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General Procedure for the Synthesis of α-Amino Phosphonates from Aldehydes and Ketones Using Indium(III) Chloride as a Catalyst

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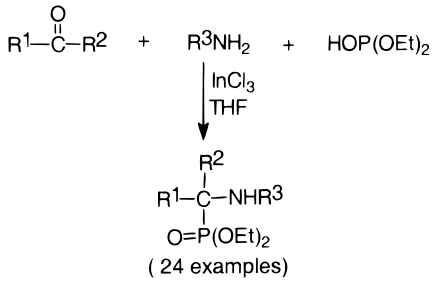
ABSTRACT



A simple, efficient, and general method has been developed for the synthesis of α-amino phosphonates through a one-pot reaction of aldehydes and ketones with amines in the presence of indium(III) chloride as a catalyst.

α-Amino phosphonates, due to their structural analogy to α-amino acids, have been the subject of considerable current interest. The potential of α-amino phosphonates as peptide mimetics,[1] enzyme inhibitors,[2] and antibiotics and pharmacologic agents[3] has been established. Thus, an efficient synthesis of these compounds is of importance. A number of synthetic methods for α-amino phosphonates have been developed during past two decades.[4] Of these methods, the nucleophilic addition of phosphites to imines, catalyzed by a base or an acid, is the most convenient. Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3{\cdot}Et_2O$, $ZnCl_2$, and $MgBr_2$ have been used. However, these reactions cannot be carried out in a one-pot operation with a carbonyl compound, amine, and dialkyl phosphite because the amines and water that exist during imine formation can decompose or deactivate Lewis acids.[5] This disadvantage has been overcome by a recent procedure[6] using a combination of lanthanide triflate and magnesium sulfate. However, although this approach is satisfactory for reactions with aromatic aldehydes and amines, the reaction of ketones has not been reported. In addition, amino phosphonates from aliphatic aldehydes and amines are obtained in low or moderate yields.[6] Thus, an efficient procedure for the synthesis of α-amino phosphonates from both aldehydes and ketones with aliphatic as well as aromatic amines is needed.

Recently indium(III) chloride has emerged as a Lewis acid imparting high regio- and chemoselectivity in various chemical transformations.[7] One of the remarkable features of $InCl_3$ is its efficient activity in aqueous medium.[7] Thus, we

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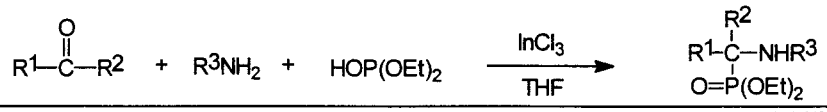
Table 1. Synthesis of α-Amino Phosphonates from Aldehydes/Ketones and Amines Catalyzed by $InCl_3$



entry	R^1	R^2	R^3	time(h) rt/reflux[a]	time(h) sonication	yield(%)[b] rt/reflux	yield(%)[b] sonication
1	Ph	H	Ph	11	5	92	93
2	Ph	H	$PhCH_2$	12	5	93	95
3	Ph	H	PhCH(Me)	12	6	90[c]	90[c]
4	Ph	H	$MeCH_2CH_2$	12	5	89	90
5	Ph	H		15	7	88	90
6	*p*-OMe–Ph	H	Ph	10	6	92	92
7	*p*-OMe–Ph	H	Me_2CH	12	7	88	90
8	*p*-NO_2–Ph	H	Ph	12	7	80	82
9	PhCH=CH (trans)	H	Ph	10	6	85	85
10	*m*-OH–Ph	H	Ph	10	6	91	93
11		H	Ph	11	7	92	92
12		H	PhCH(Me)	14	7	90[d]	90[d]
13	n-Pr–CH=C(Et)(trans)	H	$PhCH_2$	14	7	88	89
14	Me_2CH	H	$PhCH_2$	13	6	86	88
15	n-Pr	H	Me_2CH	14	6	85	87
16	Me_2C=CH$(CH_2)_2$C(Me)=CH (trans)	H	$PhCH_2$	13	6	87	89
17	Et	Et	$PhCH_2$	11	9	80	82
18	Ph	Me	$PhCH_2$	12	9	81	85
19	PhCH(OH)CH(Me)	CH(Me)CH(OH)Ph	$PhCH_2$	14	9	89	90
20	cyclohexanone		$PhCH_2$	9	6	85	87
21	4-t-butyl cyclohexanone		$PhCH_2$	10	7	80	80
22	indanone		$PhCH_2$	9	6	79	80
23	Ph–CH=CH (trans)	Me	$PhCH_2$	12	7	75	76
24	Me	CH_2COOEt	$PhCH_2$	10	7	82	85

