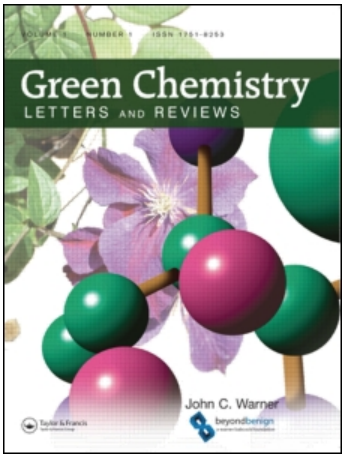


Green Chemistry Letters and Reviews
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t748292817

An efficient synthesis of α-hydroxyphosphonates and α-aminophosphonates in the presence of chlorotrimethylsilane

Rajkumar U. Pokalwar[a]; Sandip A. Sadaphal[a]; Amol H. Kategaonkar[a]; Bapurao B. Shingate[a]; Murlidhar S. Shingare[a]
[a] Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, India

First published on: 18 January 2010

To cite this Article Pokalwar, Rajkumar U. , Sadaphal, Sandip A. , Kategaonkar, Amol H. , Shingate, Bapurao B. and Shingare, Murlidhar S.(2010) 'An efficient synthesis of α-hydroxyphosphonates and α-aminophosphonates in the presence of chlorotrimethylsilane', Green Chemistry Letters and Reviews, 3: 1, 33 — 38, First published on: 18 January 2010 (iFirst)
To link to this Article: DOI: 10.1080/17518250903410082
URL: http://dx.doi.org/10.1080/17518250903410082

Green Chemistry Letters and Reviews
Vol. 3, No. 1, March 2010, 33–38

INDUSTRY LETTER

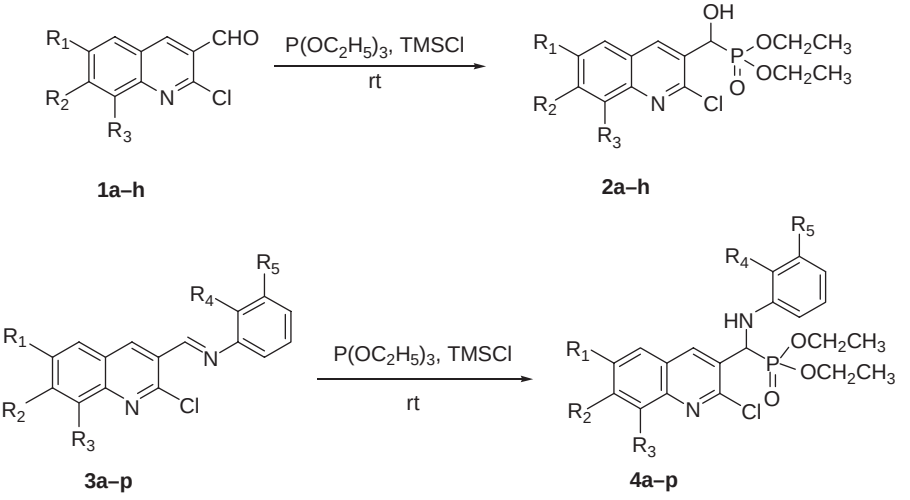
An efficient synthesis of α-hydroxyphosphonates and α-aminophosphonates in the presence of chlorotrimethylsilane

Rajkumar U. Pokalwar, Sandip A. Sadaphal, Amol H. Kategaonkar, Bapurao B. Shingate and Murlidhar S. Shingare*

Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, India

(Received 31 March 2009; final version received 13 October 2009)

Solvent free, and quantitative yielding synthesis of α-hydroxyphosphonates **(2a–h)** from 2-chloroquinolin-3-carbaldehyde **(1a–h)** and α-aminophosphonates **(4a–p)** from imines **(3a–p)**, obtained from 2-chloroquinoline-3-carbaldehyde by using triethylphosphite in the presence of chlorotrimethylsilane at room temperature in short time.



