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$TiCl_4$-Catalyzed Efficient One-Pot Synthesis of α-Amino Phosphonates

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α-Aminophosphonates are synthesized by three-component condensation of aldehydes, amines, and trimethylphosphite in acetonitrile by using $TiCl_4$ as catalyst. Compared to conventional methods, this new method consistently has advantages, including excellent yields, short reaction times, and mild reaction conditions.

Keywords α-aminophosphonates; aldehydes; amines; one-pot reaction; $TiCl_4$

INTRODUCTION

Aminophosphates are an important class of biologically active compounds,[1] because of their structural analogy to α-aminoacids. Hence, α-aminophosphonates continue to attract increased interest as synthetic targets. Also, α-aminophosphonates 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 $SnCl_2$, $SnCl_4$, $BF_3.OEt_2$, and $ZnCl_2/MgBr_2$, 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 reagents include $ZrCl_4$,[11] lanthanide

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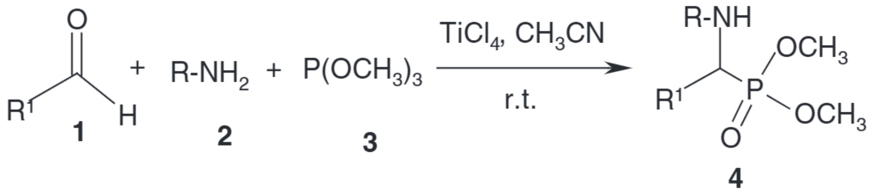


SCHEME 1

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 dialkylphosphite catalyzed by alumina under microwave conditions was also reported.[16] Most of the previously mentioned procedures employ dimethylphospite as the reagent, with a view to see the migration of a methyl carbonium ion to that of using a dimethyl (trimethyl silyl) phosphite.[17] The present study also aims at the development of a cheaper alternative reagent. Herein we report an efficient and inexpensive protocol for the synthesis of α-aminophosphonates using a catalytic amount of $TiCl_4$ under mild reaction conditions (Scheme 1).

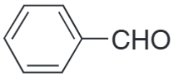
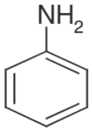
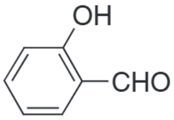
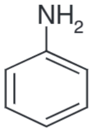
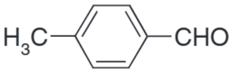
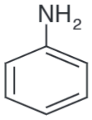
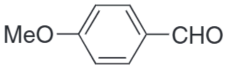
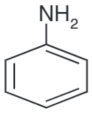
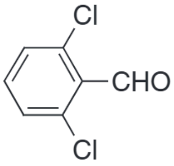
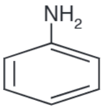
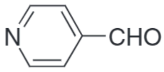
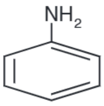
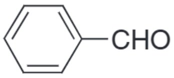
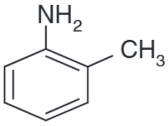
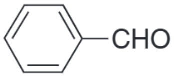
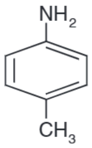
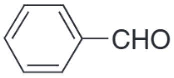
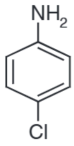
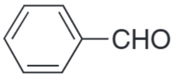
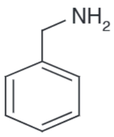
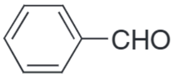
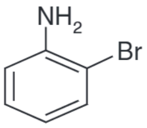
The treatment of benzaldehyde, aniline, and trimethylphosphite in the presence of 10 mole percent of $TiCl_4$ in acetonitrile medium at r.t. resulted in corresponding α-aminophosphonate. Similarly, various aldehydes and amines were treated with trimethylphosphite to afford corresponding α-aminophosphonates at an ambient temperature within 10–25 min in high yields 88–93% (Table I). The reaction conditions were very mild, and the α-aminophosphonates were exclusively formed without the formation of any undesired side products. The present method does not require any additives or promoters[10] for the reaction to proceed.

General Experimental Procedure

To a stirred solution of benzaldehyde (1.06 g, 10 mmol) and aniline (0.93 g, 10 mmol) in acetonitrile (25 mL) was added trimethylphosphite (1.40 g, 10 mmol) and $TiCl_4$ (0.189 g, 10 mol%). The reaction mixture was stirred at r.t. (Table I) until completion of the reaction as indicated by 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 correspondingly pure α-aminophosphonates in a 93% (0.80 g) yield.

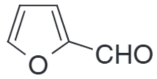
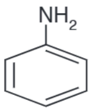
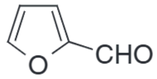
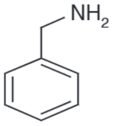
Selected spectral data of **4a**. IR (KBr): 3302 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 3.42$ (d, 3H, CH_3), 3.75 (d, 3H, CH_3), 4.53 (brs, 1H, NH), 4.80 (d, 1H, CH), 6.69–7.45 (m, 10H, Ar-H).

