Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 1125–1127
Tetrahedron Letters

# Microwave-assisted solvent-free and catalyst-free Kabachnik–Fields reactions for α-amino phosphonates

Xue-Jun Mu,[a] Mao-Yi Lei,[a] Jian-Ping Zou[a,*] and Wei Zhang[b,*]

[a]*Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Suzhou University, 1 Shizi St. Suzhou 215006, Jiangsu, China*

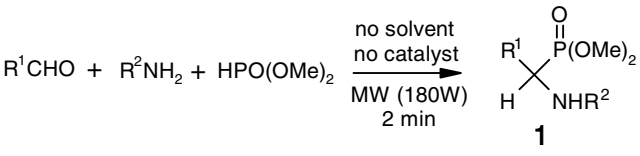
[b]*Fluorous Technologies, Inc., University of Pittsburgh Applied Research Center, 970 William Pitt Way, Pittsburgh, PA 15238, USA*

Received 4 October 2005; revised 3 December 2005; accepted 6 December 2005
Available online 27 December 2005

**Abstract**—A highly efficient solvent-free and catalyst-free method for the synthesis of α-amino phosphonates is developed by a microwave-assisted three-component Kabachnik–Fields reaction involving aldehyde, amine, and dimethyl phosphite.


α-Amino phosphonates are phosphorus analogs of amino acids,[1] which have been widely used as imaging agents and as antitumor, antihypertensive, and antibacterial agents.[2] Among the literature methods, the Kabachnik–Fields reaction[3] is one of the most convenient approaches to α-amino phosphonates. It is a one-pot, three-component reaction of carbonyl compound, amine, and dialkyl phosphite. The reaction usually needs a Lewis acid catalyst such as indium(III) chloride,[4] rare earth triflates,[5] and scandium tris(dodecyl sulfate).[6] Recently, $SmI_2$,[7] $LiClO_4$,[8] metal triflates [M(OTf)*n*, M = Li, Mg, Al, Cu, Ce],[9] $TaCl_5$-$SiO_2$,[10] montmorillonite clay,[11] $Al_2O_3$,[12] $CF_3CO_2H$,[13] scandium(tris-dodecyl sulfate),[6] $BF_3{\cdot}Et_2O$,[14] and tetra-*tert*-butyl-substituted phthalocyanines Pht-1-Pht-3[15] have also been reported as the catalysts. A broad range of catalysts has been employed for the Kabachnik–Fields reaction. However, many of these catalysts are expensive and have to be used in stoichiometric amount. The catalyst-free synthesis of α-amino phosphonates is rather limited.[16]

Microwave-promoted[17] solvent-free[18] heterogeneous reactions have received much attention due to their high efficiency, cost effective, and environmentally friend characteristics. Described in this paper is a microwave-assisted solvent-free and catalyst-free method for the synthesis of α-amino phosphonates (Scheme 1).




**Scheme 1.**

A catalyst-free Kabachnik–Fields reaction of benzaldehyde, aniline, and dimethyl phosphite was first attempted using ethanol as a solvent. After the reaction mixture was stirred at room temperature for 2 h, no desired product **1a** was detected (Table 1, entry 1). Similar results were obtained when the reactions were carried out at different temperatures and in different solvents such as toluene and $CH_2Cl_2$ (Table 1, entries 4–5).

Catalyst-free Kabachnik–Fields reactions under the solvent-free conditions were then explored. The reaction of benzaldehyde, aniline, and dimethyl phosphate at 50 °C for 2 h gave desired product **1a** in 76% yield. A higher yield (85%) was obtained after heating the reaction mixture at 80 °C for 2 h (Table 1, entry 8).[19] Finally, microwave heating was introduced to reduce the reaction time. Indeed, after the reaction mixture was irradiated in a multimood microwave reactor at 180 W for only 2 min, the reaction was completed and the yield of **1a** was increased to 98% (Table 1, entry 9).[20]

To evaluate the synthetic scope, reactions of different aldehydes and amines with dimethyl phosphite were

* Corresponding authors. Tel./fax: +86 512 65112371 (J.-P.Z.); tel.: +1 412 8263062; fax: +1 412 8263053 (W.Z.); e-mail addresses: wuyanhong@pub.sz.jsinfo.net; w.zhang@fluorous.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.12.027

**Table 1.** Catalyst-free synthesis of α-aminophosphonate **1a**

| Entry | Solvent | Temp (°C) | Time (min) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | EtOH | rt | 120 | nr[b] |
| 2 | EtOH | 50 | 120 | nr |
| 3 | EtOH | reflux | 120 | nr |
| 4 | Toluene | Reflux | 120 | nr |
| 5 | $CH_2Cl_2$ | Reflux | 120 | nr |
| 6 | Solvent-free | rt | 120 | nr |
| 7 | Solvent-free | 50 | 120 | 76 |
| 8 | Solvent-free | 80 | 120 | 85 |
| 9 | Solvent-free | 80, mw[c] | 2 | 98 |

