Direct regio- and diastereoselective diphosphonylation of cyclic enamines with P-chlorodiphenylphosphone: One-pot synthesis of α,α'-bis(diphenylphosphoryl)- and α,α'-bis(diphenylphosphorothioyl)cycloalkanones

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A straightforward regio- and diastereoselective process has been developed for the synthesis of unprecedented asymmetrical α,α'-bis(diphenylphosphoryl)- and α,α'-bis(diphenylphosphorothioyl)-cycloalkanones, through the reaction of cyclic enamines with excess P-chlorodiphenylphosphone in the presence of triethylamine, followed by oxidation or sulfurization and hydrolytic work-up.

By comparison with these existing strategies, our method which uses easily prepared enamines and commercially available P-chlorodiphenylphosphone 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.

Results and discussion

In order to establish the optimum reaction conditions for the formation of the target compounds, we used 1-morpholinocyclohexene 1a and P-chlorodiphenylphosphone as model substrates, in the presence of triethylamine. The reaction was studied by varying several conditions (solvents, molar equivalents of Ph₂PCl, temperature, reaction time). The results of these comparative experiments are summarized in Table 1.

Initially, the reaction was tested with 1 equiv Ph₂PCl and 1.1 equiv Et₃N in different solvents, in order to improve the experimental protocol for the formation of the monophosphonylated products²²,²³ 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 Ph₂PCl 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 Ph₂PCl. As shown in Table 1, when the reaction was conducted with 2 equiv 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 2 h (Table 1, entry 8). Further improvement in the yield to 35% was observed when using 3 equiv of Ph₂PCl 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 Ph₂PCl was increased to 6 molar equivalents (Table 1, entry 15). Switching to 7 equiv of Ph₂PCl brought no improvement in 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 6 equiv

Introduction

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 this kind of 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), 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 work-up, would allow a straightforward approach to unprecedented asymmetrical 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.²⁴-²⁶

To the best of our knowledge, asymmetrical 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 acid²⁷ and (ii) the bromination of 3-(diphenylphosphoryl)-3-methylbutanone followed by a Michaelis-Arbuzov cyclisation.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.

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- Electronic Supplementary Information (ESI) available: spectral data of all the new compounds. See DOI: 10.1039/x0xx00000x
of Ph₂PCl and 6.6 equiv of Et₃N in MeCN at 0 °C to reflux temperature for 2 h. 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 2 h, 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 h.

Table 1: Optimization of the reaction conditions

<table>
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<th>Entry</th>
<th>Ph₂P-Cl (equiv)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield of 2a (%)</th>
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*1.1 equiv of Et₃N for each equiv of Ph₂PCl. *2 Isolated yield.

With the optimized conditions in hand, 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(diphenyolphosphinyl)- 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 2a a mixture of cis and trans isomers is possible, trans configuration is exclusively obtained, except for the five membered cyclic compounds 2d and 2g (cis isomer present in 30 and 13% ratio respectively (Table 1)). The trans configuration was assigned on the basis of the single-crystal X-ray diffraction data of compound 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 the case of compound 2b, the 4-methylcyclohexan-1-one ring is mainly observed in the chair conformation. However, a very slight disorder was observed for this ring, adopting a boat conformation. The disorder was properly refined in two parts with final occupancy factors of 0.94 and 0.06, for the chair and boat conformations, respectively (Figure 1b). The coexistence of these two conformations could explain the observed doubling of ¹³C NMR signals for certain carbons, in the case of substituted cyclohexanones 2b and 2c (see Electronic Supplementary Information).
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 $I_1$ in equilibrium with its regioisomer $I_2$. The less substituted (less hindered) and less conjugated enamine $I_2$ was assumed to be more reactive than $I_1$, what explains the regioselectivity in the second phosphorylation step and the formation of the second C-P bond from the less hindered side, giving rise to the $\alpha,\alpha'$-bis(diphenylphosphinyl)enamine intermediate $I_3$, rather than its $\alpha,\alpha$-regioisomer. $I_2$ intermediates were not stable enough to be isolated or hydrolysed directly to obtain the corresponding $\alpha,\alpha'$-bis(diphenylphosphinyl)ketones. They were thus subjected, in situ, to oxidation or sulfurization followed by acid hydrolysis, to give the final $\alpha,\alpha'$-bis(diphenylphosphino)- or $\alpha,\alpha'$-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 $I_4$ occurs predominately from the side of the Ph$_3$P=X group on the sp$^2$ carbon, giving rise to the trans isomer. This strongly suggests that the diphenyl- phosphonyl or thiophosphoryl group Ph$_3$P=X on the sp$^2$ carbon, specifically directs the C-protonation of the double bond in $I_4$, but whether it is only sterically mediated to obtain the less hindered trans isomer, whether the Ph$_3$P=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.

