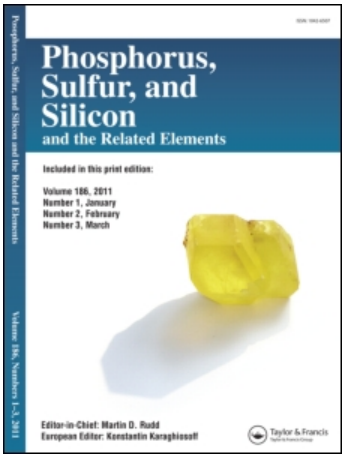


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

(*N*-Isocyanimino)triphenylphosphorane as an Efficient Reagent for the Synthesis of 1,3,4-Oxadiazoles from 3-Substituted Benzoic Acid Derivatives

Ali Ramazani[a]; Ali Souldozi[b]
[a] Chemistry Department, Zanjan University, Zanjan, Iran [b] Chemistry Department, Islamic Azad University-Urmia Branch, Urmia, Iran

Online publication date: 18 November 2009

To cite this Article Ramazani, Ali and Souldozi, Ali(2009) '(*N*-Isocyanimino)triphenylphosphorane as an Efficient Reagent for the Synthesis of 1,3,4-Oxadiazoles from 3-Substituted Benzoic Acid Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 184: 12, 3191 — 3198
To link to this Article: DOI: 10.1080/10426500802705537
URL: http://dx.doi.org/10.1080/10426500802705537

Phosphorus, Sulfur, and Silicon, 184:3191–3198, 2009

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802705537

Taylor & Francis
Taylor & Francis Group

(*N*-Isocyanimino)triphenylphosphorane as an Efficient Reagent for the Synthesis of 1,3,4-Oxadiazoles from 3-Substituted Benzoic Acid Derivatives

Ali Ramazani[1] and Ali Souldozi[2]
[1]Chemistry Department, Zanjan University, Zanjan, Iran
[2]Chemistry Department, Islamic Azad University–Urmia Branch, Urmia, Iran

*The reaction of 3-substituted benzoic acid derivatives with (*N*-isocyanimino) triphenylphosphorane proceeds smoothly at room temperature to afford corresponding 1,3,4-oxadiazoles via an intramolecular* aza*-Wittig reaction in excellent yields under neutral conditions.*

Keywords Benzoic acid derivatives; iminophosphorane; intramolecular *aza*-Wittig reaction; isocyanide; (*N*-isocyanimino)triphenylphosphorane; 1,3,4-oxadiazole

INTRODUCTION

Organophosphorus compounds[1–8] have been extensively employed in organic synthesis as useful reagents, as well as ligands, in a number of transition metal catalysts.[3] Iminophosphoranes are a class of a special type of zwitterions that bear a strongly nucleophilic electron rich nitrogen.[6–8] The electron distribution around the P^+–N^- bond and its consequent chemical implications have been probed and assessed through theoretical, spectroscopic, and crystallographic investigations.[6–8] The proton affinity of these iminophosphoranes can be used as a molecular guide to assess their utility as synthetic reagents and their function as ligands in coordination and organometallic chemistry.[6–8] The intramolecular version of the *aza*-Wittig–type reaction has attracted considerable attention recently because of its high potential for the synthesis of a wide variety of nitrogen heterocycles, which can be attributed, in good measure, to the rapid progress in the preparation

Received 25 October 2008; accepted 17 December 2008.
This work was supported by the Iran National Science Foundation (INSF) via the research project number 86053.20.
Address correspondence to Ali Ramazani, Chemistry Department, Zanjan University, P O Box 45195-313, Zanjan, Iran. E-mail: aliramazani@gmail.com

