VCL_3 CATALYZED EFFICIENT ONE-POT SYNTHESIS OF A-AMINO PHOSPHONATES

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Abstract : α-Aminophosphonates are synthesized by three component condensation of aldehydes, amines and trimethylphosphite in acetonitrile by using VCl_3 as catalyst. Compared to the conventional methods, this new method consistently has the advantages including excellent yields, short reaction times and mild reaction conditions.

Introduction

α-Aminophosphonates continue to attract increased interest as synthetic targets, because of their structural analogy to α-Aminoacids. Aminophosphates are the important class of biologically active compounds[1], They act as peptide mimics[2], enzyme inhibitors[3], antibiotics[4], crop protection agents[5] and catalytic antibodies[6]. As a result, a variety of synthetic approaches[7] have been developed for the synthesis of α-Aminophosphonates. Of these methods, the nucleophilic addition of phosphates with imines, catalyzed by an acid or a base is one of the most convenient methods. It is interesting to note that the Lewis acids catalyze the reaction in much milder conditions[8]. Among these Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3.OEt_2$, $ZnCl_2$ / $MgBr_2$ have been used for this transformation[9,10]. However, these reactions cannot be carried out in a one-pot operation starting from aldehydes[10]. Recent reagent include $ZrCl_4$[11], lanthanide triflates[12], $InCl_3$[13], $LiClO_4$-TMSCl[14] and Montimorllonite-KSF[15] were used for this transformation. Very recently a solvent free reaction between aldehydes, ammonium formate and dialkyl phosphite catalyzed by alumina under microwave conditions is also reported[16]. Most of the above mentioned procedures employ dimethylphospite as the reagent, with a view to see the migration of methyl carbonium ion to that of using dimethyl (trimethyl silyl) phosphite[17], was the primary aim of the present investigation. The present study also aims at development of cheaper alternative reagent. Herein we report an efficient and inexpensive protocol for the synthesis of α-Aminophosphonates using catalytic amount of VCl_3 under mild reaction conditions **Scheme 1.**

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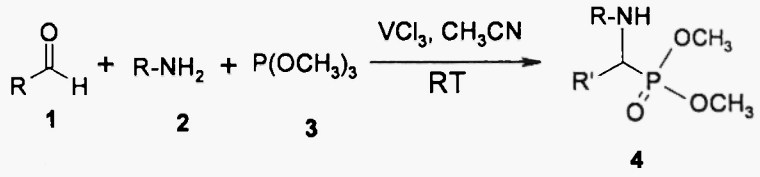

Scheme 1

Results and Discussion

The treatment of benzaldehyde, aniline and trimethylphosphite in the presence of 10 mol percent of VCl_3 in acetonitrile medium at room temperature resulted in the formation of the corresponding α-Aminophosphonates in 95% yield within 10 min. Similarly various aldehydes and amines were treated with trimethylphosphite to afford the corresponding α-Aminophosphonates at ambient temperature in high yields within 5-10 min **Table-1**. The reaction conditions are very mild and the α-Aminophosphonates are exclusively formed without formation of any undesired side products. The present method does not require any additives or promoters[10] to proceed the reaction.

Experimental

To a stirred solution of benzaldehyde (10 mmol) and aniline (10 mmol) in acetonitrile (25 mL) was added trimethylphosphite (10 mmol) and VCl_3 (10 mol %). The reaction mixture was stirred at room temperature (**Table 1**), i. e. till the completion of the reaction as indicated by the TLC. The reaction mixture was quenched with cold water and extracted with dichloromethane (2 × 50 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum and purified by column chromatography (hexane: ethyl acetate, 80:20) to afford corresponding pure α-Aminophosphonates in 95% yield.

In summary, we have demonstrated a novel and efficient protocol for the synthesis of α-Aminophosphonates using catalytic amount of VCl_3. The method offers several advantages including high yields of product, very short reaction times, inexpensive catalyst, does not involve any additives to promote the reaction.

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Table –1: VCl_3 catalyzed efficient synthesis of α-Aminophosphonates[a]

Entry	Aldehyde	Amine	Reaction Time (min)	Yield (%)[b]
4a	C_6H_5CHO	$C_6H_5NH_2$	5	95
4b	2-(OH) C_6H_4CHO	$C_6H_5NH_2$	10	90
4c	4-(CH_3) C_6H_4CHO	$C_6H_5NH_2$	5	94
4d	4-(OCH_3)	$C_6H_5NH_2$	10	92
4e	2-(Cl) C_6H_4CHO	$C_6H_5NH_2$	10	90
4f	4-(CHO) C_5H_4N	$C_6H_5NH_2$	5	93
4g	C_6H_5CHO	2-(CH_3) $C_6H_4NH_2$	10	94
4h	C_6H_5CHO	4-(CH_3) $C_6H_4NH_2$	10	90
4i	C_6H_5CHO	4-(Cl) $C_6H_4NH_2$	10	94
4j	C_6H_5CHO	$C_6H_5CH_2NH_2$	10	95
4k	C_6H_5CHO	2-(Br) $C_6H_4NH_2$	15	93
4l	2-(CHO) C_4H_3O	$C_6H_5NH_2$	15	94
4m	2-(CHO) C_4H_3O	$C_6H_5CH_2NH_2$	15	93

[a]All products were characterized by ^1H NMR, IR, and Mass spectra

[b]Isolated and unoptimized yield

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