[a] Isolated yields.
[b] nr = no reaction.
[c] mw = microwave heating.

conducted and the results are shown in Table 2. Reactions involving benzaldehydes and anilines produced products **1a**–**1e** and **1i**–**1n** in excellent yields.[19] Reactions of aliphatic amines, aliphatic aldehydes, and heterocyclic aldehydes such as 2-furylaldehyde and 2-thiophene aldehyde produced corresponding products **1f**–**1g**, **1o**–**1r**, and **1s**–**1u** in good to excellent yields. Steric hindered *tert*-butyl aldehyde and 2,6-dimethyl aniline were also evaluated. In the case of reaction involving benzaldehyde and 2,6-dimethylaniline, good yield of **1v** (78%) was produced. However, reactions involving *tert*-butyl aldehyde, *p*-toluidine, or 2,6-dimethyl aniline afforded **1w** and **1x** in 53% and 40% yields, respectively, much lower than reactions using other substrates listed in Table 2.

In summary, we have developed a novel microwave-assisted, catalysts-free, and solvent-free Kabachnik–Fields reaction for the synthesis of α-amino phosphonates. The reaction process is highly efficient, economic, and also environmentally friendly.

**Table 2.** Microwave-assisted synthesis of α-aminophosphonates

| Product[a] | $R^1$ | $R^2$ | Time (min) | Yield (%)[b] |
|---|---|---|---|---|
| **1a** | Ph | Ph | 2 | 98 |
| **1b** | Ph | *p*-$MeC_6H_4$ | 2 | 94 |
| **1c** | Ph | *p*-$ClC_6H_4$ | 2 | 96 |
| **1d** | Ph | *o*-$ClC_6H_4$ | 2 | 97 |
| **1e** | Ph | *m*-$BrC_6H_4$ | 2 | 96 |
| **1f** | Ph | Naphthyl | 2 | 86 |
| **1g** | Ph | Cyclohexyl | 2 | 87 |
| **1h** | Ph | $PhCH_2$ | 2 | 86 |
| **1i** | *p*-$MeOC_6H_4$ | Ph | 2 | 96 |
| **1j** | *p*-$MeOC_6H_4$ | *p*-$MeC_6H_4$ | 2 | 94 |
| **1k** | *p*-$MeOC_6H_4$ | *p*-$ClC_6H_4$ | 2 | 91 |
| **1l** | *p*-$NO_2C_6H_4$ | Ph | 2 | 89 |
| **1m** | *p*-$NO_2C_6H_4$ | *p*-$MeOC_6H_4$ | 2 | 87 |
| **1n** | *p*-$NO_2C_6H_4$ | *p*-$ClC_6H_4$ | 2 | 84 |
| **1o** | *i*-Propyl | Ph | 2 | 88 |
| **1p** | *i*-Propyl | *p*-$MeC_6H_4$ | 2 | 83 |
| **1q** | *i*-Propyl | *p*-$MeOC_6H_4$ | 2 | 85 |
| **1r** | *i*-Propyl | *p*-$ClC_6H_4$ | 2 | 80 |
| **1s** | 2-Furyl | *p*-$MeC_6H_4$ | 2 | 88 |
| **1t** | 2-Furyl | *p*-$ClC_6H_4$ | 2 | 76 |
| **1u** | 2-Thiophene | *p*-$NO_2C_6H_4$ | 2 | 85 |
| **1v** | Ph | 2,6-di$MeC_6H_3$ | 2 | 78 |
| **1w** | *tert*-Butyl | *p*-$MeC_6H_4$ | 2 | 53 |
| **1x** | *tert*-Butyl | 2,6-di$MeC_6H_3$ | 2 | 40 |

[a] Products were characterized by their NMR and MS spectra.
[b] After flash column chromatography.


## Acknowledgements

We thank the Key Laboratory of Organic Synthesis of Jiangsu Province and Suzhou Scientific Committee for financial supports (JSK016 and SG 0219).


## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.027.

