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Synthesis of α-Amino Phosphonates from Aldehydes and Ketones Using Scandium (III) Chloride as a Catalyst

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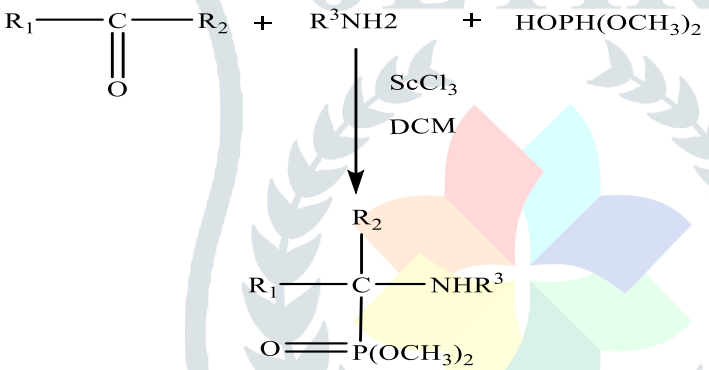
Abstract



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 Scandium (III) chloride as a catalyst.

Keywords- α -amino phosphonates, Scandium (III) chloride, one-pot reaction etc.

Introduction

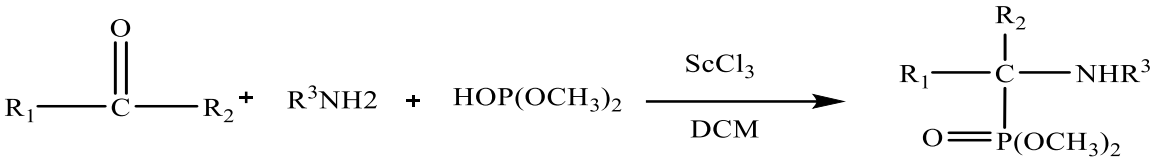
Due to the structural similarity between α-amino phosphonates and α-amino acids, they have attracted a lot of attention Recently. α-amino phosphonates have been shown to have promise as peptide mimics,[1] enzyme inhibitor,[2] antibacterial, and pharmaceutical agents.[3] Consequently, it is crucial to create these chemicals in an efficient manner. α-amino phosphonates may now be made using a variety of synthetic techniques that have been developed during the last two decades. The easiest of these processes is the nucleophilic addition of phosphites to imines, which is catalysed by a base or an acid.[4] Lewis acids have been employed, including $SnCl_2$, $SnCl_4$, BF_3-Et_2O, $ZnCl_2$, $InCl_3$ $InCl_3$, $In(OTf)_3/MgSO_4$, GaI_3, $BiCl_3$, I_2, $SbCl_3/Al_2O_3$, metal perchlorates, metal triflates, $CeCl_3$, $Na_2CaP_2O_7$, Sulfamic acid, TFA, (bromodimethyl)sulfonium bromide, TMSCl, Amberlyst-15, $Cd(ClO_4)_2.xH_2O$, ZnO nanoparticle, $NaHSO_4$–SiO_2 and acidic ionic liquids. A few catalyst-free as well as solvent-free protocols have been developed which necessitates thermal, ultrasonic or MW activation and $MgBr_2$.[5-22] With

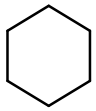
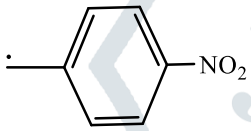
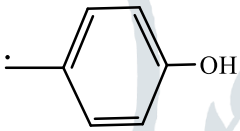
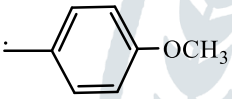
a carbonyl molecule, amine, and dialkyl phosphite, however, these reactions cannot be completed in a single pot because the amines and water produced during imine production might degrade or inactivate Lewis acids. Recent techniques that combine magnesium sulphate and lanthanide triflate have been developed to address this drawback.[23] This method works well for reactions involving aromatic aldehydes and amines, but there are no reports of how it performs with ketones.[24] Moreover, low to moderate yields of amino phosphonates are produced from aliphatic aldehydes and amines. [25] For the synthesis of α-amino phosphonates from aliphatic and aromatic amines and both aldehydes and ketones, an effective method is therefore required.[26]Scandium (III) chloride has recently made a comeback as a Lewis acid that imparts strong regio- and chemo selectivity in a variety of chemical reactions. Its effective action in aqueous media is one of $ScCl_3.H_2O$ noteworthy characteristics. We thus believed that $SnCl_3$ was the perfect Lewis acid for achieving a one-pot synthesis of α-amino phosphonates using a carbonyl molecule, amine, and diethyl phosphite. In a typical experiment, a combination of a carbonyl compound (0.5 mmol), an amine (0.5 mmol), and diethyl phosphite (0.5 mmol) was added to an $ScCl_3.H_2O$ (5 mol%) solution in DCM (4 mL), and the mixture was agitated at room temperature (for aldehydes) or refluxed (for ketones) for the duration necessary to complete the reaction (TLC). Table 1 demonstrates how effectively process for both aldehydes and ketones.