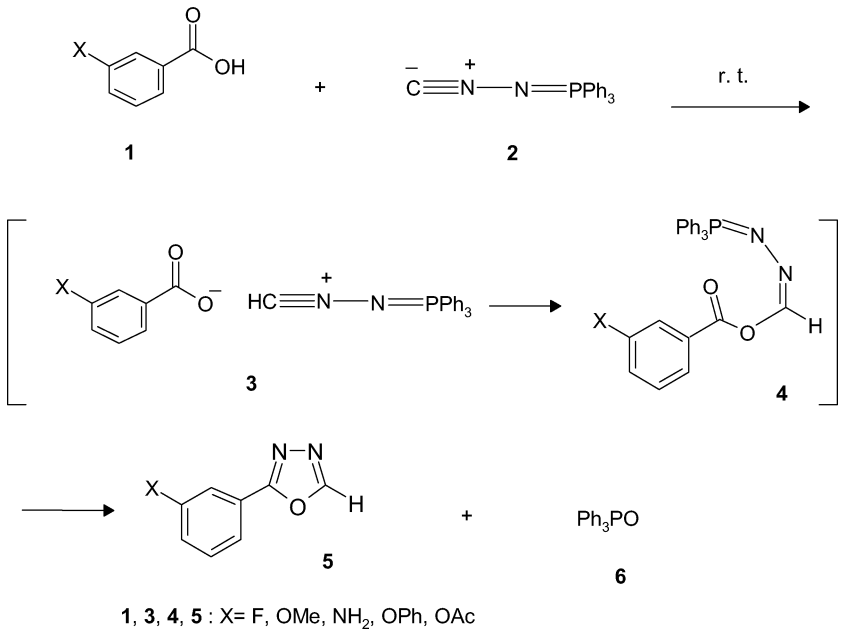
of functionalized iminophosphoranes.[6] Several interesting heterocyclization reactions involving iminophosphoranes have been reviewed.[6] These compounds can easily be converted through *aza*-Wittig reaction with isocyanates, carbon dioxide, or carbon disulfide into functionalized heterocumulenes, which exhibit a rich chemistry of unusual synthetic promise.[6] The nucleophilicity at the nitrogen is a factor of essential mechanistic importance in the use of these iminophosphoranes as *aza*-Wittig reagents.[6]

Isocyanide-based reactions have been known for about 80 years, with the first described in 1921 and named after its founder, Passerini.[9–14] The chemistry of the isocyanides began in 1859 when Lieke prepared allyl isocyanide as the first isocyanide.[14] Lieke, like many chemists today, was immediately struck by their strange repulsive odor, one of the only negatives of this branch of chemistry.[14] The classical syntheses of isocyanides were developed in 1867 by Gautier.[14] For the following century, only 12 isocyanides were known, and rather few types of reactions had been described.[14] Thus for a whole century, from 1859 to 1958, isocyanides were not readily available, and their chemistry remained an underinvestigated part of organic chemistry.[9–14] In 1921, Passerini pioneered the use of isocyanides and successfully developed a three-component synthesis of α-acyloxycarboxamide by reaction of a carboxylic acid, an aldehyde, and an isocyanide.[14] Today most IMCR chemistry relates to the classical reactions of Passerini and Ugi. Indeed, the large number of different scaffolds now available mostly builds on these two IMCRs and their combination with other types of reactions.[9–14] Passerini reactions involve an oxo-component, an isocyanide, and a nucleophile.[9–14] Ugi reactions are defined as the reaction of a Schiff base or an enamine with a nucleophile and an isocyanide, followed by a (Mumm) rearrangement reaction.[14] Passerini reactions are beginning to find utility in the drug discovery process and in total syntheses of biologically relevant natural products.[14]

1,3,4-Oxadiazoles have attracted interest in medicinal chemistry as surrogates of carboxylic acids, esters, and carboxamides.[15] They are an important class of heterocyclic compounds that have a wide range of pharmaceutical and biological activities including antimicrobial, antifungal, anti-inflammatory, and antihypertensive.[15] Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. These protocols are multistep in nature.[15–30] The most general method involves the cyclization of diacylhydrazides with a variety of reagents, such as thionyl chloride, phosphorous oxychloride, or sulfuric acid, usually under harsh reaction conditions.[29] Few reliable and operationally simple examples have been reported for the one-step

synthesis of 1,3,4-oxadiazoles, especially from readily available carboxylic acids and acid hydrazides.[30]

Iminophosphoranes are important reagents in synthetic organic chemistry, especially in the synthesis of naturally occurring products—compounds with biological and pharmacological activity.[6] However, the organic chemistry of (*N*-isocyanimino)triphenylphosphorane **2** remains almost unexplored.[7,8] (*N*-isocyanimino)triphenylphosphorane **2** is expected to have synthetic potential because it provides a reaction system in which the iminophosphorane group can react with a reagent having a carbonyl functionality.[9–11] In recent years, we have established a one-pot method for the synthesis of organophosphorus compounds.[31–41] As part of our ongoing program to develop efficient and robust methods for the preparation of organic compounds,[31–41] we sought to develop a convenient preparation of 1,3,4-oxadiazoles **5** from 3-substituted benzoic acid derivatives **1** and (*N*-isocyanimino)triphenylphosphorane **2** in excellent yields under neutral conditions (Scheme 1).



