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MoO_2Cl_2 as a novel catalyst for the synthesis of α-aminophosphonates

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ABSTRACT

This work reports the use of MoO_2Cl_2 as a novel catalyst for the synthesis of α-aminophosphonates. The system $HP(O)(OEt)_2/MoO_2Cl_2$ (5 mol%) was applied in the synthesis of several α-aminophosphonates in excellent yields under solvent-free conditions.

1. Introduction

α-Aminophosphonates and α-aminophosphonic acids [1] are structurally analogous to α-amino acids and constitute an important class of compounds with diverse biological activities and potential to be employed as enzyme inhibitors [2,3], antibiotics [4], and antitumor agents [5,6]. They also have a wide range of antiviral [7] and antifungal properties and are extensively used as insecticides and herbicides [8].

Among the various synthetic approaches for their preparation [9–13], the nucleophilic addition of dialkylphosphites to imines (Pudovik reaction) [10–13] is established as the most useful method. Several metal complexes have been used as effective catalysts for this reaction, including ytterbium [10], boron [11], aluminium [12], and zirconium [13] complexes. However, due to the biological activities of α-aminophosphonates, the search for new catalysts leading to an efficient and practical methodology for the synthesis of these compounds is highly desired.

Over the last years, we have demonstrated that high valent oxo-complexes activate X–H (X = Si and B) bonds [14–16]. We also described the efficient hydrosilylation of aldehydes and ketones [14,15] and the reduction of several functional groups such as aromatic nitro compounds [17], imines [18], amides [19], esters [20], sulfoxides [16,21–23], pyridine *N*-oxides [21], and alkenes [24] to the corresponding amines, alcohols, sulfides, pyridines, and alkanes using the catalytic systems silane/oxo-complexes or borane/oxo-complexes.

We have also demonstrated that MoO_2Cl_2 is a good catalyst for the synthesis of aromatic ketones and sulfones and for the C–C and C–S bond formation [25].

Very recently, we have reported the development of a novel method for the preparation of α-hydroxyphosphonates using the catalytic system $HP(O)(OEt)_2/MoO_2Cl_2$ (5 mol%; see Scheme 1) [26]. This methodology proved to be highly efficient for the synthesis of α-hydroxyphosphonates and for the C–P bond formation.

Our computational studies [26] indicated that this reaction proceeds with low activation barriers, starting with the coordination of the P = O bond of $HP(O)(OEt)_2$ to molybdenum and hydrogen transfer from P–H to the oxygen in Mo = O forming Mo–OH. The new intermediate reacts with the aldehyde substrate in two steps. In the first step, the aldehyde binds the metal through the carbonyl and the P–C bond forms; in the second step, the hydrogen is transferred from Mo–OH to the oxygen of the final product. These results opened a new area of catalysis for these complexes as excellent catalysts for C–P bond forming reactions.

In this work, we investigated the use of the high valent oxo-molybdenum complex MoO_2Cl_2 as a novel catalyst for the hydrophosphonylation of imines.

2. Experimental

2.1. General

Solvents were purified by conventional methods and distilled under nitrogen, prior to use. Diethylphosphonate and MoO_2Cl_2 were obtained from Aldrich. Flash chromatography was performed on MN Kieselgel 60 M 230–400 mesh. ^1H NMR, and ^{13}C NMR spectra were measured on a Bruker Avance III 400-MHz spectrometer. Chemical

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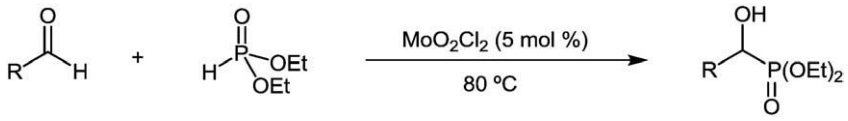
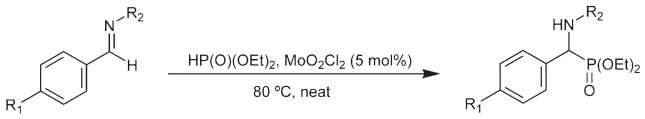


Scheme 1. Hydrophosphonylation of aldehydes catalyzed by MoO_2Cl_2.