This process successfully produced the relevant α-amino phosphonates from a broad variety of structurally different carbonyl compounds in high yields. (Table 1) presents the findings. The equivalent α-amino phosphonates are created when aromatic and aliphatic aldehydes combine with both types of amines. Open-chain, cyclic, and aromatic ketones may all be converted using this method to the corresponding α-amino phosphonates. Aldehydes were discovered to be more reactive than ketones. Conjugated aldehyde reaction did not provide any challenges.

Experimental Procedure. A mixture of benzaldehyde (53 mg, 0.5 mmol), aniline (47 mg, 0.5 mmol), and diethyl phosphite (69 mg, 0.5 mmol) was added to a solution of Scandium (III) chloride (18 mg, 0.1 mmol) in DCM (4 mL), and the mixture was stirred (1 h) at room temperature (25-30 °C). 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 (150 mg, 93%). The 1 H and 13C NMR spectra of this compound are identical with those reported.6 This procedure has been followed for the prepararion of α -amino phosphonates listed in Table 1. The compounds have been characterized by their ^{1}H (500 MHz) and ^{13}C NMR (100 MHz) spectral data and elemental analysis.

Table 1. Synthesis of α-Amino Phosphonates from Aldehydes/Ketones and Amines Catalysed by $ScCl_3.H_2O$



Entry	R1	R2	R3	Time(h) RT/reflux a	Yield %
1	Ph	H	Ph	15	95
2	Ph	H	$PhCH_2$	12	95
3	Ph	H	PhCHMe	14	92
4	Ph	H		12	92
5	Ph	H	$MeCH_2CH_2$	10	83
6		H	Ph	11	89
7		H	Ph	15	92
8		H	Ph	14	88
9	Me_2CH	H	Ph	19	87
10	Et	Et	$PhCH_2$	25[a]	90
11	Ph	Me	$PhCH_2$	20[a]	91
12	Cyclohexanone		$PhCH_2$	20[a]	94

[a] Reaction with aldehyde were carried out at room temperature and those are ketones are at reflux temperature [b] ends refer to those pure isolated products.

Spectral analysis

Dimethyl(phenyl)(phenylamino)methyl phosphonate (Entry 1, Table 1): 1 H-NMR(400 MHz, DMSO): δ 1.12(t, 3H), , 1.3(t, 3H,), 2.34(s, 3H, Ar-CH3), 3.63–3.69 (m, 1H,), 3.91–3.97 (m, 1H,), 4.09–4.15 (m, 2H,), 4.73 (d, J = 25.2 Hz, 1H, HC-P), 4.8 (br, 1H, NH), 6.61 (d, J = 7.2 Hz, 2H,), 6.7 (t, J = 7.2 Hz, 1H, Ar–H), 7.07–7.14 (m, 3H, Ar–H), 7.22–7.29 (m, 3H, Ar– H) ppm; ^{13}C-NMR (100 MHz, DMSO): δ 16.21(d, 3), 16.46 (d, 3), 21.5, 56 (d,), 63.2 (d, 2), 63.3 (d, 2), 113.5, 113.8, 118.3,125, 128.5, 128.8, 129.2, 135.8, 138.2, 146.5(d,) ppm.

dimethyl ((3-methoxyphenyl)(phenylamino)methyl)phosphonate (Entry 8, Table 1): ^{1}H NMR (500 MHz, DMSO): 1.31(t, 3H), 3.72-3.77(m, 1H), 3.81(s, 3H), 3.95-3.99(m, 1H), 4.11-4.17(m, 2H), 4.75(d, 1H), 6.62(dd, 2H, J=8.4Hz), 6.70-6.74(m, 1H), 6.82-6.85(m, 1H), 7.05-7.15(m, 4H), 7.25(d, 2H, J=7.6Hz); 13C NMR (100MHz, CDCl3): 16.4.(s) 55.2(s, 1C), 55.4(s, 1C), 56.9(s, 1C), 63.3(t, 1C, J=6.3Hz), 113.4(q, 2C, J=4.4Hz),

113.9(s, 1C), 118.4(s, 1C), 120.2(d, 1C, J=5.4Hz), 129.2(s, 1C), 129.6(s, 2C), 137.6(s, 1C), 146.3(s, 1C), 146.4(s, 1C), 159.8(s, 1C).

