

Amberlite-IR 120 catalyzed three-component synthesis of α -amino phosphonates in one-pot

Asish K. Bhattacharya*, Kalpeshkumar C. Rana

Combi Chem-Bio Resource Centre and Division of Organic Chemistry, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

Received 3 December 2007; revised 14 February 2008; accepted 16 February 2008

Available online 21 February 2008

Abstract

A simple, efficient, and environmentally benign method for a three-component reaction of an amine, an aldehyde or a ketone, and diethyl phosphite catalyzed by Amberlite-IR 120 resin has been developed to afford α -amino phosphonates in high yields and short reaction times under solvent-free reaction conditions. The major advantages of the present method are good yields, inexpensive, ecofriendly and reusable catalyst, mild and solvent-free reaction conditions and tolerance towards various functionalities present in the substrates.

© 2008 Elsevier Ltd. All rights reserved.

Keywords: α -Amino phosphonates; Aldehydes; Amines; Alkyl phosphite; Ion-exchange resin; Multi-component reaction

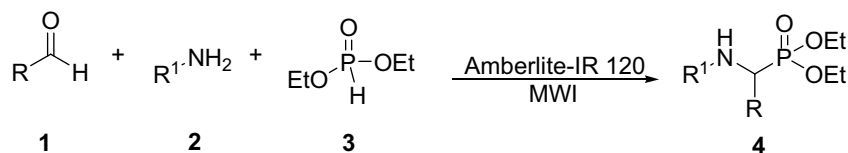
1. Introduction

The synthesis of α -amino phosphonates has attracted much attention recently due to their significant biological activities and structural analogy to α -amino acids. They have been reported to act as peptide mimics,¹ haptens of catalytic antibodies,² antibiotics and pharmacological agents³ and herbicides.⁴ Further, phosphinic acid and phosphinic amino acid analogues have also been reported to be enzyme inhibitors.⁵ Various synthetic approaches have been reported for the synthesis of α -amino phosphonates, however, nucleophilic addition reaction of phosphites with imines is one of the most preferred methods, which is usually catalyzed by an alkali metal alkoxide, for example, NaOEt or Lewis acids⁶ such as ZnCl₂, SnCl₂, SnCl₄, BF₃·Et₂O and MgBr₂.^{7,8} However, these reactions cannot proceed in one-pot from a carbonyl compound, an amine and a phosphite because the water that is generated during the course of the reaction can decompose or deactivate the Lewis acid.⁹ This drawback has been over-

come by one of our recent methods utilizing bismuth nitrate pentahydrate as an efficient Lewis acid as it is able to tolerate trace amounts of water.¹⁰ As α -amino phosphonate synthesis via three-component reactions is important acid-mediated reactions, the development of a reaction that uses an environmentally benign and reusable catalyst should be of great interest.

The use of solid acidic catalysts has gained importance in organic synthesis due to several advantages such as, operational simplicity, nontoxicity, reusability, low cost, and ease of isolation after completion of the reaction. Amberlite-IR 120 resin has emerged as an efficient heterogeneous catalyst for various chemical transformations.^{11–13} Owing to the numerous advantages associated with this cheap and nonhazardous catalyst, we considered Amberlite-IR 120 resin to be an ideal heterogeneous acid catalyst for the synthesis of α -amino phosphonates. Also, it is widely reported in the literature^{14–18} that application of microwave irradiation enables realization of reactions, which otherwise require harsh conditions and are too slow for practical purposes. Moreover, microwave-assisted reactions are believed to satisfy the demands of ‘green chemistry’ allowing for solvent-free conditions to be employed.

* Corresponding author. Tel.: +91 20 2590 2309; fax: +91 20 2590 2624.
E-mail address: ak.bhattacharya@ncl.res.in (A. K. Bhattacharya).



Scheme 1.

Herein, we report a novel one-pot synthesis of α -amino phosphonates catalyzed by Amberlite-IR 120 resin under solvent-free reaction conditions using microwave irradiation (Scheme 1).