SCHEME 1 Preparation of 1,3,4-oxadiazole derivatives **5** from 3-substituted benzoic acid derivatives **1**.

RESULTS AND DISCUSSION

In the last few years, several synthetic methods have been reported for the preparation of (*N*-isocyanimino)triphenylphosphorane ($CNNPPh_3$) **2** (Scheme 1).[7,8] There are several reports for the use of (*N*-isocyanimino)triphenylphosphorane **2** in the synthesis of metal complexes.[7,8] However, application of **2** in the synthesis of organic compounds has been reported fairly rarely.[9–11] As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[2] we sought to develop a convenient preparation of 1,3,4-oxadiazoles **5** from 3-substituted benzoic acid derivatives **1** and (*N*-isocyanimino)triphenylphosphorane **2** in excellent yields under neutral conditions (Scheme 1). The 3-substituted benzoic acid derivatives **1** and (*N*-isocyanimino)triphenylphosphorane **2** in dry solvent react together in a 1:1 ratio at room temperature to produce 1,3,4-oxadiazoles **5** and triphenylphosphine oxide **6** (Scheme 1). The reaction proceeds smoothly and cleanly under mild conditions. The mechanism of the reaction between the 3-substituted benzoic acid derivatives **1** and (*N*-isocyanimino)triphenylphosphorane **2** has not been established experimentally. However, a possible explanation is proposed in Scheme 1. On the basis of the well established chemistry of isocyanides,[9–14] it is reasonable to assume that protonation of **2** by the 3-substituted benzoic acid derivatives **1** followed by a quenching of the cationic center by the conjugate base of the carboxylic acid can generate the iminophosphorane **4**.[6] An intramolecular *aza*-Wittig[6] reaction of the iminophosphorane **4** would lead to formation of the 1,3,4-oxadiazoles **5** and triphenylphosphine oxide **6** (Scheme 1). The structures of the products **5a–e** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. The IR spectrum of **5a** showed strong absorptions at 3069 and 2923 (CH, aromatic); 1569 and 1462 (C=C, aromatic); 1231 (C–F) and 1100, 877, 808 and 739 (oxadiazole and aromatic parts) cm^{-1}, indicating the presence of the mentioned functionalities in its structure. The ^{1}H NMR spectrum of compound **5a** exhibited five signals readily recognized as arising from aromatic moiety [δ = 7.24–7.31 (m, 1 H, arom), 7.48–7.56 (m, 1 H, arom), 7.78–7.81 (m, 1 H, arom), and 7.88–7.91 (m, 1 H, arom)] and a CH of oxadiazole ring (δ = 8.50, s, 1 H). The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed eight distinct resonances [δ = 114.18 (d, 1 CH, $^2J_{CF}$ = 24.4 Hz, arom), 119.13 (d, 1 CH, $^2J_{CF}$ = 21.4 Hz, arom), 122.89 (d, 1 CH, $^4J_{CF}$ = 3.2 Hz, arom), 125.19 (d, 1C, $^3J_{CF}$ = 8.50 Hz, arom), 131.03 (d, 1 CH, $^3J_{CF}$ = 8.2 Hz, arom), 152.81 (1CH, oxadiazole), 162.34 (d, 1C, $^1J_{CF}$ = 183.8 Hz, arom), and 164.79 (1C, oxadiazole)] that are in agreement with the

formula and structure of **5a**. Partial assignment of these resonances is given in the spectral analysis section (see the Experimental section).

CONCLUSION

In summary, we have found a new method for the preparation of 1,3,4-oxadiazoles **5** from 3-substituted benzoic acid derivatives **1** and (*N*-isocyanimino)triphenylphosphorane **2** in excellent yields under neutral conditions. We believe that the reported method offers a mild and simple route for the preparation of these derivatives. Its ease of workup and reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

EXPERIMENTAL

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Flash chromatography columns were prepared from Merck silica gel powder. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-250 Avance spectrometer at 250.0 and 62.5 MHz, respectively. The methods were used to follow the reactions were TLC and NMR. TLC and NMR indicated that there is no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 20 eV. (*N*-Isocyanimino)triphenylphosphorane **2** was prepared based on a reported procedure.[7,8]