TABLE I $TiCl_4$-Catalyzed Efficient Synthesis of α-Aminophosphonates[a]

Entry	Aldehyde	Amine	Reaction Time (min)	Yield (%)[b]
4a			10	93
4b			15	89
4c			10	91
4d			15	90
4e			15	88
4f			15	90
4g			15	91
4h			25	89
4i			10	90
4j			15	92
4k			15	90

(Continued on next page)

TABLE I $TiCl_4$-Catalyzed Efficient Synthesis of α-Aminophosphonates[a] (*Continued*)

Entry	Aldehyde	Amine	Reaction Time (min)	Yield (%)[b]
4l			15	91
4m			15	92

[a] Yields refer to pure products, and all products were characterized by comparison of their physical and spectral data with those of authentic samples.

[b] All α-aminophosphonates are known compounds.

4d. IR (KBr): 3316 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 3.45$ (d, 3H, CH_3), $\delta = 3.64$ (d, 3H, CH_3), 3.78 (d, 3H, OCH_3), 4.72 (brs, 1H, NH), 6.59 (d, 1H, CH), 6.54–7.11 (m, 9H, Ar-H).

4e. IR (KBr): 3322 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 3.54$ (d, 3H, CH_3), $\delta = 3.72$ (d, 3H, CH_3), 5.27 (brs, 1H, NH), 5.83 (d, 1H, CH), 6.54–6.63 (d, 2H), 6.65–6.78 (t, 1H), 7.05–7.42 (m, 5H).

CONCLUSION

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

REFERENCES

[1] (a) S. C. Fileds, *Tetrahedron*, **55,** 1237 (1999); (b) E. K. Fields, *J. Am. Chem. Soc.*, **74,** 1528 (1952); (c) C. Yuan and S. Chen, *Synthesis*, 1124, (1992); (d) D. R. More, *J. Org. Chem.*, **43,** 992 (1978); (e) T. Yokomatsu, Y. Yoshida, and S. Shibuya, *J. Org. Chem.*, **59,** 7930 (1994).

[2] P. Kafarski and B. Lejczak, *Phosphorous, Sulfur, and Silicon*, **63,** 1993 (1991).

[3] (a) M. C. Allen, W. Fuhrer, B. Tuck, R. Wade, and J. M. Wood, *J. Med. Chem.*, **32,** 1652 (1989); (b) P. P. Giannousis and P. A. Bartlet, *J. Med. Chem.*, **30,** 1603 (1987).

[4] F. R. Atherton, C. H. Hassall, and R. W. Lambert, *J. Med. Chem.*, **29,** 29 (1986).

[5] (a) P. Wieczorek, B. Lejczak, M. Kaczanowska, and P. Kafarski, *Pestic. Sci.*, **30,** 43 (1990); (b) I. A. Nachev, *Liebigs Ann. Chem.*, 861 (1988).

[6] R. Hirschmann, A. B. Smith III, C. M. Taylor, P. A. Benkovic, S. D. Taylor, K. M. Yager, P. A. Sprengler, and S. J. Venkovic, *Science*, **265,** 234 (1994).

[7] (a) V. P. Kukhar and V. A. Solodenko, *Rus. Chem. Rev. (Engl. Trans.)*, **56,** 859 (1987); (b) D. Redmore, *Topics in Phosphorous Chemistry, Vol. 8*, ed. E. J. Griffith and M. Grayson, p. 515. (Wiley: New York, 1976).

[8] A. N. Pudovik, Dokl, and S. Akad Nauk, **83,** 865 (1952); *Chem. Abstr.*, **47,** 4300 (1953).

[9] E. K. Baylis, C. D. Campbell, and J. G. Dingwall, *J. Chem. Soc. Perkin. Trans. 1*, 2845 (1984).

[10] J. Zon and Pol, *J. Chem.*, **55,** 643 (1981); *Chem. Abstr.*, **96,** 199793 (1982).

[11] J. S. Yadav, B. V. S. Reddy, R. K Sarita, B. K. Reddy, and A. R. Prasad, *Synthesis*, 2277 (2001).

[12] C. Quian and T. Huang, *J. Org. Chem.*, **63,** 4125 (1998).

[13] B. C. Ranu and A. Hajra Jana, *J. Org. Lett.*, **1,** 1141 (1999).

[14] M. R. Sidi and N. Azizi, *Synlett.*, 1347 (2002).

[15] J. S. Yadav, U. Basi, S. Reddy, and C. H. Madan, *Synlett.*, **7,** 1131 (2001).

[16] (a) B. Kaboudin, *Chem. Lett.*, 880 (2001); (b) B. Kaboudin and R. Nazari, *Tetrahedron Lett.*, **42,** 8211 (2001).

[17] A. Haydari, M. Zarei, A. Reza, and H. Tavakol, *Tetrahedron Lett.*, **42,** 3629 (2001).