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Direct regio- and diastereoselective diphosphonylation of cyclic enamines with *P*-chlorodiphenylphosphine: 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 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 work-up.

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),[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 work-up, 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-

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.

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*-chlorodiphenylphosphine as model substrates, in the presence of triethylamine. The reaction was studied by varying several conditions (solvents, 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 1 equiv Ph_2PCl and 1.1 equiv 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 2 equiv of the phosphorus electrophile in MeCN at room temperature, the desired product **2a** was isolated and 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 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 6 molar equivalents (Table 1, entry 15). Switching to 7 equiv of Ph_2PCl 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

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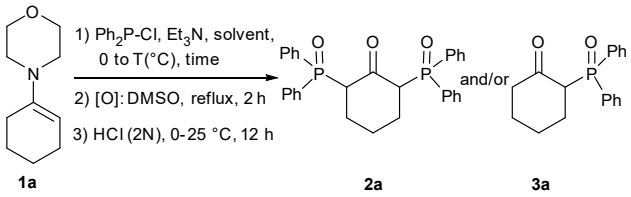
† Electronic Supplementary Information (ESI) available: spectral data of all the new compounds. See DOI: 10.1039/x0xx00000x

of Ph_2PCl and 6.6 equiv of Et_3N 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



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

Entry	Ph_2P-Cl (equiv)[a]	Solvent	T (°C)	Time (h)	Yield of **2a** (%)[b]	Yield of **3a** (%)[b]
1	1	ether	25	2	2	64
2	1	ether	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.

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(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, *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 ^{13}C NMR signals for certain carbons, in the case of substituted cyclohexanones **2b** and **2c** (see Electronic Supplementary Information).

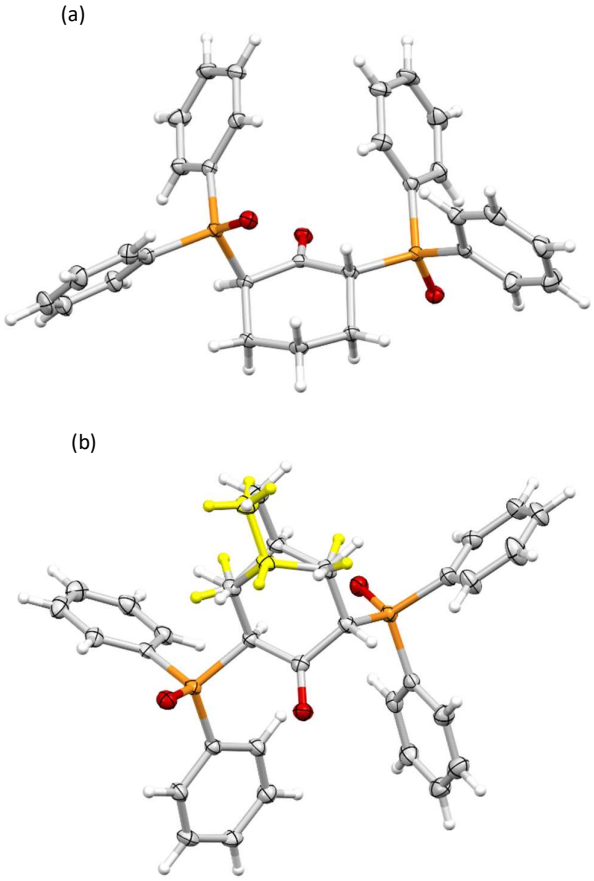
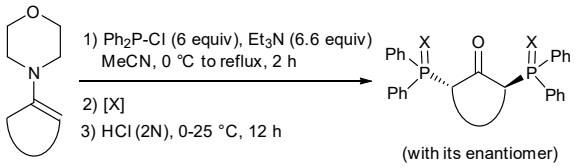