2. Results and discussions

Initially, benzaldehyde was reacted with aniline and diethyl phosphite in the presence of Amberlite-IR 120 and irradiated with microwaves for 2 min to give the corresponding α -amino phosphonate in 90% yield (Table 1, entry 1). Several structurally diverse carbonyl compounds and aniline/substituted anilines were subjected to this novel procedure to give the corresponding α -amino phosphonates in high to excellent yields. The results are summarized in Table 1. The presence of electron-donating groups on the aldehyde resulted in the corresponding products in low yields and the reaction was sluggish, however, aldehydes possessing electron-withdrawing groups afforded the corresponding α -amino phosphonates in shorter reaction times and in higher yields. Also, amines possessing electron-donating groups gave the corresponding products in good yields. However, in the case of a diene aldehyde (entry 24), the corresponding product was obtained in poor yield. The wide applicability of the present method is evident from the fact that it is tolerant towards various functional groups including alkoxy, halides, nitro, methylenedioxy, carboxylic and hydroxy groups. Moreover, the catalyst can be reused without affecting the yield of the desired product and reaction time thus, making it environmentally friendly.

3. Conclusion

In conclusion, Amberlite-IR 120 was found to be an efficient catalyst for the one-pot reaction of aldehydes, amines, and diethyl phosphite to afford α -amino phosphonates in good to excellent yields. The main advantages of the present synthetic protocol are mild, solvent-free conditions, ecofriendly catalyst and easy reaction work-up procedure. It is expected that the present methodology will find application in organic synthesis.

4. Experimental

4.1. Typical experimental procedure

Carbonyl compound (1 mmol), amine (1 mmol), diethylphosphite (1 mmol) and Amberlite-IR 120 (100 mg)

were taken in a Pyrex test tube and exposed to microwave irradiation (Kenstar Model No. OM-9918 C; 2450 MHz, 2350 W) for the appropriate time (see Table 1). After completion of the reaction (TLC), the reaction mixture was cooled and DCM (25 mL) was added. The catalyst was filtered from the reaction mixture and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (100–200 mesh) eluting with petroleum ether–ethyl acetate (15–30%) to afford the corresponding pure α -amino phosphonates. All the products were characterized from their spectral data.

4.1.1. Compound 4d

Solid; mp 98–99 °C; 1H NMR (200 MHz, Acetone- d_6 , TMS): δ = 7.41–6.56 (m, 9H), 4.70 (d, $^1J_{PH}$ = 23.0 Hz, 1H), 4.19–3.63 (m, 4H), 3.77 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, Acetone- d_6 , TMS): δ = 159.3, 146.5, 129.2, 129.0, 128.9, 127.7, 118.4, 114.1, 114.0, 113.9, 63.37 (d, $^2J_{PC}$ = 7.3 Hz, $-OCH_2CH_3$), 63.23 (d, $^2J_{PC}$ = 7.0 Hz, $-OCH_2CH_3$), 55.3 (d, $^1J_{PC}$ = 152.2 Hz, $-CHP$), 55.2, 16.5 (d, $^3J_{PC}$ = 5.5 Hz, $-OCH_2CH_3$), 16.3 (d, $^3J_{PC}$ = 5.5 Hz, $-OCH_2CH_3$); MS (ESI): m/z = 388 $[M+K]^+$, 372 $[M+Na]^+$, 350 $[M+H]^+$. Anal. Calcd for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 4.01. Found: C, 61.90; H, 6.86; N, 3.95.

