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LETTERS

Three component coupling catalyzed by $TaCl_5$–SiO_2: synthesis of α-amino phosphonates[†]

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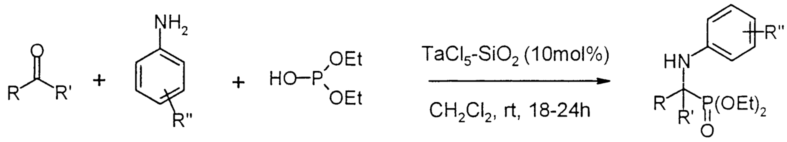
Abstract—$TaCl_5$–SiO_2 has been utilized as an efficient Lewis acid catalyst for the three component coupling of carbonyl compounds, aromatic amines and diethyl phosphite to produce α-amino phosphonates. © 2001 Published by Elsevier Science Ltd.

Of late, the synthesis and use of α-amino phosphonates have received attention as structural analogues of the corresponding α-amino acids. Peptido mimetics[1] made out of this class of compounds have shown promising pharmacological properties.[2] They also play an important role in hapten design for antibody generation[3] and enzyme inhibitors.[4] Thus, a variety of synthetic approaches are desirable to synthesize α-amino phosphonates. Of the methods available, the nucleophilic addition of phosphites to imines is convenient and is usually activated by an alkali metal alkoxide or by an acid.[5] Lewis acids such as $SnCl_2$, $SnCl_4$ and $BF_3{\cdot}OEt_2$, $ZnCl_2$ and $MgBr_2$ have also been used to promote the addition reaction.[6] However, the synthesis cannot proceed in one-pot from a carbonyl compound, an amine and a phosphite. To address some of the limitations posed by known reagents, we initiated a programme to explore the use of $TaCl_5$ and $TaCl_5$–SiO_2 for Lewis acid promoted reactions.[7] Herein we disclose the $TaCl_5$-catalyzed three component coupling of carbonyl compounds, amines and diethyl phosphite for the synthesis of various amino phosphonates (Scheme 1).

We investigated the reaction between *p*-tolualdehyde (Table 1, entry 1), aniline and diethyl phosphite by stirring equimolar quantities in dichloromethane in the presence of $TaCl_5$–SiO_2 for 22 hours and isolated the desired amino phosphonate in a 92% yield. After this success, several aldehydes, amines and diethyl phosphite were examined in the presence of 10 mol% $TaCl_5$–SiO_2 in dichloromethane. The results are summarized in Table 1. It is demonstrated for the first time, that the $TaCl_5$–SiO_2 coordinates with the nitrogen of the imine and facilitates the nucleophilic addition of diethyl phosphite to yield the α-amino phosphonate. In all cases, the three component coupling proceeded smoothly and the corresponding α-amino phosphonates were isolated. The examples studied included electron-rich aromatic aldehydes (entries 1, 2, 3, 6, 7, 8 and 9) and amines (entries 3, 4, 7, 8, 10 and 13); and electron deficient aromatic aldehydes (entries 12 and 13) and amines (entries 9, 11, 15, 16 and 18). Ketones (entries 17 and 18) also gave α-amino phosphonates in good yields at room temperature. Unlike lanthanide triflate[8] and indium chloride,[9] where reflux conditions are required,



R = alkyl,aryl
R' = H,alkyl.
R''= H, NO_2, OMe, OH, F.

Scheme 1.

Keywords: carbonyl compound; amine; diethyl phosphite; α-amino phosphonate; $TaCl_5$.

