

# Solvent-Free *N*-Nitrosation of Secondary Amines Mediated by Polymeric Nitrosation Reagent

Mohammad Ali Karimi Zarchi, Jalil Noei

Department of Chemistry, College of Science, Yazd, Iran

Received 26 July 2008; accepted 27 January 2009

DOI 10.1002/app.30192

Published online 2 July 2009 in Wiley InterScience (www.interscience.wiley.com).

**ABSTRACT:** A combination of cross-linked poly(4-vinylpyridinium) chloride [P<sub>4</sub>-H] Cl, [II], and sodium nitrite or quaternized cross-linked poly(*N*-methyl-4-vinylpyridinium) nitrite [P<sub>4</sub>-Me] NO<sub>2</sub>, [IV], was used as effective nitrosating agents for the *N*-nitrosation of secondary amines under solvent-free conditions in high yields. The spent polymeric

reagents can usually be removed quantitatively and regenerated. © 2009 Wiley Periodicals, Inc. *J Appl Polym Sci* 114: 2134–2138, 2009

**Key words:** *N*-nitrosation; secondary amines; solvent-free conditions; *N*-nitrosoamines

## INTRODUCTION

*N*-nitrosation of amines is an important reaction in organic synthesis. *N*-nitrosoamines have drawn considerable interest in recent years mainly due to their strong mutagenic and carcinogenic properties,<sup>1</sup> it has also been found that these compounds have vasorelaxant activity and have been used as pesticides.<sup>2</sup> These compounds are also useful synthetic intermediates for the preparation of various *N,N*-bonded functionalities. Furthermore, owing to their easy lithiation, followed by reaction with electrophiles and subsequent denitrosation, they can be used for the electrophilic substitution of the secondary amines at the  $\alpha$ -carbon in a regio- and stereoselective manner.<sup>3</sup> Also nitrosation chemistry has been a fruitful area for mechanistic organic and biological chemists,<sup>4–6</sup> and effort has also been made to combine both the synthetic and mechanistic aspects of nitrosation or transnitrosation.<sup>7</sup> A hindered rotation about the N–N bond, being a consequence of a partial double-bond character between two adjacent nitrogens, results in many intriguing stereochemical features in this class of compounds.<sup>8,9</sup> The most general reagent for synthesis of nitrosoamines is nitrous acid generated from sodium nitrite and mineral acid, in water or in mixed alcohol-water solvents.<sup>10,11</sup> Other nitrosating agents such as Fremy's salt,<sup>12</sup> *N*-haloamides, and sodium nitrite under phase-transfer conditions,<sup>13</sup> oxyhyponitrite,<sup>14</sup> dinitrogen tetroxide,<sup>15</sup> oxalic acid

dihydrate<sup>16</sup> or trichloroisocyanuric acid,<sup>17</sup> and sodium nitrite have also been used.

Although polymer-supported reagents especially anion-exchange resins have been widely applied in organic synthesis,<sup>18–32</sup> there is only one report in the literature for the synthesis of *N*-nitroso compounds based on polymer-supported reagents under heterogeneous conditions in ethanol.<sup>30</sup>