Table 1
Hydrophosphonylation of imines catalyzed by MoO_2Cl_2.[a]



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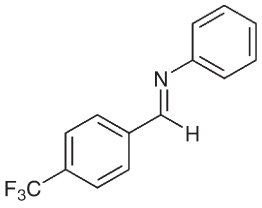
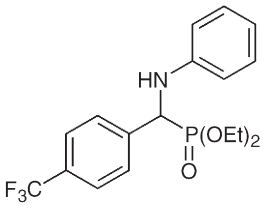
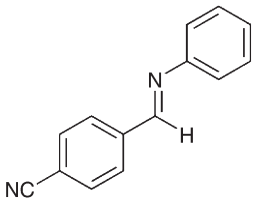
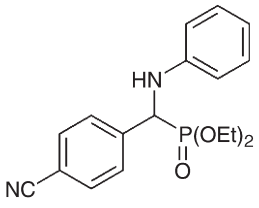
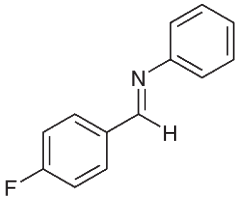
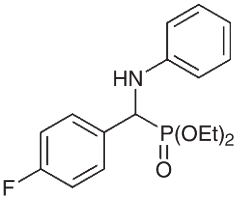
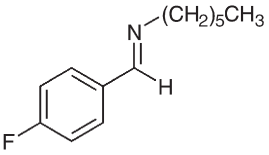
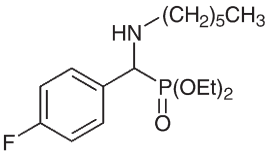
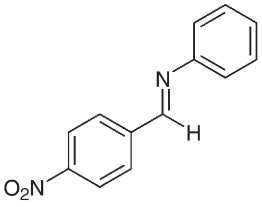
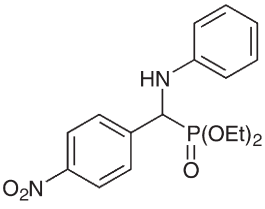
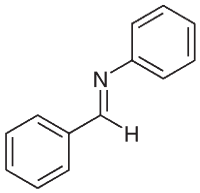
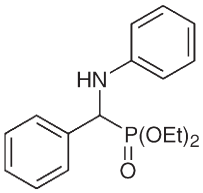
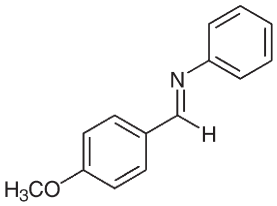
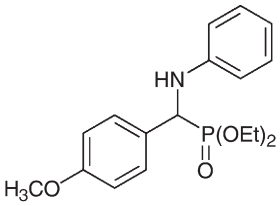
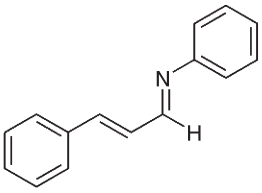
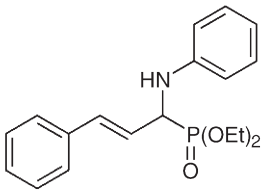
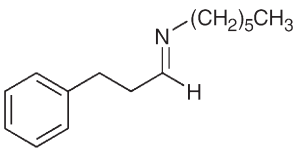
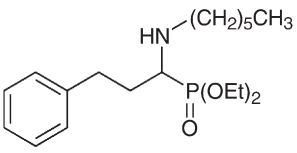
1			5	95
2			5	89
3			5	90
4			60	85
5			15	80
6			15	87

Table 1 (*continued*)

Entry	Substrate	Product	Time (min)	Yield (%)[b]
				
7			20	80
8			5	95
9			30	95

[a] All reactions were carried out with 2.0 mmol of imine, 2.4 mmol of $HP(O)(OEt_2)_2$ and 5 mol % of MoO_2Cl_2.
[b] Isolated yield.

shifts are reported in parts per million (ppm) downfield from an internal standard.

2.2. General procedure for the hydrophosphonylation of imines with the system $HP(O)(OEt)_2/MoO_2Cl_2$

In a typical experiment, to a mixture of imine (2 mmol) and MoO_2Cl_2 (5 mol%) was added $HP(O)(OEt)_2$ (2.4 mmol). The reaction mixture was stirred at 80 °C under inert atmosphere and the progress of the reaction was monitored by TLC and ^1H NMR. When the reaction is complete, water (3 mL) was added and the mixture was stirred at 80 °C. After 1 hour, the reaction mixture was cooled to ambient temperature and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Whenever necessary the residue was purified by flash chromatography with appropriate mixtures of *n*-hexane and ethyl acetate to afford the α-aminophosphonates, which are well known compounds.