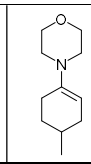
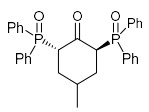
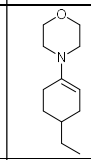
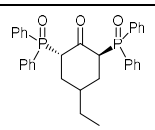
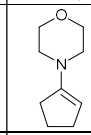
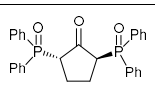
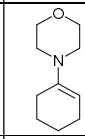
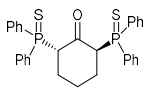
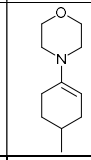
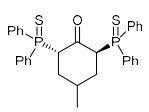
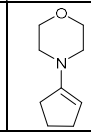
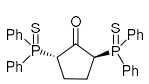
Fig. 1 (a) X-ray structure of compound **2a**. (b) X-ray structure of compound **2b** showing both chair and boat conformations.

Table 2: Substrate scope studies



1 **2**

Entry	Enamine	[X][a]	Product	% (*trans*/*cis*)[b]	Yield (%)[c]
1		[o]		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.

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 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 I_3, rather than its α,α-regioisomer. I_3 intermediates were not stable enough to be isolated or hydrolysed 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 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 diphenyl- phosphoryl or thiophosphoryl group $Ph_2P=X$ on the sp^3 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 $Ph_2P=X$ 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.

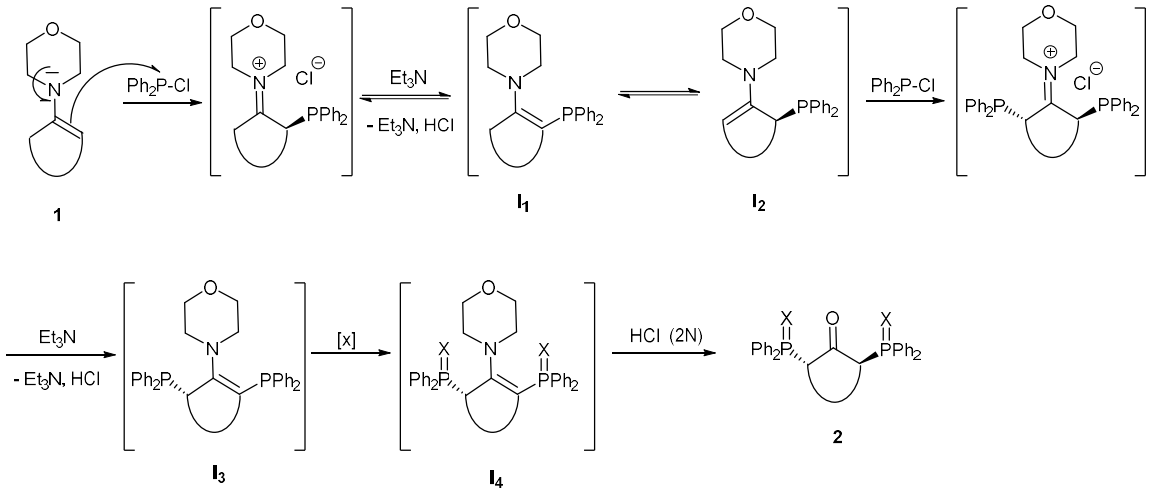
Conclusions

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 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 A°). 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. ^1H, ^{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 ω scans and CuKα (λ = 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.



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

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 (N_2) 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 CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude 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 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 CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude 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 Electronic Supplementary Information).