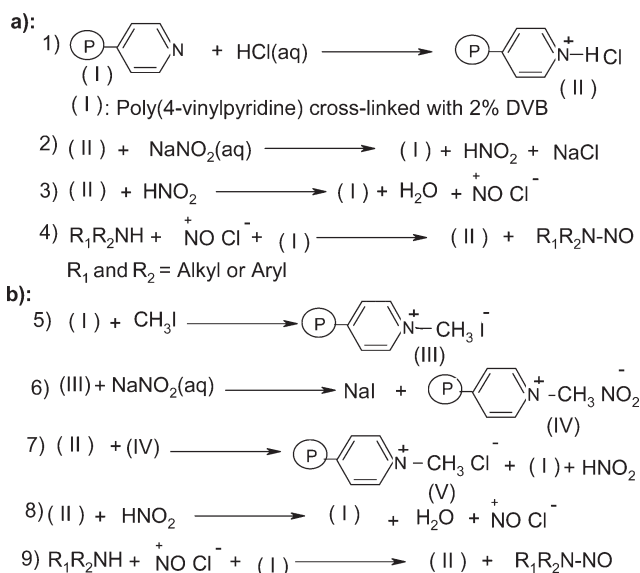
In continuing our studies on the development of application of [P<sub>4</sub>-Me] NO<sub>2</sub>, [IV], in the organic synthesis here we report *N*-nitrosation of secondary amines under solvent-free conditions with grinding the mixture of a secondary amine, [P<sub>4</sub>-Me] NO<sub>2</sub>, [IV], or NaNO<sub>2</sub> and [P<sub>4</sub>-H] Cl, [II], in a mortar. Heterogeneous reaction under solvent-free conditions has received attention in recent years.<sup>33–51</sup>

On the other hand, any reduction in the amount of strong inorganic acids needed and any simplification in handling procedures are required for risk reduction, economic advantage, and environment protection.<sup>21</sup> In addition, there is current research and general interest in solvent-free conditions because of the importance such systems have in industry and in developing technologies.

We hoped that the [P<sub>4</sub>-H] Cl, [II], would be a superior proton source to all of the reported acidic solid supports or acidic resins such as polystyrene sulfonic acid and Nafion-H.<sup>23</sup> Therefore, we were interested in using this acidic resin as a new solid acid for the generation of HNO<sub>2</sub> (as a nitrosating agent) when used in conjunction with sodium nitrite (procedure a in Scheme 1) or [P<sub>4</sub>-Me] NO<sub>2</sub>, [IV], (procedure b in Scheme 1).

Since the *N*-nitrosoamines are highly toxic and carcinogenic chemicals, its production with any dispersion is very interesting for organic and biological

Correspondence to: M. A. K. Zarchi (makarimi@yazduni.ac.ir).



**Scheme 1** *N*-nitrosation of secondary amines by grinding the mixture of polymeric acid (II), secondary amine, and NaNO<sub>2</sub> (procedure a) or polymer-supported nitrite ion (IV) (procedure b).

chemists. Although a key feature of this article is its clean work-up with easy removal of nitroso products from the reaction mixture, all due precaution should be taken. We wish to report a simple, cheap, and chemoselective method for the effective nitrosation of secondary amines under solvent-free conditions.

## RESULTS AND DISCUSSION

In connection with our organic program to develop environmentally benign methods using polymer-supported reagents,<sup>20,28–32</sup> herein we wish to report an extremely convenient and simple method for preparation of different *N*-nitroso compounds with different secondary amines in the presence of NaNO<sub>2</sub> or [P<sub>4</sub>-Me] NO<sub>2</sub>, [IV], and [P<sub>4</sub>-H] Cl, [II], under solvent-free conditions (Schemes 1 and 2). [P<sub>4</sub>-H] Cl, [II], is easily prepared by treatment of commercially available poly(4-vinylpyridine) cross-linked with 2% DVB; 100–200 mesh with HCl (aq) [eq. (1) in Scheme 1] and [P<sub>4</sub>-Me] NO<sub>2</sub>, [IV], is also easily prepared according to our reported previous procedure.<sup>20</sup> These polymeric reagents are used as efficient reagents for the chemoselective *N*-nitrosation of secondary amines under solvent-free conditions. Different types of secondary amines were subjected to the nitrosation reactions in the presence of [P<sub>4</sub>-H] Cl, [II], and NaNO<sub>2</sub> or [P<sub>4</sub>-Me] NO<sub>2</sub>, [IV], in a mortar and grinding the mixture for the time specified in Table I. The reaction take place with excellent to moderate yields (Table I).

