Montmorillonite Clay-Catalyzed One-Pot Synthesis of α-Amino Phosphonates[#]

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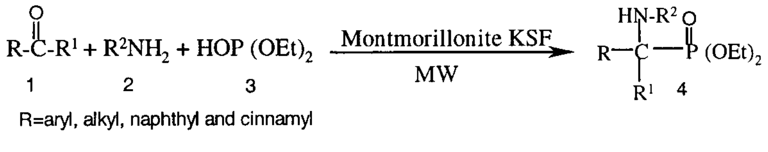
Abstract: α-Aminophosphonates are synthesized by three component condensation of aldehydes, amines and diethyl phosphite using montmorillonite KSF under microwave irradiation in solvent-free conditions to afford enhanced yields and reduced reaction times compared to conventional methods.

Key words: montmorillonite KSF, α-aminophosphonates, microwave irradiation

α-Amino phosphonates are an important class of biologically active compounds[1] and their synthesis has received an increasing amount of interest because of their structural analogy to α-amino acids. Also, α-aminophosphonates act as peptide mimics,[2] enzyme inhibitors,[3] antibiotics and pharmacologic agents.[4] Generally, they are prepared from the addition of phosphorous nucleophiles to imines in the presence of either a base or an acid. Lewis acids such as $SnCl_4$, $BF_3 \cdot OEt_2$, $ZnCl_2$, and $MgBr_2$ have been used for this transformation.[5,6] However, these reactions cannot be carried out in a one-pot operation with a carbonyl compound, amine and diethyl phosphite, because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids.[6] In order to circumvent some of these problems recently one-pot procedures have also been developed for this conversion using lanthanide triflates[7] and indium trichloride[8] as catalysts. Although, these procedures do not require the isolation of unstable imines prior to the reactions, longer reaction times (10-20 hours) are required to obtain the desired products in good yields. In addition, the use of harmful organic solvents is undesirable from the view of today's environmental consciousness. Further, metal triflates[7] are found to be effective for the reactions with aldehydes and not with ketones and also they are highly expensive. In recent years, the use of solid acidic catalysts such as clays and zeolites has received considerable attention in different areas of organic synthesis[9] because of their environmental compatibility, reusability, greater selectivity, operational simplicity, non-toxic, non-corrosiveness, low cost and ease of isolation. Particularly, clay catalysts make the reaction processes convenient, more economic, environmentally benign and act as both Bronsted and Lewis acids in their natural and ion-exchanged forms, enabling them to function as efficient catalysts for various transformations.[10] Further, solvent-free microwave assisted reactions[11] have gained more popularity as they provide an opportunity to work with open vessels. This avoids the risk of development of high pressure and provides a possibility of upscaling the reaction on a preparative scale and helps the induction of the reaction under dry conditions.

In this communication, we wish to report a novel and highly efficient procedure for the synthesis of α-amino phosphonates using an inexpensive and reusable catalyst, montmorillonite KSF under microwave irradiation.

The reaction of benzaldehyde, benzylamine and diethyl phosphite in the presence of KSF clay resulted in the formation of α-amino phosphonate in 90% yield after 3 minutes irradiation under microwaves. Similarly various aldehydes and amines were reacted with diethyl phosphite to afford the corresponding α-amino phosphonates in high yields. The reactions proceeded smoothly in solvent - free conditions and completed within 3-5 min of reaction time. Both aromatic and aliphatic aldehydes provided excellent yields of products (80-92%) in a short reaction time whereas ketones gave phosphanates in good yields (65-80%) after a longer irradiation time (6-8 min). Several aromatic, α,β-unsaturated, heterocyclic and aliphatic aldehydes worked well to give the phosphonates in high yields. The advantage of the use of clay catalyst for this transformation is that KSF clay was easily recovered by filtration, washed with methanol and reused after activation at 120 °C for 3-4 hours. The reactions of several aldehydes, amines and diethyl phosphite were examined in the presence of KSF clay and the results were summarized in the Table. The reactions were carried out under microwave as well as thermal conditions. When the reactions were carried out conventionally in refluxing toluene they took longer reaction times to achieve good yields of products. Whereas under microwave irradiation the reactions