Keywords: 2-chloroquinoline-3-carbaldehyde; α-hydroxyphosphonate; imines; α-aminophosphonate; TMSCl

Introduction

Quinolines (*1–3*) are an important class of heterocyclic compounds and have been screened for several biological activities such as bactericidal (*4*), antitumor (*5*), anti-inflammatory (*6*), and antimalarial (*7*). Quinolines such as 2-chloroquinoline-3-carbaldehyde occupy a prominent position as they are key intermediates for further annelation and for various functional group interconversions (*8,9*). It is also reported that organophosphates are potent pesticides which have wide variety of application (*10*). Recently, some new vinyl phosphates have been reported as potent inhibitors of phosphatase (*11–13*) and phosphodiesterase (*14,15*).

There are only a few reports on the synthesis and bioactivity of C–P bonds which have been found to have insecticidal (*16*) and antifungal (*17*) activities. Also α-hydroxyphosphonates (*18*) and α-aminophosphonates are important biologically active compounds (*19,20*). α-Aminophosphonates, due to their structural analogy to amino acids, have been the subject of considerable current interest. They act as peptide mimics (*21*), enzyme inhibitors (*22,23*), antibiotics, and pharmacological agents (*24,25*).

*Corresponding author. Email: prof_msshingare@rediffmail.com

ISSN 1751-8253 print/ISSN 1751-7192 online

DOI: 10.1080/17518250903410082
http://www.informaworld.com

α-Hydroxyphosphonates may serve as precursors for the synthesis of α-amino-phosphonates which are analogs of amino acids. A number of synthetic methods for the synthesis of α-hydroxyphosphonates have been reported (*26–29*). But the disadvantage associated with the existing methodologies is either long reaction times or the requirement of drastic conditions.

In the literature, α-hydroxyphosphonates have been prepared using: quinine catalyst in toluene as solvent (*30*), DBU or n-BuLi in THF (*31*), HCl: ether media in DCM (*32*), $LiClO_4$: diethyl ether solution in the presence of trimethylsilyl chloride (TMSCl) (*33*), toluene and $Ti(OiPr)_4$ (*34*), hydroxyphosphorylation of aldehydes catalyzed by guanidine hydrochloride in water (*35*), BF_3.etherate and $AlCl_3$ (*36*), and TFA or TfOH (*37*).

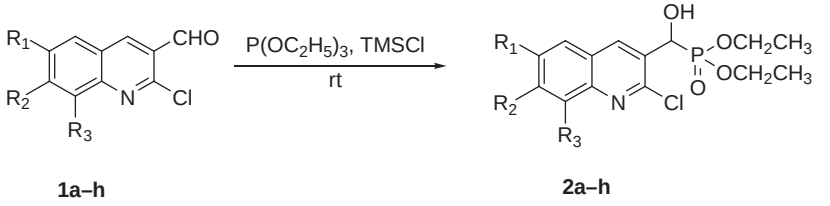
Generally, α-aminophosphonates are prepared in the presence of Lewis acids or bases by the addition of phosphorous nucleophiles to the imines. Lewis acids such as $SnCl_4$, $SnCl_2$, $ZrCl_4$, $ZnCl_2$, and $MgBr_2$ have been used as catalysts for such reactions (*38–40*). Recently, Lewis and Bronsted acids such as $LiClO_4$ (*41*), $InCl_3$ (*42*), lanthanide triflates (*43*), $TaCl_5$–SiO_2 (*44*), montmorillonite clay-MW (*45*), Al_2O_3-MW (*46*), and CF_3COOH (*47*) were found to be effective in the preparation of α-aminophosphonates. However, many of these procedures require expensive reagents, long reaction times and suffer from poor yields. These reactions cannot be carried out in one step by the reaction between a carbonyl compounds, an amine and dialkylphosphite because the amine and water present during imine formation can decompose or deactivate the Lewis acid (*48*). In continuation of our work on phosphorus chemistry (*49–52*), herein we wish to report the solvent free synthesis of α-hydroxyphosphonates and α-aminophosphonates at room temperature in quantitative yield.