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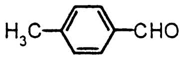
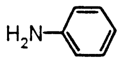
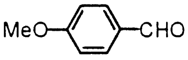
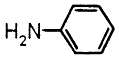
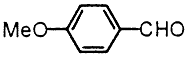
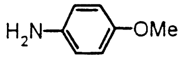
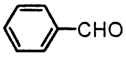
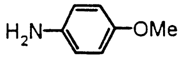
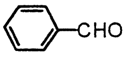
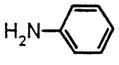
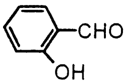
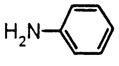
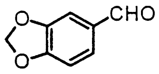
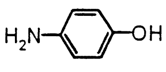
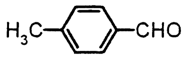
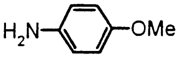
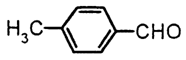
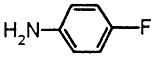
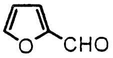
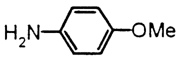
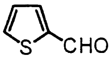
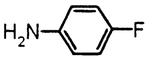
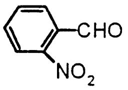
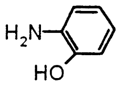
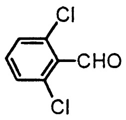
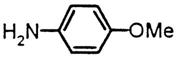
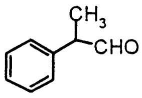
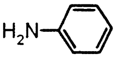
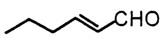
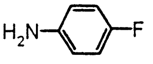
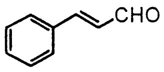
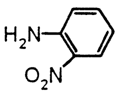
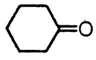
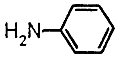
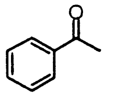
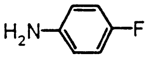
following the present protocol the reaction proceeded at room temperature. The overall yield of this multicomponent coupling was between 81 and 94% irrespective of the nature of aldehyde or amine. The only limitation detected was that aliphatic amines gave non-characterizable products. However, aliphatic aldehydes (entry 14) and conjugated aldehydes (entries 15 and 16) reacted well.

Table 1. Tantalum(V) chloride–silica gel catalyzed one-pot synthesis of α-amino phosphonates from aldehydes/ketones and amines[a]

Entry	Aldehyde/ketone	Amine	Time (h)	Yield (%)[b]
1.			22	92
2.			19	88
3.			18	94
4.			18	93
5.			20	90
6.			24	84
7.			24	81
8.			18	93
9.			18	94
10.			20	92
11.			20	93
12.			24	87
13.			18	88
14.			20	92
15.			22	85
16.			24	82
17.			22	81
18.			24	87

[a] All products were determined by ^{1}H NMR and mass spectral data.

[b] Isolated yield.

In conclusion, it has been demonstrated that $TaCl_5$–SiO_2 is an efficient catalyst for the three component coupling of a carbonyl compound, an amine and diethyl phosphite to yield α-amino phosphonates, which can serve as peptide mimetics. The advantages of this procedure are the operational simplicity, the general applicability to aldehydes and ketones at room temperature and the high yields obtained. We believe that this method presents a better and more practical alternative to existing methodologies for the synthesis of α-amino phosphonates. Also, it was demonstrated for the first time that $TaCl_5$ is an efficient coordinating metal for nitrogen facilitating the nucleophilic addition of diethyl phosphite.

Experimental procedure

A mixture of *p*-tolualdehyde (100 mg, 1 mmol), aniline (77 mg, 1 mmol) and diethyl phosphite (114 mg, 1 mmol) was added to a solution of $TaCl_5$–SiO_2 (10 mol%,[10] 29 mg, 0.1 mmol) in dichloromethane (4 mL), and the mixture was stirred 22 hours at room temperature under a nitrogen atmosphere. Upon completion (TLC), the reaction was filtered through Celite, diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2×10 mL). The organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuum and the crude product was column chromatographed on a silica gel column to afford pure α-amino phosphonate.

Acknowledgements

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9. Ranu, B. C.; Hajra, A.; Jana, U. *Org*. *Lett*. **1999**, *1*, 1141.
10. Preparation of $TaCl_5$–silica gel: Tantalum(V) chloride–silica gel was prepared by mechanically shaking chromatography grade silica gel (10 g, 100–200 mesh, dried overnight at 100°C) and tantalum(V) chloride (3 g) for 20 h.