Scheme 1

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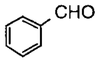
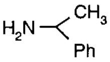
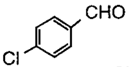
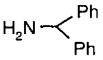
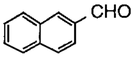
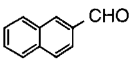
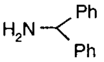
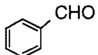
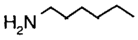
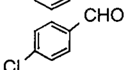
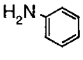
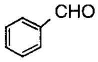
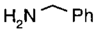
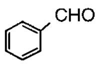
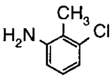
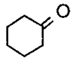
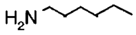
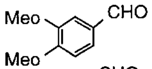
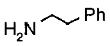
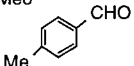
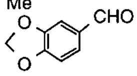
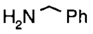
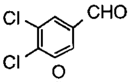
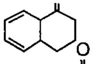
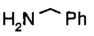
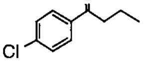
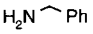
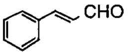
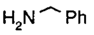
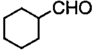
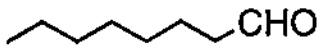
were completed in a short reaction time with excellent yields. The reaction temperature was controlled in a microwave oven by pulsed irradiation (1 min with 20 s intervals). The temperature was measured at the end of each pulsed irradiation. The lowest observed temperature was 75 °C after one minute irradiation at 450 W and the highest temperature was 105 °C after 3 min irradiation at the same power. The reaction rates and yields were dramatically enhanced by microwave irradiation. Further, the reactions proceeded only to a minor extent (10-15%) when the reactants were subjected to microwaves in the absence of KSF clay. Thus, we have compared the reaction rates and yields under microwave as well as thermal conditions. All the products were characterized by ^{1}H NMR, IR, and mass spectral analysis and also by comparison with authentic samples.

Table Clay-catalyzed one-pot synthesis of α-amino phosphonates

Entry	Carbony Compound	Amine	Microwave irradiation[a]		Conventional heating[b]	
			time(min)	Yield(%)	time(h)	Yield(%)
a)			3 min	(85)	6h	(70)
b)			3 min	(82)	8h	(75)
c)		H_2N-Ph	5 min	(90)	10h	(72)
d)			6 min	(81)	8h	(70)
e)			4 min	(89)	5h	(74)
f)			5 min	(83)	7h	(80)
g)			3 min	(90)	5h	(72)
h)			5 min	(85)	7h	(70)
i)			6 min	(80)	10h	(65)
j)			5 min	(91)	8h	(75)
k)		H_2N-Ph	4 min	(88)	6h	(77)
l)			3 min	(92)	5h	(80)
m)		H_2N-Ph	5 min	(87)	6h	(73)
n)			8 min	(78)	12h	(68)
o)			7 min	(75)	10h	(70)
p)			5 min	(90)	6h	(75)
q)		H_2N-Ph	4 min	(85)	6h	(78)
r)			3 min	(87)	7h	(80)

[a] Microwave irradiation was carriedout at 450 W using BPL, BMO, 700T microwave oven by pulsed irradiation technique (20 s interval for each min.) [b] Conventional heating in refluxing toluene

In conclusion the paper describes a facile synthesis of α-amino phosphonates using montmorillonite KSF under microwave as well as thermal conditions. The method offers several advantages including high yields of products, very short reaction times, cleaner reactions, greater selectivity, inexpensive catalyst, ease of isolation of the products, regeneration of the catalyst and solvent-free conditions which makes the reaction process convenient, more economic and environmentally benign.