Acknowledgements

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Notes and references

1 A.N. Turanov, V.K. Karandashev and V.V. Ragulin, *Radiochemistry*, 2005, **47**, 278-283.
2 M.N. Litvina, M.K. Chmutova, Yu.M. Kulyako and B.F. Myasoedov, *Radiokhimiya*, 2001, **43**, 61.
3 H.H. Dam, D.N. Reinhoudt, and W. Verboom, *Chem. Soc. Rev*, 2007, **36**, 367.
4 Q. Jia, Q. Shang and W. Zhou, *Ind. Eng. Chem. Res*, 2004, **43**, 6703-6707.
5 B. Michel and C. Bruno, *J. Phys. Chem,* 1982, **86**, 4817-4821.
6 J.L. Martin and M.J. Leroy, *Chem. Res. (S)*, 1978, 88.
7 B.W. McCann, N. De Silva, T. L. Windus, M. S. Gordon, B. A. Moyer, V.S. Bryantsev and B.P. Hay, *Inorg. Chem*, 2016, in press, DOI: 10.1021/acs.inorgchem.5b02995.
8 A. Florido, I. Casas, J. Garcıa-Raurich, R. Arad-Yellin and A. Warshawsky, *Anal. Chem*, 2000, **72**, 1604.
9 L.J. Charbonniere, R. Ziesse, M. Montalti, L. Prodi, N. Zaccheroni, C. Boehme, and G. Wipff, *J. Am. Chem. Soc*, 2002, **124**, 7779.
10 A. Florido, L.G. Bachas, M. Valiente and I. Villaescusa, *Analyst*, 1994, **119**, 2421-2425.

11 H. Jian, L. Yunpeng, L. Yongxin and Z. Jianrong (Steve), *Chem. Commun*, 2013, **49**, 9425-9427.
12 P. Das, P. Chutia and D.K. Dutta, *Chem. Lett*, 2002, **31**, 766.
13 C.J. Chapman, C.G. Frost, M.P. Gill-Carey, G. Kociok-Köhn, M.F. Mahon, A.S. Weller, and M.C. Willis, *Tetrahedron Asymmetry*, 2003, **14**, 705-710.
14 E. Ichikawa, M. Suzuki, K. Yabu, M. Albert, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc*, 2004, **126**, 11808-11809.
15 O. Piechazyk, M. Doux, L. Ricard and P. le Floch, *Organometallics*, 2005, **24**, 1204-1213.
16 A.A. Boezio, J. Pytkowicz, A. Côté and A.B. Charette, *J. Am. Chem. Soc*, 2003, **125**, 14260-14261.
17 H. Xu, K. Yin and W. Huang, *Chem. Phys. Chem*, 2008, **9**, 1752-1760.
18 H. Slimani, S. Touil, *Phosphorus Sulfur Silicon Relat. Elem*, 2011, **186**, 1655.
19 H. Slimani, S. Touil, *Tetrahedron Lett*, 2011, **52**, 6481.
20 S. Touil, H. Zantour, *Phosphorus Sulfur Silicon Relat. Elem*, 2001, **175**, 183.
21 H. Slimani, S. Touil, *Heterocycles*, 2012, **85**, 2987.
22 A. A. Tolmachev, L. N. Morozova, A. N. Kostyuk, R. D. Lampeka, E. S. Kozlov, A. M. Pinchuk, *Zh. Obshch. Khim., 1989,* **59**, 2388. *C.A.*, 1990, **112**, 139184 n.
23 S. Barkallah, M. Boukraa, H. Zantour, B. Baccar, *Phosphorus Sulfur Silicon Relat. Elem*, 1996, **51**, 56.
24 B. Ceccaroli, J. Alstad, M.J.F. Leory, *Polyhedron*, 1982, **1**, 257.
25 R. Babecki, A.W.G. Platt, and J. Fawcett, *J. Chem. Soc. Dalton. Trans*, 1992, 675.
26 W. E. Van Zyl, *Comments Inorg. Chem*, 2010, **31**, 13.
27 J.K. Kim, E. Shokova, V. Tafeenko, V. Kovalev, *Beilstein J. Org. Chem*, 2014**, 10***,* 2270–2278.
28 D. Howells and S. Warren, *J. Chem. Soc. Perkin II*, 1973, 1645.
29 G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc,* 1963, **85**, 207.