4.1.2. Compound 4m

Solid; mp 97–98 °C; 1H NMR (200 MHz, Acetone- d_6 , TMS): δ = 7.99–7.29 (m, 9H), 5.57 (d, $^1J_{PH}$ = 12.8 Hz, 1H), 3.92–3.44 (m, 4H), 0.94 (m, 6H); ^{13}C NMR (50 MHz, Acetone- d_6 , TMS): δ = 167.6, 138.0, 137.4, 132.2, 132.0, 129.2, 128.8, 126.5, 125.2, 124.6, 124.4, 63.8 (d, $^2J_{PC}$ = 7.0 Hz, $-OCH_2CH_3$), 62.6 (d, $^2J_{PC}$ = 7.3 Hz, $-OCH_2CH_3$), 59.2 (d, $^1J_{PC}$ = 153.7 Hz, $-CHP$), 16.0 (d, $^3J_{PC}$ = 5.1 Hz, $-OCH_2CH_3$), 15.8 (d, $^3J_{PC}$ = 6.9 Hz, $-OCH_2CH_3$); MS (ESI): m/z = 384 $[M-H_2O+K]^+$, 368 $[M-H_2O+Na]^+$, 346 $[M-H_2O+H]^+$. Anal. Calcd for $C_{18}H_{22}NO_5P$: C, 59.50; H, 6.10; N, 3.85. Found: C, 59.15; H, 6.02; N, 3.78.

4.1.3. Compound 4s

Solid; mp 168–169 °C; 1H NMR (200 MHz, Acetone- d_6 , TMS): δ = 6.95–6.42 (m, 7H), 5.81 (s, 2H), 4.63 (d, $^1J_{PH}$ = 24.3 Hz, 1H), 4.05–3.56 (m, 4H), 1.11 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, Acetone- d_6 , TMS): δ = 149.7, 147.7, 147.1, 140.0, 131.1, 121.9, 115.4, 115.5, 108.5, 107.6, 101.1, 62.5 (d, $^2J_{PC}$ = 7.3 Hz, $-OCH_2CH_3$), 62.3 (d, $^2J_{PC}$ = 7.3 Hz, $-OCH_2CH_3$), 55.9 (d, $^1J_{PC}$ = 153.3 Hz, $-CHP$), 15.9 (d,

Table 1
One-pot synthesis of α -amino phosphonates catalyzed by Amberlite-IR 120

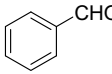
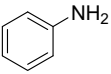
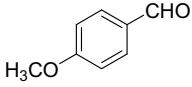
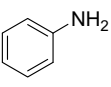
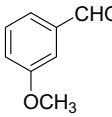
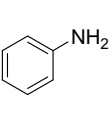
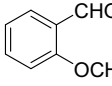
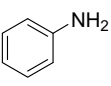
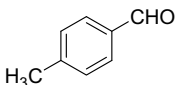
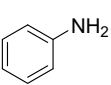
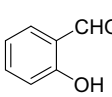
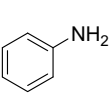
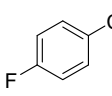
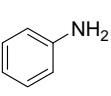
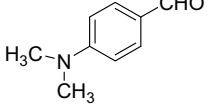
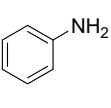
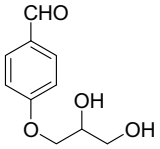
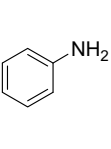
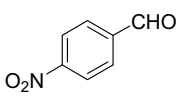
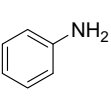
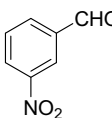
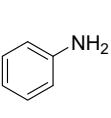
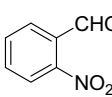
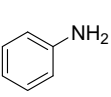
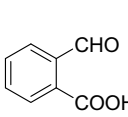
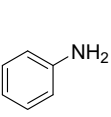
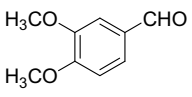
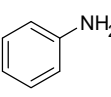
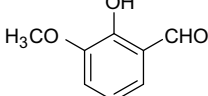
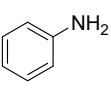
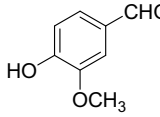
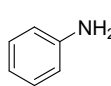
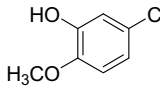
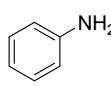
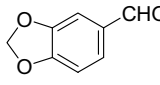
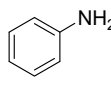
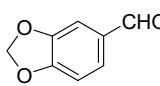
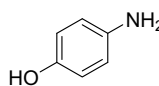
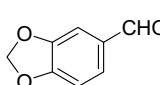
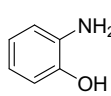
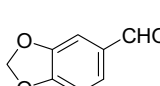
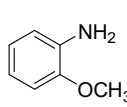
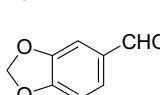
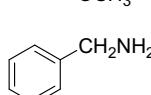
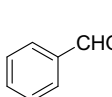
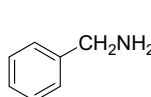
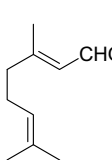
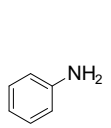
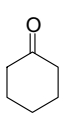
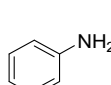
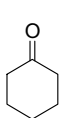
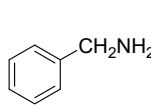
Entry	R-CHO	R ¹ -NH ₂	Product	Time (min)	Yield ^a (%)
1			4a	2	90
2			4b	5	81
3			4c	1	92
4			4d	1	87
5			4e	1	89
6			4f	1.5	91
7			4g	1	87
8			4h	3	70
9			4i	2	67
10			4j	1	95
11			4k	2.5	88
12			4l	3	75
13			4m	1	78
14			4n	2	90
15			4o	2	95