Experimental

a) *Microwave irradiation:* Aldehyde (5 mmol), amine (5 mmol), diethyl phosphite (5 mmol) and montmorillonite (1.5 g, Aldrich, montmorillonite, KSF) were admixed in a pyrex test tube and exposed to microwave irradiation at 450 W using (BPL, BMO, 700T, indicates the commertial name of microwave oven) focused microwave oven for an appropriate time (pulsed irradiation 1 min with 20 s interval). After complete conversion of the reaction, as indicated by TLC, the reaction mixture was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate-hexane (3:7) to afford corresponding pure α-amino phosphonate.

b) *Conventional method:* A mixture of aldehyde (5 mmol), amine (5 mmol), diethyl phosphite (5 mmol) and montmorillonite clay (1.5 g) was refluxed in toluene (20 ml) for an appropriate time (Table). On completion, the reaction mixture was filtered and purified by column chromatography on silica gel (Merck, 100-200 mesh, ethyl acetate-hexane, 3:7) to afford pure α-amino phospohonate. Representative spectroscopic data for compound. **4g**: liquid, ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, J = 7.0Hz, 3H), 1.25 (t, J = 7.0Hz, 3H), 2.20 (brs, NH), 3.55 (d, J = 14.8 Hz, 1H), 3.70-4.18 (m, 6H), 7.20-7.45 (m, 10H). ^{13}C NMR (Proton decoupled, $CDCl_3$) δ: 16.09, 16.2, 16.28, 16.40, 51.04, 51.38, 58.12, 61.17, 62.64, 62.79, 62.94, 127.05, 127.83, 128.26, 128.56, 128.68, 129.3, 130.05, 136.0, 146.7. ^{31}P NMR ($CDCl_3$) δ: 24.007. FAB Mass: m/z: 333 M^+, 281, 196, 147, 123, 109, 91, 69, 55.

References and Notes

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(1) a) Fields, S.C.; *Tetrahedron.* **1999**, 55, 12237. b) Fields, E.K.; *J. Am. Chem. Soc* **1952**, 74, 1528. c) Yuan, C.; and Chen, S.; *Synthesis* **1992**, 1124. d) More, D.R. *J. Org. Chem.* **1978**, 43, 992. e) Hirschmann, R.; Smith III, A.B.; Taylor, C.M.; Benkovic, P.A.; Taylor, S.D.; Yager, K.M.; Sprengler, P.A.; Venkovic, S. J. *Science* **1994**, 265, 234. f) Yokomatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem* **1994**, 59, 7930.
(2) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, 63, 1993.
(3) a) Allen, M.C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J.M. *J. Med. Chem.* **1989**, 32, 1652. b) Giannousis, P.P.; Bartlett, P.A. *J. Med. Chem.* **1987**, 30, 1603.
(4) a) Atherton, F.R.; Hassal, C.H.; Lambert, R.W. *J. Med. Chem.* **1986**, 29,29. b) Baylis, E.K; Campbell, C.D; Dingwall, J.G. *J. Chem. Soc. Perkin Trans 1* **1984**, 2845
(5) Lashat, S and Kunz, H. *Synthesis* **1992**, 90.
(6) Zon, J. *Pol. J. Chem.* **1981**, 55, 643.
(7) a) Qian, C.; and Huang T. *J. Org. Chem.* **1998**, 63, 4125. b) Manabe, K. and Kobayashi, S. *Chem. Commun.* **2000,** 669.
(8) Ranu, B.C.; Hajra, A. and Jana, U. *Org. Lett.* **1999,** 1, 1141.

(9) Balogh, M.; and Laszlo, P. In *Organic Chemistry using Clays*, Spinger-Verlag, Ed,; Berlin, 1993 and references cited therein.

(10) Cornelis, A. and Laszlo, P. *Synlett* **1994**, 155.

(11) a) Caddik, S. *Tetrahedron* **1995**, 51, 10403. b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P. and Mathe., D. *Synthesis* **1998**, 1213. c) Varma, R.S. *Green Chem.* **1999**, 43

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