[a] Reactions with aldehydes were carried out at room temperature and those of ketones are at reflux temperature. [b] Yields refer to those of pure isolated products fully characterized by spectral and analytical data ; [c] de 66% (NMR) ; [d] de 56% (NMR).

considered $InCl_3$ to be an ideal Lewis acid for effecting one-pot synthesis of α-amino phosphonates from a carbonyl compound, amine and diethyl phosphite.

In a typical experimental procedure, a mixture of a carbonyl compound (1 mmol), an amine (1 mmol), and diethyl phosphite (1 mmol) was added to a solution of $InCl_3$ (10 mol %) in THF (4 mL) and the mixture was stirred at room temperature (in the case of aldehydes) or refluxed (for ketones) under nitrogen for the period of time required to complete the reaction (TLC). Sonication effects the reaction for aldehydes as well as ketones very efficiently, as shown in Table 1.

A wide range of structurally varied carbonyl compounds were subjected to this procedure and converted to the corresponding α-amino phosphonates in high yields. The results are reported in Table 1. Both aromatic and aliphatic aldehydes react with aromatic as well as aliphatic amines to form the corresponding α-amino phosphonates. This procedure is equally effective for conversion of open-chain, cyclic, and aromatic ketones to the respective α-amino phosphonates. It was found that aldehydes are more reactive than ketones. No difficulty was encountered with the reaction of conjugated aldehydes (entries 9, 13, and 16). However, conversion of conjugated ketones is not always satisfactory. Several sensitive functionalities such as OH, OMe, NO_2, CO_2Et, and the C−C double bond are unaffected under the present reaction conditions. When the commercially available chiral amine (*S*)-α-methylbenzylamine has been used, moderate diastereoselectivities are obtained (66% for entry 3 and 56% for entry 12, as determined by NMR).

In conclusion, the present procedure using indium trichloride provides an efficient one-pot synthesis of α-amino phosphonates from the reaction of a carbonyl compound, amine, and diethyl phosphite. The notable advantages of this procedure are (a) operational simplicity and requirement of no additive, (b) general applicability to aldehydes and ketones, (c) participation of aromatic as well as aliphatic amines, (d) reaction conditions tolerant to a variety of sensitive functional groups, and (e) high yields. We believe that this will present a better and more practical alternative to the existing methodologies for the synthesis of α-amino phosphonates.

Experimental Procedure. A mixture of benzaldehyde (106 mg, 1 mmol), aniline (93 mg, 1 mmol), and diethyl phosphite (138 mg, 1 mmol) was added to a solution of indium(III) chloride (22 mg, 0.1 mmol) in THF (4 mL), and the mixture was stirred (11 h) at room temperature (25−30 °C) or sonicated (5 h) in an ultrasonic bath under nitrogen. The reaction mixture was then diluted with water and extracted with diethyl ether. The ether extract, after being washed with brine and dried over sodium sulfate, was evaporated to leave the crude product, which was purified by column chromatography over silica gel to provide pure amino phosphonate (293 mg, 92%). The ^1H and ^{13}C NMR spectra of this compound are identical with those reported.[6]

This procedure has been followed for the preparartion of all α-amino phosphonates listed in Table 1. The compounds have been characterized by their ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectral data and elemental analysis.

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Supporting Information Available: Spectral and analytical data for the α-amino phosphonates, not reported earlier,[6] designated by their entries in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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