Table 1 (continued)

Entry	R-CHO	R ¹ -NH ₂	Product	Time (min)	Yield ^a (%)
16			4p	2	90
17			4q	2	87
18			4r	2	92
19			4s	3	98
20			4t	2	79
21			4u	2	91
22			4v	1	81
23			4w	1	87
24			4x	1	11
25			4y	3	78
26			4z	2	84

^a Yields refer to those of pure isolated products fully characterized by spectral data.

³J_{PC} = 5.9 Hz, –OCH₂CH₃), 15.7 (d, ³J_{PC} = 5.9 Hz, –OCH₂CH₃); MS (ESI): *m/z* = 418 [M+K]⁺, 402 [M+Na]⁺, 380 [M+H]⁺. Anal. Calcd for C₁₈H₂₂NO₆P: C, 56.99; H, 5.85; N, 3.69. Found: C, 56.60; H, 5.73; N, 3.62.

4.1.4. Compound **4t**

Solid; mp 132–133 °C; ¹H NMR (200 MHz, Acetone-*d*₆, TMS): δ = 6.97–6.47 (m, 7H), 5.87 (s, 2H), 4.79 (d, ¹J_{PH} = 25.0 Hz, 1H), 4.32–3.69 (m, 4H), 1.29 (t,

$J = 7.1$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, Acetone- d_6 , TMS): $\delta = 147.9, 147.3, 145.3, 135.0, 129.6, 121.6, 119.9, 118.4, 114.3, 112.0, 108.5, 108.3, 101.1, 64.2$ (d, $^2J_{\text{PC}} = 7.0$ Hz, $-\text{OCH}_2\text{CH}_3$), 63.7 (d, $^2J_{\text{PC}} = 7.0$ Hz, $-\text{OCH}_2\text{CH}_3$), 55.7 (d, $^1J_{\text{PC}} = 155.9$ Hz, $-\text{CHP}$), 16.4 (d, $^3J_{\text{PC}} = 5.9$ Hz, $-\text{OCH}_2\text{CH}_3$), 16.2 (d, $^3J_{\text{PC}} = 5.9$ Hz, $-\text{OCH}_2\text{CH}_3$); MS (ESI): $m/z = 402$ $[\text{M}+\text{Na}]^+$, 380 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_6\text{P}$: C, 56.99; H, 5.85; N, 3.69. Found: C, 56.65; H, 5.77; N, 3.60.

