Tetrahedron 74 (2018) 1817–1825

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Direct Aminophosphonylation of aldehydes catalyzed by cyclopentadienyl ruthenium(II) complexes

Ivânia R. Cabrita, Sara C.A. Sousa, Pedro R. Florindo, Ana C. Fernandes*

Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal

ARTICLE INFO

Article history:
Received 12 December 2017
Received in revised form
5 February 2018
Accepted 20 February 2018
Available online 23 February 2018

Keywords:
Aminophosphonylation
Aldehydes
α-Aminophosphonates
Ruthenium complexes

ABSTRACT

This work reports a novel method for the direct aminophosphonylation of aldehydes catalyzed by cyclopentadienyl ruthenium(II) complexes. The system $HP(O)(OEt)_2$/$[CpRu(PPh_3)_2Cl]$ was very efficient for the aminophosphonylation of aldehydes with primary and secondary amines, producing the corresponding α-aminophosphonates in good to excellent yields. This novel method has several advantages including the use of a small amount of catalyst (0.5 mol%), high chemoselectivity, solvent-free conditions and application of the catalyst $[CpRu(PPh_3)_2Cl]$ for at least 12 cycles with excellent activity.

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] Thus, a number of methods have been developed for the synthesis of α-aminophosphonates both in racemic and in optically active forms.[9–15] Among the available synthetic methods for α-aminophosphonates, the three-component reaction of aldehyde, amine, and phosphite, also known as Kabachnik–Fields reaction, has gained much attention due to its one-pot manner and convenience of synthesis of these compounds.[16,17] Different catalysts have been employed for the synthesis of α-aminophosphonates including $SnCl_2 \cdot 2H_2O$,[18] $ZnBr_2$,[19] $HfCl_4$,[20] lanthanide triflate,[21] $Yb(PFO)_3$,[22] SmI_2,[23] $TaCl_5$,[24] $Cd(ClO_4)_2 \cdot xH_2O$,[25] $BiCl_3$,[26] $LiClO_4$,[27] $FeCl_3$[28] or MoO_2Cl_2.[29] In the last years, several methods for the synthesis of α-aminophosphonates have also been developed using microwaves radiations.[30–34] However, the use of ruthenium complexes as catalysts for the synthesis of α-aminophosphonates has never been studied. In this work we reported the first method for the synthesis of α-aminophosphonates with high yields catalyzed by cyclopentadienyl ruthenium(II) complexes.

2. Results and discussion

The catalytic activity of several cyclopentadienyl ruthenium(II) complexes (Fig. 1) was evaluated in the aminophosphonylation of 4-(methylthio)benzaldehyde with aniline and $HP(O)(OEt)_2$ under solvent-free conditions in air atmosphere (Table 1). All the catalysts were very efficient, producing the α-aminophosphonate in excellent yields. The best result (95%) was obtained in the presence of 0.5 mol% of $[CpRu(PPh_3)_2Cl]$ after 15 min (Table 1, entry 1). Using 0.25 mol% of this catalyst the reaction required 1 h and the α-aminophosphonate was isolated in only 51% yield (Table 1, entry 2). The reaction carried out at room temperature afforded the product in only 42% yield after 24 h (Table 1, entry 3). The catalysts $[CpRu(PPh_3)(2,2'\text{-bipy})][PF_6]$ **2**, $[CpRu(dppe)Cl]$ **3** and $[CpRu(PPh_3)(phen)][PF_6]$ **4** were also very efficient, giving excellent yields of α-aminophosphonate (Table 1, entries 4–6). The reactions carried out with the complexes containing a carbohydrate moiety derived from xylose and fructose also produced excellent yields of the product (Table 1, entries 7 and 8). Finally, in the absence of catalyst only 19% of product was obtained after 1 h (Table 1, entry 9).

Aminophosphonylation of 4-(methylthio)benzaldehyde with aniline catalyzed by $[CpRu(PPh_3)_2Cl]$ (0.5 mol%) was investigated with the H-phosphonates $HP(O)(OEt)_2$, $HP(O)(OMe)_2$, $HP(O)(OBu)_2$ and $HP(O)(OPh)_2$ under solvent-free conditions at 80 °C in air

* Corresponding author.
E-mail address: anacristinafernandes@tecnico.ulisboa.pt (A.C. Fernandes).

https://doi.org/10.1016/j.tet.2018.02.047
0040-4020/

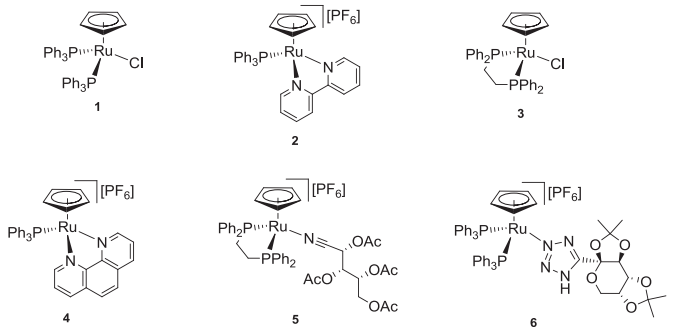


Fig. 1. Structure of catalysts **1**–**6**.

atmosphere (Table 2). Although all H-phosphonates afforded the α-aminophosphates in excellent yields, the reaction with $HP(O)(OEt)_2$ was much faster, requiring only 15 min (Table 2, entry 1). In contrast, the reaction performed with $HP(O)(OPh)_2$ needed 24 h to be completed (Table 2, entry 4).