Results and discussion

We have reported the synthesis of α-hydroxyphosphonates (*51*) from 2-chloroquinolin-3-carbaldehyde at reflux temperature in toluene; while at reflux temperature, TMSCl was added. To add TMSCl at the reflux temperature is not ecofriendly because it emits gases during addition. Azizi et al. (*33*) reported that for the same system at room temperature costly moisture sensitive reagents such as $LiClO_4$ and diethyl ether media could be used. To overcome these difficulties we have developed a new method for the synthesis of α-hydroxyphosphonate from 2-chloroquinolin-3-carbaldehyde. Herein we wish to report the newer method which is economically viable, solvent free, and carried out at room temperature in quantitative yield.

To the mixture of triethylphosphite and 2-chloroquinolin-3-carbaldehyde (**1a–h**) TMSCl was added in stirring at room temperature. During addition, we observed that the reaction was exothermic (temperature rise from 25 to 40°C). 2-Chloroquinolin-3-carbaldehyde has two reaction centers: chlorine at the second and a formyl group at the third position of quinoline ring. However, the formyl group has higher reactivity in the presence of TMSCl. TMSCl reacts with the formyl group to generate a carbonium ion and a TMS protected hydroxyl group. Triethylphosphite attacks the generated carbonium ion and the mentioned compound rearranges to α-trimethylsilyloxyphophonate. By adding methanol, unreacted TMSCl was reacted with methanol and generates gaseous HCl which yielded desired product (**2a–h**) (Scheme 1, Table 1). Through this method, there was significant improvement in the yields of the products. The reported yields of α-hydroxyphosphonates in the presence of solvent and at higher temperature were 76–83% (*51*). The yields of the α-hydroxyphosphonates using this new process are now in the range of 95–97%. Here we have synthesized eight compounds by applying the same procedure and obtained each in quantitative yield. All the synthesized compounds are characterized by spectral analysis, physical constants, and compared with their authentic.

Previously we have synthesized α-aminophosphonates (*52*) containing highly bioactive quinoline moiety in two steps. In the first step, imines of 2-chloroquinoline-3-carbaldehyde were synthesized and converted to α-aminophosphonates using TMSCl and triethylphosphite in acetonitrile at reflux in the next step. Herein we report a newer method which is economically viable, solvent free and carried out at



1a–h **2a–h**

Scheme 1. Synthesis of α-hydroxyphosphonates.

Table 1. TMSCl facilitated synthesis of α-hydroxyphosphonates.

Entry	R_1	R_2	R_3	Time (min)	Yield (%)	Yield (*51*) (%)	MP (°C)
2a	H	H	H	25	96	76.4	124–126
2b	CH_3	H	H	30	96	80.6	145–147
2c	H	CH_3	H	24	96	81.4	126–128
2d	H	H	CH_3	25	95	80.6	141–143
2e	OCH_3	H	H	30	95	83.3	170–172
2f	H	OCH_3	H	25	97	80.3	154–156
2g	OC_2H_5	H	H	25	95	79.2	168–170
2h	H	H	C_2H_5	30	97	77.1	145–147

room temperature in quantitative yield. Imines (**3a–p**) (Scheme 2) were prepared at room temperature from derivatives of 2-chloroquinoline-3-carbaldehyde and 3-fluoroaniline or 2-methylaniline in ethanol using a catalytic amount of acetic acid in excellent yields and were characterized by mass spectra. α-Aminophosphonates (**4a–p**) (Scheme 2, Table 2) were then prepared in quantitative yields by reacting imines (**3a–p**) with triethylphosphite in the presence of TMSCl at room temperature. After completion of the reaction, the excess TMSCl was removed using methanol. The reported yields of α-aminophosphonates in the presence of solvent and at higher temperature were 89–93% (*52*). The yields of the α-aminophosphonates using this new process are now in the range of 95–98%. Here we have synthesized 16 compounds by applying the same procedure and obtained each in quantitative yield. All the compounds synthesized were unequivocally characterized on the basis of analytical data.