3. Results and discussion

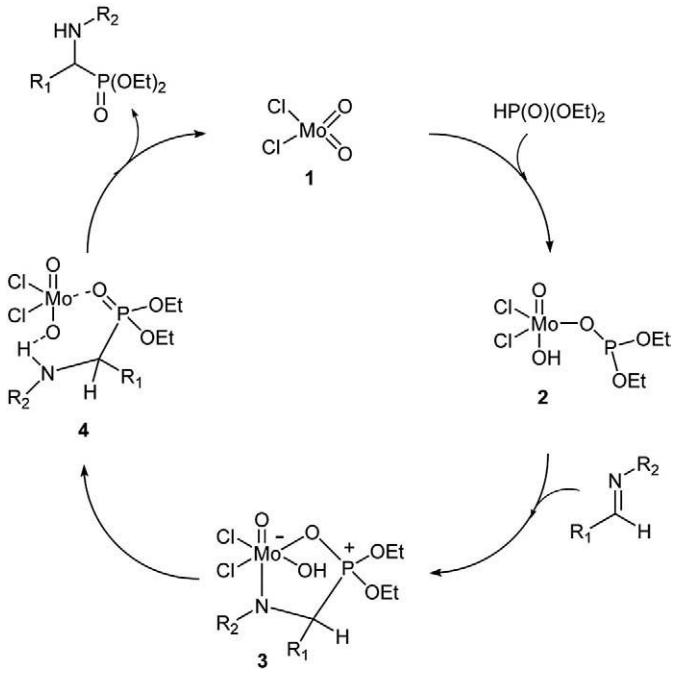
In order to explore the scope and the limitations of this novel method, we investigated the reaction of several imines with the system $HP(O)(OEt)_2/MoO_2Cl_2$ (5 mol%) at 80 °C under solvent-free conditions (Table 1). The progress of the reactions was monitored by thin layer chromatography and by ^1H NMR. The analysis of the Table 1 results showed that the hydrophosphonylations were very fast, producing the α-aminophosphonates in good to excellent yields.

The reactions of the aryl-*N*-aryl imines containing the trifluoromethyl-, cyano- and fluoro- groups required only 5 minutes to give the corresponding α-aminophosphonates in excellent isolated yields (Table 1, entries 1–3). Longer reaction times (30–60 min) were needed for the reactions of aryl-*N*-alkyl imines (Table 1, entries 4 and 9).

The hydrophosphonylation of the imines, prepared from hydrocinnamaldehyde and cinnamaldehyde, also afforded the corresponding α-aminophosphonates in good to excellent yields within 5–30 minutes (Table 1, entries 8 and 9).

Excellent chemoselectivity was observed for substrates containing various substituents such as CF_3, F, CN, NO_2, and OCH_3 (Table 1, entries 1–5 and 7) and also having a double bond conjugated to the imino group (entry 8). To the best of our knowledge, this is the first example of the synthesis of α-aminophosphonates catalyzed by a high valent oxo-molybdenum complex.

Unfortunately, it was not possible to characterize, by spectroscopic methods, the species formed in the reaction between $HP(O)(OEt)_2$ and MoO_2Cl_2, due to its instability. For this reason, we propose a mechanism for this reaction (Scheme 2) based on the DFT studies performed for the hydrophosphonylation of aldehydes with the same catalytic system [26]. We suggest a similar initial activation of



Scheme 2. Proposed catalytic system for the hydrophosphonylation of imines with the catalytic system $HP(O)(OEt)_2/MoO_2Cl_2$.

$HP(O)(OEt)_2$ by coordination of P = O bond to molybdenum and hydrogen transfer from P–H to the oxygen in Mo = O, forming Mo–OH (see Scheme 2) as reported before [26]. In the next step, the imine binds to the molybdenum of the intermediate 2 through the nitrogen, followed by the C–P bond formation. Finally, the hydrogen is transferred from Mo–OH to the nitrogen of the final product.

In conclusion, we have demonstrated that MoO_2Cl_2 is a novel and efficient catalyst for the synthesis of α-aminophosphonates by the addition of $HP(O)(OEt)_2$ to imines. This methodology has high yields, good chemoselectivity, and short reaction times under mild and solvent-free conditions.

These results extend the use of the high valent oxo-molybdenum complexes as excellent catalysts for C–P bond forming reactions. We believe that this procedure will be a useful and attractive alternative to the existing methods for the synthesis of α-aminophosphonates.

The application of oxo-complexes to other C-X bond forming reactions and to the asymmetric hydrophosphonylation of imines are currently being investigated in our group.

Acknowledgments

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