To evaluate the efficiency of the system $HP(O)(OEt)_2$/$[CpRu(PPh_3)_2Cl]$ (0.5 mol%), it was tested in the direct aminophosphonylation of a large variety of aldehydes with aniline under solvent-free conditions at 80 °C in air atmosphere (Table 3). In general, the reactions were very fast, affording the corresponding α-aminophosphonates in good to excellent yields, with high chemoselectivity, tolerating several functional groups such as $-OCH_3$, $-SCH_3$, -F, -Br, $-CF_3$, -OH, $-CO_2R$, and heterocyclic or Cp rings.

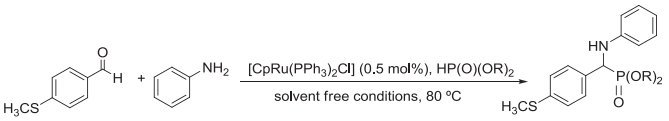
Direct aminophosphonylation of 4-(methylthio)benzaldehyde was also explored using different anilines containing electron-donating and electron-withdrawing groups with the system $HP(O)(OEt)_2$/$[CpRu(PPh_3)_2Cl]$ (0.5 mol%) producing the corresponding α-aminophosphonates in excellent yields (Table 4).

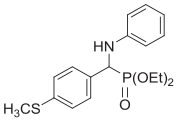
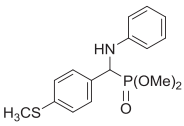
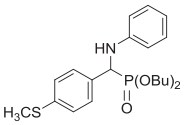
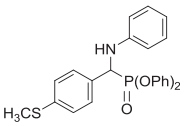
Finally, the direct aminophosphonylation of different aldehydes using methyl-*N*-aniline with the system $HP(O)(OEt)_2$/$[CpRu(PPh_3)_2Cl]$ (0.5 mol%) was studied, obtaining the corresponding tertiary α-aminophosphonates in good to excellent yields (Table 5).

To study the possible use of the complex $[CpRu(PPh_3)_2Cl]$ (0.5 mol%) as catalyst in multiple cycles, successive reactions were carried out by sequential addition of fresh substrate 4-(methylthio) benzaldehyde, aniline and $HP(O)(OEt)_2$ to the reaction mixture. The results showed that $[CpRu(PPh_3)_2Cl]$ can be used for at least 12 catalytic cycles with excellent yields (Fig. 2).

Aminophosphonylation of aldehydes catalyzed by cyclopentadienyl ruthenium complexes should start with the formation of the imine by reaction between the aldehyde and aniline. Then, the activation of the H-phosphonate by the catalyst $[CpRu(PPh_3)_2Cl]$ should occur, producing the species $[CpRu(PPh_3)Cl(PO)(OEt)_2]^-$, detected by mass spectrometry. Finally, the reaction between this species and the imine lead to the formation of α-aminophosphonate.

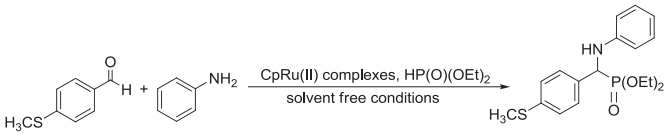
Table 2
Direct aminophosphonylation of 4-(methylthio)benzaldehyde with aniline catalyzed by $[CpRu(PPh_3)_2Cl]$ using different $HP(O)(OR)_2$[a].



Entry	$HP(O)(OR)_2$	Product	Time	Yield (%)[b]
1	$HP(O)(OEt)_2$		15 min	95
2	$HP(O)(OMe)_2$		25 min	94
3	$HP(O)(OBu)_2$		1 h	94
4	$HP(O)(OPh)_2$		24 h	94

[a] The reactions were carried out with 2.0 mmol of 4-(methylthio)benzaldehyde, 2.0 mmol aniline and 2.0 mmol of $HP(O)(OR)_2$.
[b] Isolated yields.

Table 1
Direct aminophosphonylation of aldehydes catalyzed by CpRu(II) complexes.[a]



Entry	Catalyst	Catalyst (mol%)	Temp. (°C)	Time	Yield (%)[b]
1	$[CpRu(PPh_3)_2Cl]$ **1**	0.5	80	15 min	95
2	$[CpRu(PPh_3)_2Cl]$ **1**	0.25	80	1 h	51
3	$[CpRu(PPh_3)_2Cl]$ **1**	0.5	r.t.	24 h	42
4	$[CpRu(PPh_3)(2,2'\text{-bipy})][PF_6]$ **2**	0.5	80	30 min	94
5	[CpRu(dppe)Cl] **3**	0.5	80	40 min	93
6	$[CpRu(PPh_3)(phen)][PF_6]$ **4**	0.5	80	50 min	91
7	$[CpRu(PPh_3)_2(NCXylAc)][PF_6]$ **5**	0.5	80	40 min	95
8	$[CpRu(PPh_3)_2(Fru)][PF_6]$ **6**	0.5	80	20 min	92
9	Without catalyst	–	80	1 h	19

[a] All reactions were carried out with 2.0 mmol of 4-(methylthio)benzaldehyde, 2.0 mmol of aniline and 2.0 mmol of $HP(O)(OEt)_2$.
[b] Isolated yields.