The mechanism of the formation of α-hydroxyphosphonates and α-aminophosphonates in the presence of TMSCl have shown in Figures 1 and 2, respectively.

Experimental

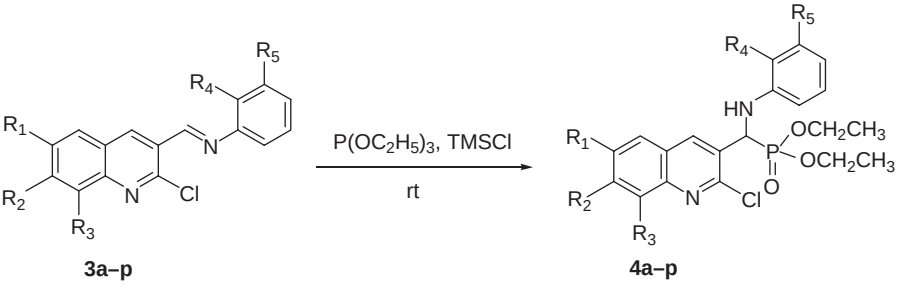
2-Chloroquinoline-3-carbaldehydes were prepared in the laboratory by the reported method (*53*). Triethylphosphite and chlorotrimethylsilane were procured from Lancaster; methanol and *N,N*-dimethylformamide (DMF) were procured from S.D. Fine-chem.

All melting points were determined in open capillaries on Kumar's melting point apparatus. The products were characterized by their spectral data. ^{1}H NMR spectra were recorded on Varian Gemini in $CDCl_3$ at 400 MHz using TMS as an internal standard. IR spectra were recorded on a Perkin–Elmer FTIR using KBr discs. Mass spectra were recorded on Micromass Quatrro-II using electrospray Ionization technique, showing (m+1) peak as a molecular ion peak. The test for the purity of products and the progress of the reactions was accomplished by TLC on Merck silica gel plates.

General procedure

(2a) Diethyl (2-chloro-quinolin-3-yl) (hydroxy) methylphosphonate

To the mixture of 2-chloroquinoline-3-carbaldehyde (0.95 gm, 5 mmol), triethylphosphite (1.66 gm, 10 mmol), and chlorotrimethylsilane (1.08 gm, 10 mmol) were added dropwise and stirred at room temperature. The progress of the reaction was monitored by TLC using hexane:ethyl acetate (7:3) as the solvent system. After completion of the reaction (25 min), the reaction mixture was dissolved in methanol for the quenching of excess TMSCl and removal of the residual silyl ester linkages. This methanolic solution was concentrated to get crude product. Further purification was achieved by



Scheme 2. Synthesis of α-aminophosphonates.

Table 2. TMSCl facilitated synthesis of α-aminophosphonates.

Entry	R_1	R_2	R_3	R_4	R_5	Time (min)	Yield (%)	Yield (*52*) (%)	MP (°C)
4a	H	H	H	H	F	30	96	92.1	146–148
4b	CH_3	H	H	H	F	25	98	90.1	136–138
4c	H	CH_3	H	H	F	30	96	92.5	163–165
4d	H	H	CH_3	H	F	30	97	89.2	113–115
4e	OCH_3	H	H	H	F	25	97	91.0	153–155
4f	H	OCH_3	H	H	F	30	95	93.3	155–157
4g	OC_2H_5	H	H	H	F	30	97	91.0	160–162
4h	H	H	C_2H_5	H	F	30	95	92.2	159–161
4i	H	H	H	CH_3	H	25	96	90.0	139–141
4j	CH_3	H	H	CH_3	H	25	98	89.5	104–106
4k	H	CH_3	H	CH_3	H	30	96	92.0	143–145
4l	H	H	CH_3	CH_3	H	30	95	92.0	160–162
4m	OCH_3	H	H	CH_3	H	25	97	90.0	98–100
4n	H	OCH_3	H	CH_3	H	30	97	92.0	126–128
4o	OC_2H_5	H	H	CH_3	H	30	96	90.5	146–148
4p	H	H	C_2H_5	CH_3	H	30	98	91.2	133–135

dissolving the crude compound in dichloromethane and precipitated by hexane. The solid obtained was stirred for 15 min and filtered, washed with hexane and dried at 40°C (1.56 gm, yield 96%, m.p. 124–126°C).