dimethyl ((3-nitrophenyl)(phenylamino)methyl)phosphonate (Entry 6, Table 1): ^{1}H NMR (500 MHz, DMSO): : δ 1.33(t, 3H,) 3.93(m, 1H), 4.06(m, 1H), 4.17(m, 2H), 4.87(d, 1H), 6.59(d, 2H, J=7.6Hz), 6.76 (s, 1H), 7.13-7.15(m, 2H), 7.55 (d, 1H, J=7.6Hz), 7.85 (d, 1H, J=7.6Hz), 8.15-8.18(m, 1H), 8.37(d, 1H, J=2.0Hz); 13C NMR (100MHz, DMSO): δ 16.4(d, 1C, J=5.6Hz), 54.9(s, 1C), 56.4(s, 1C), 63.3(q, 1C, J=7.1Hz), 113.8(s, 2C), 119.1(s, 1C), 122.8(t, 1C, J=12.0Hz), 129.4(s, 2C), 129.6(s, 1C), 133.8(d, 1C, J=4.8Hz), 138.8(s, 1C), 145.5(s, 1C), 145.7(s, 1C), 148.5(s, 1C).

dimethyl (4-hydroxyphenyl)amino)(phenyl)methyl)phosphonate (Entry 7, Table 1): ^{1}H NMR (500 MHz, DMSO): δ 1.30(s, 6H,), 1.35(t, 3H, J=6.8Hz), 3.67-3.73(m, 1H), 3.88-3.92(m, 2H), 3.94-3.97(m, 1H), 4.10-4.16(m, 2H), 4.71(d, 1H), 6.55(d, 2H, J=8.8Hz), 6.70 (d, 2H, J=8.8Hz), 7.30(s, 1H), 7.33(t, 2H, J=7.2Hz), 7.39(t, 2H, J=7.2Hz); ^{13}C NMR (100MHz, DMSO): δ 16.3(d, 1C, J=5.8Hz), 16.4(d, 1C, J=5.6Hz), 50.6(s, 1C), 52.2(s, 1C), 55.6(s, 1C), 63.3(q, 1C, J=6.8Hz), 108.8(d, 2C, J=7.1Hz), 110.8(s, 2C), 114.7(s, 2C), 115.6(s, 2C), 140.0(d, 1C, J=14.2Hz), 142.4(d, 1C, J=2.9Hz), 149.6(s, 1C), 153.1(s, 1C).

dimethyl (3-(benzylamino)pentan-3-yl)phosphonate (Entry 10, Table 1): ^{1}H NMR (500 MHz, DMSO): δ 1.30(s, 6H,), 3.67-3.73(t, 6H), 3.88-3.92(m, 6H), 3.94-3.97(m, 1H), 4.10-4.16(m, 2H), 4.71(d, 1H), 6.55(d, 2H, J=8.8Hz), 7.37 (d, 2H, J=8.8Hz), 7.30(s, 1H), 7.33(t, 2H, J=7.2Hz), 7.39(t, 2H, J=7.2Hz); ^{13}C NMR (100MHz, DMSO): δ 16.3(d, 1C, J=5.8Hz), 16.4(d, 1C, J=5.6Hz), 50.9(s, 1C), 52.2(s, 1C), 55.7(s, 1C), 63.3(q, 1C, J=6.8Hz), 108.8(d, 2C, J=7.1Hz), 110.8(s, 2C), 128.3.7(s, 2C), 128.6(s, 1C), 141.0(d, 1C, J=14.2Hz), 142.4(d, 1C, J=2.9Hz), 149.6(s, 1C), 153.1(s, 1C).

dimethyl -(1-(benzylamino)-1-phenylpropyl) phosphonate (Entry 11, Table 1): ^{1}H NMR (500 MHz, DMSO): δ 1.15(T, 3H,), 1.27(t, 3H), 3.88-3.92(m, 6H), 1.90(m, 3H), 4.10-4.16(m, 6H), 4.71(d, 1H), 6.55(d, 4H, J=8.8Hz), 7.37 (d, 4H, J=8.8Hz), 7.30(s, 1H), 7.33(t, 1H, J=7.2Hz), 7.39(t, 2H, J=7.2Hz); ^{13}C NMR (100MHz, DMSO): δ 16.3(d, 1C, J=5.8Hz), 16.9(d, 1C, J=5.6Hz), 4606(s, 1C), 52.2(s, 1C), 55.7(s, 1C), 63.3(q, 1C, J=6.8Hz), 108.8(d, 2C, J=7.1Hz), 110.8(s, 2C), 128.3.7(s, 2C), 128.6(s, 2C), 131.0(d, 2C, J=14.2Hz), 142.4(d, 2C, J=2.9Hz), 149.6(s, 2C), 153.1(s, 1C).

Conclusion

Finally, the current method utilising indium trichloride offers an effective one-pot synthesis of α -amino phosphonates from the reaction of a carbonyl molecule, amine, and diethyl phosphite. The following features of this process stand out: (a) operational simplicity and the absence of an additive need; (b) universal application to aldehydes and ketones; (c) participation of aromatic as well as aliphatic amines; (d) reaction conditions tolerant of a variety of sensitive functional groups; and (e) excellent yields. The existing methods for the synthesis of α -amino phosphonates, in our opinion, will be replaced by this as a superior and more useful option.

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