4.1.5. Compound 4u

Syrupy liquid; ^1H NMR (200 MHz, Acetone- d_6 , TMS): $\delta = 6.96\text{--}6.39$ (m, 7H), 5.93 (s, 2H), 5.27 (t, $J = 8.0$ Hz, 1H), 4.67 (dd, $^1J_{\text{PH}} = 24.0, 8$ Hz, 1H), 4.16–3.85 (m, 4H), 3.88 (s, 3H) 1.28 (t, $J = 7.2$ Hz, 3H), 1.20 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, Acetone- d_6 , TMS): $\delta = 148.0, 147.9, 147.3, 136.0, 129.8, 121.4, 121.0, 117.7, 111.2, 109.6, 108.3, 108.2, 101.1, 63.4$ (d, $^2J_{\text{PC}} = 7.0$ Hz, $-\text{OCH}_2\text{CH}_3$), 63.2 (d, $^2J_{\text{PC}} = 7.0$ Hz, $-\text{OCH}_2\text{CH}_3$), 55.6 (d, $^1J_{\text{PC}} = 152.6$ Hz, $-\text{CHP}$), 16.5 (d, $^3J_{\text{PC}} = 5.8$ Hz, $-\text{OCH}_2\text{CH}_3$), 16.3 (d, $^3J_{\text{PC}} = 5.8$ Hz, $-\text{OCH}_2\text{CH}_3$); MS (ESI): $m/z = 432$ $[\text{M}+\text{K}]^+$, 416 $[\text{M}+\text{Na}]^+$, 394 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_6\text{P}$: C, 58.01; H, 6.15; N, 3.56. Found: C, 57.78; H, 6.10; N, 3.46.

4.1.6. Compound 4v

Syrupy liquid; ^1H NMR (200 MHz, Acetone- d_6 , TMS): $\delta = 7.35\text{--}6.77$ (m, 8H), 5.97 (s, 2H), 4.13–3.77 (m, 6H), 3.52 (d, $^1J_{\text{PH}} = 13.3$ Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, Acetone- d_6 , TMS): $\delta = 147.9, 147.4, 139.3, 129.4, 128.4, 128.3, 127.2, 122.4, 108.7, 108.2, 101.1, 62.9$ (t, $^2J_{\text{PC}} = 6.6, 7.3$ Hz, $-\text{OCH}_2\text{CH}_3$), 59.2 (d, $^1J_{\text{PC}} = 155.2$ Hz, $-\text{CHP}$), 51.0 (d, $^3J_{\text{PC}} = 17.6$ Hz, $-\text{NHCH}_2\text{Ph}$), 16.4 (t, $^3J_{\text{PC}} = 6.2, 5.6$ Hz, $-\text{OCH}_2\text{CH}_3$); MS (ESI): $m/z = 416$ $[\text{M}+\text{K}]^+$, 400 $[\text{M}+\text{Na}]^+$, 378 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_5\text{P}$: C, 60.47; H, 6.41; N, 3.71. Found: C, 60.29; H, 6.28; N, 3.62.

4.1.7. Compound 4x

Syrupy liquid; ^1H NMR (200 MHz, Acetone- d_6 , TMS): $\delta = 7.13\text{--}6.54$ (m, 5H), 5.12–4.95 (m, 2H), 4.38 (dd, 1H, $^1J_{\text{PH}} = 20.7$ Hz, $^3J_{\text{CH}} = 9.4$ Hz), 4.15–3.97 (m, 4H), 2.06–1.97 (m, 2H), 1.72–1.71 (m, 2H), 1.61 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 1.27–1.17 (m, 6H); ^{13}C NMR (50 MHz, Acetone- d_6 , TMS): $\delta = 146.8, 141.6, 131.8, 129.1, 123.6, 119.9, 118.4, 113.9, 63.1$ (d, $^2J_{\text{PC}} = 6.6$ Hz, $-\text{OCH}_2\text{CH}_3$), 62.8 (d, $^2J_{\text{PC}} = 7.3$ Hz, $-\text{OCH}_2\text{CH}_3$), 50.6 (d, $^1J_{\text{PC}} = 158.5$ Hz, $-\text{CHP}$), 39.6, 26.2, 25.6, 17.7, 17.1, 16.5, 16.4; MS (ESI): $m/z = 404$ $[\text{M}+\text{K}]^+$, 388 $[\text{M}+\text{Na}]^+$, 366 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{20}\text{H}_{32}\text{NO}_3\text{P}$: C, 65.73; H, 8.83; N, 3.83. Found: C, 65.62; H, 8.76; N, 3.72.