IR (KBr), cm^{-1}: 3246 (−OH); 1218 (−P=O); 1033 (−P–O–C). **^{1}H NMR ($CDCl_3$), δ; ppm:** 1.2 (t, 3H, O–CH_2–CH_3); 1.3 (t, 3H, O–CH_2–CH_3); 2.0 (s, 1H, −CH–OH); 4.0 (m, 4H, O–CH_2–CH_3 and O–CH_2–CH_3); 5.6 (d, 1H, −CH–P=O); 7.5 (t, 1H, Ar–H, C_6); 7.7 (t, 1H, Ar–H, C_7); 7.8 (d,1H, Ar–H, C_5); 8.0 (d, 1H, Ar–H, C_8); 8.6 (s, 1H, Ar–H, C_4). **ES–MS**: m/z 330 (m+1) and 331.9 (m+3).

Elemental analysis: $C_{14}H_{17}ClNO_4P$ calculated: C: 51.00%, H: 5.20%, N: 4.25%; found: C: 51.027%, H: 5.393%, N: 4.35%.

(4a) Diethyl (3-fluorophenylamino)(2-chloroquinolin-3-yl)methylphosphonate

To a mixture of *N*-((2-chloroquinolin-3-yl-methylene)-3-fluorobenzenamine (1.12 gm, 4 mmol) and triethylphosphite (1.66 gm, 10 mmol) was added TMSCl (1.08 gm, 10 mmol). The progress of the reaction was monitored by TLC using hexane:ethyl acetate (8:2) as the solvent system. After the completion of the reaction, the reaction mixture was

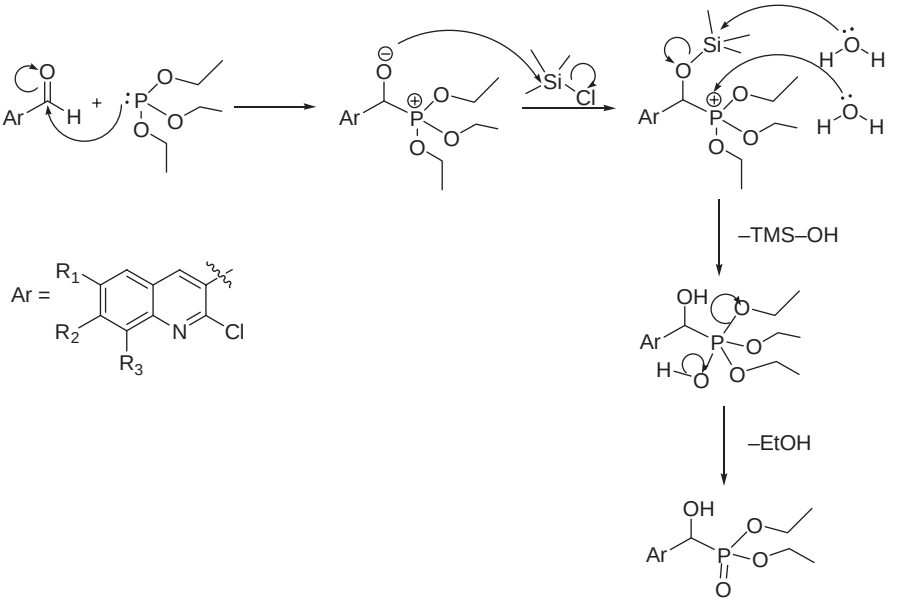


Figure 1. Mechanism of the synthesis of α-hydroxyphosphonates.