**Conclusions**

In summary, we have successfully developed a straightforward regio- and diastereoselective approach to unprecedented symmetrical $trans$- $\alpha,\alpha'$-bis(diphenylphosphoryl)- and $\alpha,\alpha'$-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 work-up. 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.

**Experimental**

**General**

Commercially available reagents and solvents were used without further purification. Acetonitrile was dried by distillation from sodium and stored over activated molecular sieves (4 Å). When necessary the reactions were performed in oven-dried glassware under dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR, NMR and mass spectrometry. IR spectra were recorded on a Nicolet IR200 spectrometer. $^1$H, $^{31}$P, $^{13}$C and $^{13}$C APT NMR spectra were recorded on a 300 or 400 MHz-spectrometer. Chemical shifts (δ) are reported in part per million (ppm) relative to the residual solvent peak. High-resolution-MS spectra were performed on a Thermo LTQ Orbitrap XL mass spectrometer. Single crystal X-ray diffraction analysis was done on a Rigaku Oxford Diffraction Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using $\omega$ scans and CuKα ($\lambda = 1.54184$ Å) radiation. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluent. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F254). When necessary they were developed with KMnO$_4$ and SiO$_2$/I$_2$. 

$^a$ [K]: [O]: DMSO, reflux, 2 h; [S]: 1/8 S$_2$, 25 °C, 2 h. 
$^b$ Determined from the $^{31}$P NMR spectra. 
$^c$ Isolated yield.
Synthesis of cyclic enamines 1

The starting cyclic enamines 1 were prepared according to the procedure reported by Stork,29 with slight modification:

A mixture of cyclic ketone (1 mol) and morpholine (1.7 mol) in dry toluene (30 mL) was heated at reflux, with Dean-Stark separation of water, for 4 h. The solvent was then removed under vacuum and the crude obtained was distilled under reduced pressure to give pure enamine 1 in more than 90% yield.

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 triethylamine (6.6 mmol) in dry acetonitrile (15 mL), maintained under an inert atmosphere (N2) and cooled at 0 °C, P-chlorodiphenylphosphine (1 mmol) in dry acetonitrile (3 mL) was added dropwise within 15 min. The resulting solution was warmed up to room temperature 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 acetonitrile (15 mL) was added in the same manner as before. The mixture was allowed to warm up to room temperature 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, 2N aqueous HCl solution (30 mL) was added dropwise at 0 °C and stirring was continued at room temperature for 12 h. The mixture was then extracted with CH₂Cl₂ (3 × 10 mL). The organic phase was dried over MgSO₄ and concentrated under vacuum. The crude obtained was chromatographed on a silica gel column using CH₂Cl₂ 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 room temperature until complete dissolution of the sulfur in 2 h. 2N aqueous HCl solution (30 mL) was then added dropwise at 0 °C and stirring was continued at room temperature for 12 h. The mixture was then extracted with CH₂Cl₂ (3 × 10 mL). The organic phase was dried over MgSO₄ and concentrated under vacuum. The crude obtained was chromatographed on a silica gel column using CH₂Cl₂ as eluent.

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

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Notes and references