AUGE/11/029 '3D-SPACE: 3D Structural Platform Aiming for Chemical Excellence') for funding.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588970.

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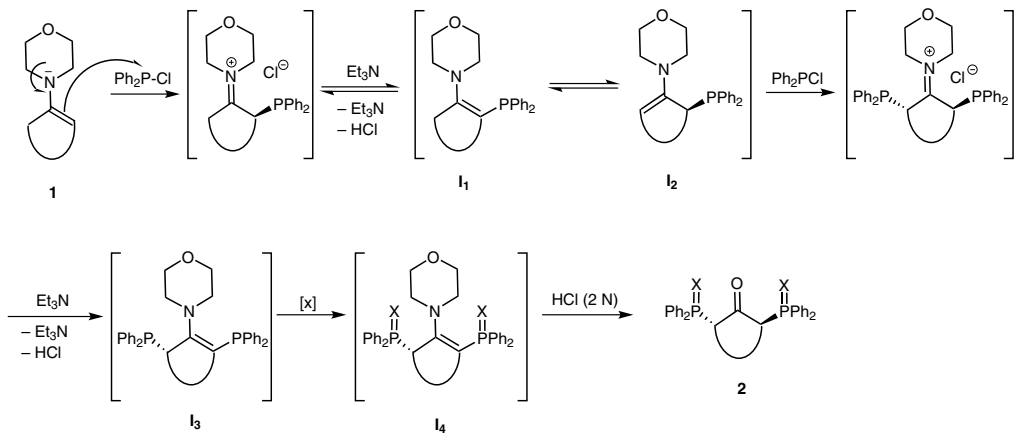

Scheme 1 Proposed mechanism for the formation of compounds **2**

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(28) Howells, D.; Warren, S. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1645.
(29) **General Procedure for the Synthesis of α,α′-Bis(diphenylphosphoryl)- and α,α′-Bis(diphenylphosphorothioyl)cycloalkanones 2**

To a well-stirred solution of enamine **1** (1 mmol) and Et_3N (6.6 mmol) in dry MeCN (15 mL), maintained under an inert atmosphere (N_2) and cooled at 0 °C, *P*-chlorodiphenylphosphine (1 mmol) in dry MeCN (3 mL) was added dropwise within 15 min. The resulting solution was warmed up to r.t. and stirred for 1 h. The reaction mixture was cooled again at 0 °C, and the second portion of *P*-chlorodiphenylphosphine (5 mmol) in dry MeCN (15 mL) was added in the same manner as before. The mixture was allowed to warm up to r.t. and then refluxed for an extra 2 h. The reaction mixture was then cooled and treated with DMSO or sulfur as follows.

Oxidation

DMSO (6 mmol) was added, and the mixture was heated under reflux for 2 h. After cooling, 2 N aq HCl solution (30 mL) was added dropwise at 0 °C and stirring was continued at r.t. for 12 h. The mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The residue obtained was chromatographed on a silica gel column using CH_2Cl_2 as eluent or recrystallized from toluene (in the case of compounds **2a** and **2c**).

Sulfurization

Ground sulfur (6 mmol) was added, and the reaction mixture was stirred at r.t. until complete dissolution of the sulfur in 2 h. 2 N aq HCl solution (30 mL) was then added dropwise at 0 °C and stirring was continued at r.t. for 12 h. The mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The residue obtained was chromatographed on a silica gel column using CH_2Cl_2 as eluent.

The compounds obtained were characterized by various spectroscopic tools including IR, NMR (^1H, ^{31}P, ^{13}C) spectroscopy, mass spectrometry, and single-crystal X-ray diffraction (see the Supporting Information).

***trans*-2,6-Bis(diphenylphosphoryl)cyclohexanone (2a)**

Yield 51%; white solid; mp 249–250 °C. IR (neat): $\nu_{P=O}$ = 1245 cm^{-1}; $\nu_{C=O}$ = 1706 cm^{-1}. ^{31}P NMR (161.97 MHz, CD_3OD): δ = 33.3 (s, 2 P). ^1H NMR (400.13 MHz, CD_3OD): δ = 2.01–2.22 (m, 6 H, 3 CH_2), 4.15–4.20 (m, 2 H, 2 CHP), 7.38–7.83 (m, 20 H, ArH). ^{13}C NMR (100.61 MHz, CD_3OD): δ = 21.7 (t, CH_2, $^3J_{C-P}$ = 6.0 Hz), 27.1 (s, 2 CH_2), 51.7 (d, 2 CHP, $^1J_{C-P}$ = 66.4 Hz), 201.7 (s, C=O); ArC: δ = 128.3, 128.4, 128.7, 128.8, 130.4, 129.9, 130.4, 130.5, 130.6, 130.9, 131.4, 131.8, 131.9,132.2. ESI-HRMS: *m/z* calcd for $C_{30}H_{28}O_3P_2$ $[M + H]^+$: 499.15864; found: 499.15796.