General Procedure for the Preparation of Compounds 4 and 5

To a magnetically stirred solution of (*N*-isocyanimino) triphenylphosphorane[7,8] **2** (0.302 g, 1 mmol) in dry $CHCl_3$ (4 mL), a solution of 3-substituted benzoic acid derivatives **1** (1 mmol) in dry $CHCl_3$ (4 mL) was added dropwise over 15 min. The mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure, and the viscous residue was purified by flash column chromatography [silica gel; petroleum ether/ethyl acetate (10:2)]. The solvent was removed under reduced pressure, and the product **5** was obtained. The characterization data of the compounds are given below:

2-(3-Fluorophenyl)-1,3,4-oxadiazole 5a

White crystals; mp: 135.6°C; Yield: 82.2%. IR (KBr) (υ_{max}, cm^{-1}): 3069 and 2923 (CH, aromatic); 1569 and 1462 (C=C, aromatic); 1231 (C−F) and 1100, 877, 808 and 739 (oxadiazole and aromatic parts). ^1H NMR ($CDCl_3$) δ_H: 7.24–7.31 (m, 1 H, arom), 7.48–7.56 (m, 1 H, arom), 7.78–7.81 (m, 1 H, arom) and 7.88–7.91 (m, 1 H, arom); 8.50 (s, 1 H, CH of oxadiazole ring). ^{13}C NMR ($CDCl_3$) δ_C: 114.18 (d, 1 CH, $^2J_{CF}$ = 24.4 Hz, arom), 119.13 (d, 1 CH, $^2J_{CF}$ = 21.4 Hz, arom), 122.89 (d, 1 CH, $^4J_{CF}$ = 3.2 Hz, arom), 125.19 (d, 1C, $^3J_{CF}$ = 8.50 Hz, arom), 131.03 (d, 1 CH, $^3J_{CF}$ = 8.2 Hz, arom), 152.81 (s, 1CH, oxadiazole), 162.34 (d, 1C, $^1J_{CF}$ = 183.8 Hz, arom) and 164.79 (s, 1C, oxadiazole). MS: *m*/*z* (%); 164 (M^+, 15), 152 (49), 123 (45), 77 (100) and 51 (63).

2-(3-Methoxyphenyl)-1,3,4-oxadiazole 5b

White crystals; mp: 108.8°C; Yield: 87.5%. IR (KBr) (υ_{max}, cm^{-1}): 3123 and 3008 (CH, aromatic); 2954 (CH, OMe); 1502 and 1485 (C=C, aromatic) and 1231 (C-O). ^1H NMR ($CDCl_3$) δ_H: 3.88 (s, 3 H, OCH_3), 7.07–7.11 (m, 1H, arom); 7.42 (t, 1H, $^3J_{HH}$ = 8.0 Hz, arom); 7.61–7.66 (m, 2H, arom) and 8.47 (s, 1H, oxadiazole). ^{13}C NMR ($CDCl_3$) δ_C: 55.50 (1C, OCH_3); 111.68, 118.47, 119.43 and 130.27 (4CH, arom); 124.54 (C, arom); 152.64 (1CH, oxadiazole); 159.95 (C-O, arom); 164.71 (1C, oxadiazole). MS: *m*/*z* (%); 176 (M^+, 100), 135 (85), 107 (33), 92 (13), 77 (21), 63 (12) and 51 (10).

3-(1,3,4-Oxadiazol-2-yl)aniline 5c

Yellow crystals; mp: 142.7°C; Yield: 80.1%. IR (KBr) (υ_{max}, cm^{-1}): 3346 and 3231 (NH_2); 3010 (CH, aromatic); 1615 and 1339 (C=C, aromatic); 1108 (C-N) and 739(C=C, aromatic). ^1H NMR ($CDCl_3$) δ_H: 4.01 (s, 2H, NH_2); 6.79–6.83 (m, 1H, arom); 7.20–7.25 (m, 1H, arom); 7.32–7.33 (m, 1H, arom); 7.42–7.43 (m, 1H, arom) and 8.41 (s, 1H, oxadiazole). ^{13}C NMR ($CDCl_3$) δ_C: 112.91, 116.88, 118.49 and 130.04 (4CH, arom); 124.13 (C, arom); 147.24 (C-N, arom); 152.58 (1CH, oxadiazole) and 164.98 (1C, oxadiazole). MS: *m*/*z* (%); 161 (M^+, 100), 120 (66), 92 (47), 77 (13), 65 (26), 51 (20) and 41 (12).