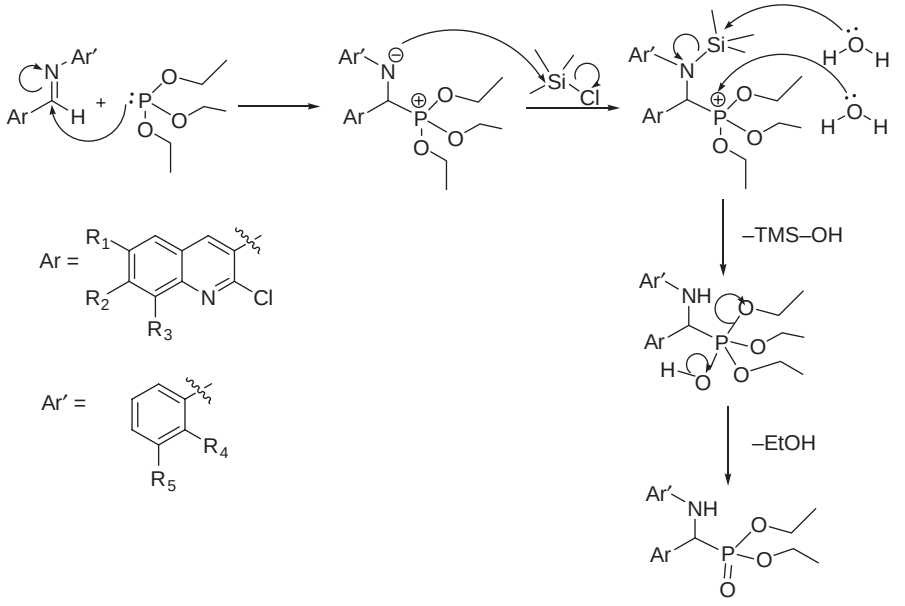


Figure 2. Mechanism of the synthesis of α-aminophosphonates.

dissolved in methanol for the quenching of excess TMSCl and removal of the residual silyl ester linkages. This methanolic solution was concentrated to get crude product. The solid was further recrystallized from DMF and water mixture, dried in an oven at 50°C for 8.0 h (dry wt. = 1.59 gm, yield 96%).

IR (KBr): 3311 cm^{-1} (−NH); 1234 cm^{-1} (−P=O); 1032 cm^{-1} (−P–O–C). **^{1}H NMR ($CDCl_3$, δ; ppm):** 1.05 (t, 3H, O–CH_2–CH_3, J = 8 Hz); 1.35 (t, 3H, O–CH_2–CH_3, J = 8 Hz); 3.7 (m, 1H, O–CH_2–CH_3); 3.9 (m, 1H, O–CH_2–CH_3); 4.2 (m, 2H, O–CH_2–CH_3); 5.4 (d, 1H, –NH–CH–P=O, J = 24 Hz); 6.3–6.5 (m, 3H, Ph–H, C_2, C_4, C_6); 7.0 (dd, 1H, Ph–H, C_5, J = 8 Hz); 7.5 (t, 1H, Quinolin-H, C_5, J = 8 Hz); 7.69 (t, 1H, Quinolin-H, C_6, J = 8 Hz); 7.75 (d, 1H, Quinolin-H, C_7, J = 8 Hz); 7.99 (d, 1H, Quinolin-H, C_8, J = 8 Hz); 8.34 (d, 1H, Quinolin-H, C_4, J = 8 Hz). **ES–MS**: m/z 423.1 (m + 1) and 425.1 (m + 3).

Elemental analysis: $C_{20}H_{21}ClFN_2O_3P$ calculated: C: 56.81%, H: 5.01%, N: 6.63%; found: C: 56.72%, H: 4.95%, N: 6.65%.

Conclusion

In conclusion, a new methodology was developed for the synthesis of α-hydroxyphosphonates **2a–h** from 2-chloroquinolin-3-carbaldehyde **1a–h** by using triethylphosphite in the presence of TMSCl at room temperature in quantitative yields. Also a new methodology was developed for the synthesis of α-aminophosphonate **(4a–p)** derivatives from imines of 2-chloroquinoline-3-carbaldehydes for the first time using TMSCl at room temperature. All the reactions were performed under mild reaction conditions, shorter reaction times and in quantitative yields (Tables 1 and 2). The methodology developed will be of much use to combinatorial chemist.