## References and notes


1. Sheridan, R. P. J. *Chem. Inf. Comput. Sci.* **2002**, *42*, 103.
2. (a) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 1993; (b) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652; (c) Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. *J. Med. Chem.* **2003**, *46*, 2641; (d) Moore, J. D.; Sprott, K. T.; Fisher, A. J.; Tony, M. *Biochemistry* **2002**, *67*, 8123; (e) Liu, W.; Rogers, C. J.; Fisher, A. J.; Toney, M. *Biochemistry* **2002**, *41*, 12320; (f) Kim, K. S.; Hurh, E. Y.; Youn, J. N.; Park, J. I. *J. Org. Chem.* **1999**, *64*, 9272; (g) Osipov, S. N.; Artyushin, O. I.; Kolomeits, A. F.; Bruneau, C.; Dixneuf, P. H. *Synlett* **2000**, 1031; (h) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845; (i) Atherton, F. R.; Hassal, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29.
3. (a) Kabachnik, M. I.; Medved, T. Y. *Dokl. Akad. Nauk SSSR.* **1952**, 689; *Chem. Abstr.* **1953**, *47*, 2724b; (b) Fields, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 1528; (c) For a review on the Kabachnik–Fields reaction, see: Cherkasov, R. A.; Galkin, V. I. *Russ. Chem. Rev.* **1998**, *67*, 857.
4. Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141.
5. (a) Qian, C. T. T.; Huang, S. *J. Org. Chem.* **1998**, *63*, 4125; (b) Lee, S.; Park, J. H.; Kang, J.; Lee, J. K. *Chem. Commun.* **2001**, 1698.
6. Manabe, K.; Kobayashi, S. *Chem. Commun.* **2000**, 669.
7. Xu, F.; Luo, Y. Q.; Deng, M. Y.; Shen, Q. *Eur. J. Org. Chem.* **2003**, 4728.
8. Saidi, M. R.; Azizi, N. *Synlett* **2002**, 1347.
9. Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Synthesis* **2004**, *16*, 2692.
10. Chandrasekhar, S.; Prakash, S. J.; Jagadeshwar, V.; Narsihmulu, C. *Tetrahedron Lett.* **2001**, *42*, 5561.
11. Yadav, J. S.; Reddy, B. V. S.; Madan, C. *Synlett* **2001**, 1131.
12. Kaboudin, B.; Nazari, R. *Tetrahedron Lett.* **2001**, *42*, 8211.
13. Akiyama, T.; Sanada, M.; Fuchibe, K. *Synlett* **2003**, 1463.
14. Ha, H.-J.; Nam, G.-S. *Synth. Commun.* **1992**, *22*, 1143.
15. Matveeva, E. D.; Podrugina, T. A.; Tishkovskaya, E. V.; Tomilova, L. G.; Zefirov, N. S. *Synlett* **2003**, *15*, 2321.
16. Ranu, B. C.; Hajra, A. *Green Chem.* **2002**, *4*, 551.
17. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.
18. For a general review on solvent-free reactions, see: Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.
19. General procedures for preparation of α-amino phosphonates under conventional heating: Benzaldehyde (1 mmol),

aniline (1 mmol), and dimethyl phosphite (2 mL) were added into a 25 mL three-necked flask. The mixture was stirred at 80 °C for 2 h. The reaction mixture was then diluted with water and extracted with $CH_2Cl_2$ (20 mL). The organic layer was washed with $H_2O$ (3 × 10 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The crude product was purified by silica gel flash column chromatography eluted with 2:1 petroleum ether/acetone to give pure α-amino phosphonate **1a** in 85% yield.

20. General procedures for preparation of α-amino phosphonates under microwave irradiation: Benzaldehyde (1 mmol), aniline (1 mmol), and dimethyl phosphite (2 mL) were added into a 25 mL three-necked flask. The mixture was then heated at 80 °C for 2 min at 180 W in a multimood microwave oven. The reaction mixture was diluted with water and extracted with $CH_2Cl_2$ (20 mL). The organic layer was washed with $H_2O$ (3 × 10 mL), dried over anhydrous $Na_2SO_4$, filtered, concentrated, and the crude product was purified by silica gel flash column chromatography eluted with 2:1 petroleum ether/acetone to give pure α-amino phosphonate **1a** in 98% yield, mp 90–91 °C. $^1$H NMR (400 MHz) ($CDCl_3$): $\delta$ 7.48–6.59 (10H, m, $2C_6H_5$), 4.81 (1H, d, $^1J_{PH} = 24.40$ Hz, CH), 3.76 (3H, d, $^2J_{PH} = 10.60$ Hz, $OCH_3$), 3.46 (3H, d, $^2J_{PH} = 10.60$ Hz, $OCH_3$); $^{13}$C NMR (100 MHz) ($CDCl_3$): $\delta$ 146.4, 135.9, 129.6, 129.2, 128.5, 128.2, 118.9, 114.2, 55.5 (d, $^1J_{CP} = 150.2$ Hz, CH), 54.3, 54.2; HRMS calcd for $C_{15}H_{18}NO_3P$ 291.1024, found 291.1022.