2-(3-Phenoxy-phenyl)-[1,3,4]oxadiazole 5d

White crystals; mp: 64.3–64.5°C; Yield: 8.0%. IR (KBr) (υ_{max}, cm^{-1}): 3154 (CH, aromatic); 1592, 1554, 1446 and 1323 (C=C, aromatic); 1246 and 1108 (2 C-O). ^1H NMR ($CDCl_3$) δ_H: 7.09 (d, 2H, $^3J_{HH}$ = 8.0 Hz, arom); 7.17–7.24 (m, 2H, arom); 7.37–7.54 (m, 3H, arom); 7.72–7.73 (m, 1H, arom); 7.82–7.85 (m, 1H, arom); 8.48 (s, 1H, oxadiazole). ^{13}C NMR ($CDCl_3$) δ_C: 116.73, 119.44, 121.65, 122.04, 124.15, 130.04 and

130.65 (9CH, arom); 124.96 (C, arom); 152.70 (1CH, oxadiazole); 156.22 and 158.18 (2C-O, arom) and 164.30 (1C, oxadiazole). MS: m/z (%); 238 (M^+, 100), 237 (67), 221 (28), 197 (45), 169 (15), 141 (28), 115 (23), 77 (34), 63 (19) and 51 (44).

3-(1,3,4-Oxadiazol-2-yl)phenyl Acetate 5e

White crystals; mp: 91.6°C; Yield: 84.7%. IR (KBr) (υ_{max}, cm^{-1}): 3085 (CH, aromatic); 1769 (C=O, ester) and 1207 (C-O). ^1H NMR ($CDCl_3$) δ_H: 2.34 (s, 3H, CH_3); 7.29 (d, 1H, $^3J_{HH}$ = 8.2 Hz, arom); 7.54 (t, 1H, $^3J_{HH}$ = 8.2 Hz, arom), 7.82 (s, 1H, arom); 7.96 (d, 1H, $^3J_{HH}$ = 8.2 Hz, arom) (4H, arom), and 8.48 (s, 1H, oxadiazole). ^{13}C NMR ($CDCl_3$) δ_C: 21.06 (CH_3), 120.45, 124.47, 125.37 and 130.34 (4CH, arom); 124.79 (C, arom); 151.08 (C-O, arom); 152.75 (1CH, oxadiazole); 163.98 (1c, oxadiazole) and 169.08 (C=O). MS: m/z (%); 204 (M^+, 16), 162 (100), 121 (57), 105 (7), 93 (8), 78 (8), 63 (8) and 43 (62).

REFERENCES

[1] O. I. Kolodiazhnyi, *Phosphorus Ylides: Chemistry and Applications in Organic Chemistry* (Wiley, New York, 1999).
[2] A. Ramazani, A. R. Kazemizadeh, E. Ahmadi, N. Noshiranzadeh, and A. Souldozi, *Curr. Org. Chem.*, **12,** 59 (2008).
[3] W. C. Kaska, *Coord. Chem. Rev.*, **48,** 1 (1983).
[4] A. Ramazani, A. R. Kazemizadeh, E. Ahmadi, K. Slepokura, and T. Lis, *Z. Naturforsch.*, **61b,** 1128 (2006).
[5] D. E. C. Cobridge, *Phosphorus: An Outline of Chemistry, Biochemistry and Uses*, 5th ed. (Elsevier, Amsterdam, 1995).
[6] P. Molina and M. J. Vilaplana, *Synthesis*, 1197 (1994).
[7] H. Stolzenberg, B. Weinberger, W. P. Fehlhammer, F. G. Pühlhofer, and R. Weiss, *Eur. J. Inorg. Chem.*, **21,** 4263 (2005).
[8] T. W. Chiu, Y. H. Liu, K. M. Chi, Y. S. Wen, and K. L. Lu, *Inorg. Chem.*, **44,** 6425 (2005).
[9] A. Souldozi, A. Ramazani, N. Bouslimani, and R. Welter, *Tetrahedron Lett.*, **48,** 2617 (2007).
[10] A. Souldozi and A. Ramazani, *Tetrahedron Lett.*, **48,** 1549 (2007).
[11] A. Souldozi, K. Ślepokura, T. Lis, and A. Ramazani, *Z. Naturforsch.*, **62b,** 835 (2007).
[12] E. Ahmadi, A. Tofangchi Mahyari, A. Ramazani, and M. Nekomanesh-Haghighi, *Lett. Org. Chem.*, **5,** 540 (2008).
[13] E. Ahmadi, A. Ramazani, and M. Nekomanesh Haghighi, *Tetrahedron Lett.*, **48,** 6954 (2007).
[14] A. R. Kazemizadeh and A. Ramazani, *Arkivoc*, **xv,** 159 (2008).
[15] W. R. Tully, C. R. Gardner, R. J. Gillespie, and R. Westwood, *J. Med. Chem.*, **34,** 2060 (1991).
[16] C. Chen, C. H. Senanayake, T. J. Bill, R. D. Larsen, T. R. Verhoeven, and P. J. Reider, *J. Org. Chem.*, **59,** 3738 (1994).
[17] B. S. Holla, R. Gonsalves, and S. Shenoy, *Eur. J. Med. Chem.*, **35,** 267 (2000).
[18] M. J. Crimmin, P. J. O'Hanlon, N. H. Rogers, and G. Walker, *J. Chem. Soc., Perkin Trans. 1*, 2047 (1989).