Acknowledgements

Authors are thankful to the Head, Department of Chemistry, Dr. B.A.M. University, Aurangabad for providing laboratory facilities.

References

(1) Elderfield, R. *Heterocycl. Compd.* **1952,** *4*, 125–129.
(2) Meth-Cohn, O.; Narine, B. *Tetrahedron* **1978,** *19,* 2045–2048.
(3) Ali, M.M.; Tasneem, K.C.; Rajanna, K.C.; Saiprakash, P.K. *Synletters* **2001,** *2*, 251–253, and references cited therein.
(4) Patel, H.V.; Vyas, K.V.; Fernandes, P.S. *Indian J. Chem.* **1990,** *29* (B), 836–842.
(5) Sukhova, N.M.; Lidak, M.; Zidermane, A.; Pelevina, I.S.; Voronia, S.S. *Khim. Farm. Zh.* **1989,** *23*, 1226–1229.
(6) Dillard, R.D.; Pavey, D.E.; Benslay, D.N. *J. Med. Chem.* **1973,** *16*, 251–253.
(7) Craig, J.C.; Person, P.E. *J. Med. Chem.* **1971,** *14,* 1221–1222.
(8) Meth-Cohn, O. *Heterocycles* **1993,** *35,* 539–557, and references cited therein.
(9) Rajendran, S.P.; Manonmoni, M.; Vijaya-Lakshmi, S. *Org. Prep. Proced. Int.* **1994,** *26,* 383–385.