Acknowledgments

A.K.B. is grateful to the Department of Biotechnology (DBT), Government of India, New Delhi, India for financial support. K.C.R. is grateful to the Council of Scientific and Industrial Research, New Delhi, India for the award of a Senior Research Fellowship. The authors are grateful to Dr. Ganesh Pandey, FNA, Head, Division of Organic Chemistry for constant support and encouragement.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2008.02.102](https://doi.org/10.1016/j.tetlet.2008.02.102).

References and notes

- Kafarski, P.; Leczak, B. *Phosphorus Sulfur Silicon Relat. Elem* **1991**, 63, 193.
- (a) Hirschmann, R.; Smith, A. B., III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengler, P. A.; Benkovic, S. J. *Science* **1994**, 265, 234; (b) Smith, A. B., III; Taylor, C. M.; Benkovic, S. J.; Hirschmann, R. *Tetrahedron Lett.* **1994**, 35, 6853.
- (a) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, 29, 29; (b) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, 272, 56; (c) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Antimicrob. Agents Chemother.* **1979**, 15, 684; (d) Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W.; Ringrose, P. S. *Antimicrob. Agents Chemother.* **1979**, 15, 677; (e) Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W.; Lloyd, W. J.; Ringrose, P. S. *Antimicrob. Agents Chemother.* **1979**, 15, 696.
- Antibiotics*; Hassall, C. H., Hahn, E. F., Eds.; Springer: Berlin, 1983; Vol. VI, pp 1–11.
- (a) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, 30, 1603; (b) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, 32, 1652; (c) Skropeta, D.; Schwoerer, R.; Schmidt, R. R. *Bioorg. Med. Chem. Lett.* **2003**, 13, 3351.
- (a) Petrov, K. A.; Chauzov, V. A.; Erokhina, T. S. *Usp. Khim.* **1974**, 43, 2045; *Chem. Abstr.* **1975**, 82, 43486; (b) Kirby, A. J.; Warren, S. G. *The Organic Chemistry of Phosphorus*; Elsevier: Amsterdam, 1967.
- Laschat, S.; Kunz, H. *Synthesis* **1992**, 90.
- Zon, J. *Pol. J. Chem.* **1981**, 55, 643.
- Genet, J. P.; Uziel, J.; Port, M.; Touzin, A. M.; Roland, S.; Thorimbert, S.; Tanier, S. *Tetrahedron Lett.* **1992**, 33, 77.
- Bhattacharya, A. K.; Kaur, T. *Synlett* **2007**, 745.
- Tewari, N.; Katiyar, D.; Tiwari, V. K.; Tripathi, R. P. *Tetrahedron Lett.* **2003**, 44, 6639.
- Akagawa, K.; Sakamoto, S.; Kudo, K. *Tetrahedron Lett.* **2007**, 48, 985.
- Park, T.-J.; Weiwer, M.; Yuan, X.; Baytas, S. N.; Munoz, E. M.; Murugesan, S.; Linhardt, R. J. *Carbohydr. Res.* **2007**, 342, 614.
- Zlotorzynsky, A. *Crit. Rev. Anal. Chem.* **1995**, 25, 43.
- Varma, R. S. *Green Chem.* **1999**, 43.
- Caddick, S. *Tetrahedron* **1995**, 51, 10403.
- Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, 57, 9225.
- Perreux, L.; Loupy, A. *Tetrahedron* **2001**, 57, 9199.