[19] U. V. Laddi, S. R. Desai, R. S. Bennur, and S. C. Bennur, *Ind. J. Heterocycl. Chem.*, **11,** 319 (2002).
[20] I. R. Baxendale, S. V. Ley, and M. Martinelli, *Tetrahedron*, **61,** 5323 (2005).
[21] S. Liras, M. P. Allen, and B. E. Segelstein, *Synth. Commun.*, **30,** 437 (2000).
[22] B. J. Brown, I. R. Clemens, and J. K. Neesom, *Synlett*, 131 (2000).
[23] F. T. Coppo, K. A. Evans, T. L. Graybill, and G. Burton, *Tetrahedron Lett.*, **45,** 3257 (2004).
[24] C. T. Brain, J. M. Paul, Y. Loong, and P. J. Oakley, *Tetrahedron Lett.*, **40,** 3275 (1999).
[25] C. T. Brain and S. A. Brunton, *Synlett*, **3,** 382 (2001).
[26] V. K. Tandon and R. B. Chhor, *Synth. Commun.*, **31**, 1727 (2001).
[27] S. H. Mashraqui, S. G. Ghadigaonkar, and R. S. Kenny, *Synth. Commun.*, **33,** 2541 (2003).
[28] F. Bentiss, M. Lagrenee, and D. Barbry, *Synth. Commun.*, **31,** 935 (2001).
[29] E. Jedlovska and J. Lesko, *Synth. Commun.*, **24,** 1879 (1994).
[30] Y. Wang, D. R. Sauer, and S. W. Djuric, *Tetrahedron Lett.*, **47,** 105 (2006).
[31] I. Yavari and A. Ramazani, *Synth. Commun.*, **27,** 1385 (1997).
[32] I. Yavari and A. Ramazani, *Phosphorus, Sulfur, and Silicon*, **130,** 73 (1997).
[33] A. Ramazani and A. Bodaghi, *Tetrahedron Lett.*, **41,** 567 (2000).
[34] P. Pakravan, A. Ramazani, N. Noshiranzadeh, and A. Sedrpoushan, *Phosphorus, Sulfur, and Silicon*, **182,** 545 (2007).
[35] A. Ramazani, M. Rahimifard, and A. Souldozi, *Phosphorus, Sulfur, and Silicon*, **182,** 1 (2007).
[36] A. Ramazani, M. Rahimifard, N. Noshiranzadeh, and A. Souldozi, *Phosphorus, Sulfur, and Silicon*, **182,** 413 (2007).
[37] I. Yavari, A. Ramazani, and A. Yahya-Zadeh, *Synth. Commun.*, **26,** 4495 (1996).
[38] A. Ramazani, E. Ahmadi, A. R. Kazemizadeh, L. Dolatyari, N. Noshiranzadeh, I. Eskandari, and A. Souldozi, *Phosphorus, Sulfur, and Silicon*, **180,** 2419 (2005).
[39] A. Ramazani and M. Mohammadi-Vala, *Phosphorus, Sulfur, and Silicon*, **176,** 223 (2001).
[40] A. Ramazani, I. Amini, and A. Massoudi, *Phosphorus, Sulfur, and Silicon*, **181,** 2225 (2006).
[41] A. Ramazani, A. R. Kazemizadeh, and F. Marandi, *Phosphorus, Sulfur, and Silicon*, **180,** 1537 (2005).