(10) Engel, R., Ed. In *Handbook of Organophosphorus Chemistry*; Marcel Dekker: New York, **1992**.
(11) Hang, S.B.; Mullins, T.S.; Shim, H.; Raushal, F.M. *Biochemistry* **1997,** *36*, 9022–9028.
(12) Berggren, M.M.; Burns, L.A.; Abraham, R.T.; Powis, G. *Cancer Res*. **1993,** *53*, 1862–1866.
(13) Cao, X.D.; Moran, E.J.; Siev, D.; Lio, A.; Ohashi, C.; Mjalli, A.M. *Bioorg. Med. Chem. Lett*. **1995,** *5*, 2953–2958.
(14) Widlanski, T.S.; Myer, J.K.; Stec, B.; Holtz, K.M.; Kantroewitz, E.R. *Chem. Biol*. **1997,** *4*, 489–498.
(15) Stowell, J.K.; Widlanski, T.S. *J. Org. Chem*. **1995,** *60*, 6930–6936.
(16) Maurer, F.; Riebel, H.J.; Hammann, I.; Behrenz, W.; Homeyer, B. *Ger. Offen*. 2533601, **1977**.
(17) Molodykh, Z.V.; Aleksandrova, I.A.; Belyalov, R.U.; Gazizor, T.K.; Reznik, V.S. *Khim. Farm. Zh*. **1990,** *24*, 136–139.
(18) Drake, G.L.; Calamari, T.A. In *Industrial Uses of Phosphonates (Review)*; Hilder Brand, R.L. Ed.; CRC Press: Boca Raton, FL, **1983**; Chapter 7.
(19) Fields, S.C. *Tetrahedron* **1999,** *55*, 12237–12273.
(20) Yokomatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem*. **1994,** *59*, 7930–7933.
(21) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur, Silicon Relat. Elem*. **1991,** *63*, 193–215.
(22) Allen, M.C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J.M. *J. Med. Chem*. **1989,** *32*, 1652–1661.
(23) Giannousis, P.P.; Bartlett, P.A. *J. Med. Chem*. **1987,** *30*, 1603–1609.
(24) Atherton, F.R.; Hassal, C.H.; Lambert, R.W. *J. Med. Chem*. **1986,** *29*, 29–40.
(25) Baylis, E.K.; Campbell, C.D.; Dingwall, J. *J. Chem. Soc. Perkin Trans. I* **1984,** 2845–2953.
(26) Lerner, R.A.; Benkovic, S.J.; Schultz, P.G. *Science* **1991,** *252*, 659–667.
(27) Groger, H.; Hammer, B. *Chem. Eur. J*. **2000,** *6*, 943–948.
(28) Olah, G.O.; Wu, A.H. *J. Org. Chem*. **1991,** *56*, 902–904.
(29) Jeanmaire, T.; Hervaud, Y.; Boutevin, B. *Phosphorus, Sulfur, Silicon Relat. Elem*. **2002,** *177*, 1137–1145.
(30) Smaardijk, A.A.; Noorda, S.; van Bolhuis, F.; Wynberg, H. *Tetrahed. Lett*. **1985,** *26*, 493–496.
(31) Oscar, P.; Backvall, J-E. *J. Org. Chem*. **2003,** *68*, 4815–4818.
(32) Goldman, W.; Soroka, M. *Synthesis* **2006,** 3019–3024.
(33) Azizi, N.; Saidi, M.R. *Phosphorus, Sulfur, Silicon Relat. Elem*. **2003,** *178*, 1255–1259.
(34) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *J. Chem. Soc. Perkin Trans. I* **1997,** 1527–1533.
(35) Heydari, A.; Arefi, A.; Khaksar, S.; Tajbakhsh, M. *Catal. Commun*. **2006,** *7*, 982–984.
(36) Pudovic, A.N.; Zimin, M.G.; Sobanov, A.A.; Musina, A.A. *Zh. Obshch. Khim*. **1976,** *46*, 1455–1461.
(37) Nifant'ev, E.E.; Kukhareva, T.S.; Popkova, T.N.; Davydocchkina, O.V. *Zh. Obshch. Khim*. **1986,** *56*, 304–309.
(38) Kudzin, Z.H.; Lyzwa, P.; Luczak, J.; Andrijewski, G. *Synthesis* **1997,** 44–46.
(39) Yadav, J.S.; Reddy, B.V.S.; Sarita Raj, K.; Bhaskar Reddy, K.; Prasad, A.R. *Synthesis* **2001,** 2277–2780.
(40) Lee, S.G.; Park, J.H.; Kang, J.; Lee, J.K. *Chem. Commun*. **2001,** 1698–1699.
(41) Saidi, M.R.; Azizi, N. *Synletters* **2002,** 1347–1349.
(42) Ranu, B.C.; Hajra, A.; Jana, U. *Org. Lett*. **1999,** *1*, 1141–1143.
(43) Qian, C.; Huang, T. *J. Org. Chem*. **1998,** *63*, 4125–4128.
(44) Chandrasekher, S.; Prakash, S.J.; Jagadeshwar, V.; Narsihmulu, C. *Tetrahed. Lett*. **2001,** *42*, 5561–5563.
(45) Yadav, J.S.; Reddy, B.V.S.; Madan, C. *Synletters* **2001,** 1131–1133.
(46) Kaboudin, B.; Nazari, R. *Tetrahed. Lett*. **2001,** *42*, 8211–8213.
(47) Akiyama, T.; Sanada, M.; Fuchibe, K. *Synletters* **2003,** 1463–1464.
(48) Zon, J. *Pol. J. Chem*. **1981,** *55*, 643–646.
(49) Mane, A.S.; Chavan, V.P.; Karale, B.K.; Hangarge, R.V.; Gaikwad, M.S.; Shingare, M.S. *Synthetic Commun*. **2002,** *32* (17), 2633–2636.
(50) Chavan, V.P.; Mane, A.S.; Shingare, M.S. *Indian J. Chem*. **2001,** *40B*, 339–341.
(51) Pokalwar, R.U.; Hangarge, R.V.; Maske, P.V.; Shingare, M.S. *Arkivoc* **2006,** *xi* 196–204.
(52) Pokalwar, R.U.; Hangarge, R.V.; Madje, B.R.; Ware, M.N.; Shingare, M.S. *Phosphorus, Sulfur, Silicon Relat. Elem*. **2008,** *183*, 1461–1470.
(53) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J. Chem. Soc. Perkin Trans. I* **1981,** 1520–1530.