This method is very fast and purification of products is very easy. The plausible mechanism is given in Scheme 1. Using acidic resin, [P<sub>4</sub>-H] Cl, [II], in conjunction with NaNO<sub>2</sub> or [P<sub>4</sub>-Me] NO<sub>2</sub>, [IV], the HNO<sub>2</sub>

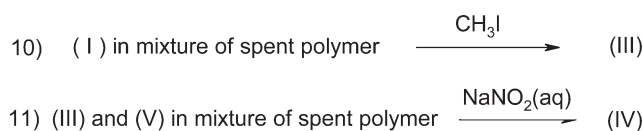
(as a nitrosating agent) is generated. The HNO<sub>2</sub> in the presence of [P<sub>4</sub>-H] Cl is converted to nitrosonium ion (NO<sup>+</sup>) [eqs. (2) and (7) in Scheme 1]. The NO<sup>+</sup> attacks the nitrogen sites of the secondary amines to produce the *N*-nitroso compounds [eqs. (4) and (9) in Scheme 1] in excellent to moderate yields (86–98%). After completion of the reaction, CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added and the spent polymeric reagent was recovered by filtration and regenerated by treatment successively with methyl iodide [eq. (10) in Scheme 2], and then treatment with a solution of aqueous NaNO<sub>2</sub> [eq. (11) in Scheme 2]. The filtrate was dried by Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated of the solvent and the *N*-nitroso compounds were achieved in high yields (Table I). When secondary amines were converted to the *N*-nitroso compounds in their IR spectra the weakly N–H stretching (3340–3350) were disappeared and the N=O stretching can be seen in the 1500–1590 cm<sup>-1</sup> range that produced by *N*-nitroso products. Also in their <sup>1</sup>H-NMR the broad peak at 0.5–3.0 ppm disappeared.

To demonstrate the chemoselectivity of this method, a competitive reaction was performed between diphenylamine and anisole. It was observed that amine nitrosation occurred exclusively whereas anisole remained intact in the reaction mixture after 1 h. The nitrosation reaction of diphenylamine further showed the chemoselectivity of the method, as the *N*-nitrosodiphenylamine is the only product. The nitrosation of a mixture of *N*-arylamine and *N,N*-diarylamines shows further the chemoselectivity of the method as the *N*-nitrosoarylamine was the only product. Thus, this system behaves differently to some other reported methods<sup>10,11,17</sup> in that nitrosonium ion (NO<sup>+</sup>) attacks the nitrogen sites of the secondary amines even where an aromatic moiety is connected directly to the nitrogen atom (Scheme 3).

## EXPERIMENTAL

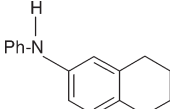
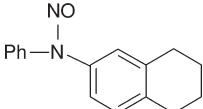
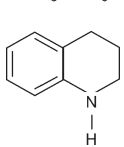
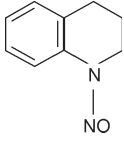
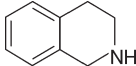
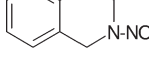
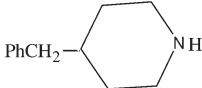
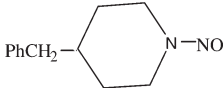
### General

Poly(4-vinylpyridine) cross-linked with 2% DVB; 100–200 mesh, [I], was purchased from Fluka and other chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Quaternized cross-linked [P<sub>4</sub>-Me] NO<sub>2</sub>, [IV], and [P<sub>4</sub>-H] Cl, [II], were synthesized according to our reported previous procedure.<sup>20,30</sup> The reactions were monitored by TLC, and on completion of the reaction, CH<sub>2</sub>Cl<sub>2</sub> (10 mL)



**Scheme 2** Regeneration of polymeric reagent.

TABLE I  
Conversion of Secondary Amines to their Corresponding *N*-Nitrosoamines

Entry	Substrate	Product <sup>a</sup>	(I) <sup>b</sup>		(II) <sup>c</sup>	
			Time (min)	Yield <sup>d</sup> (%)	Time (min)	Yield <sup>d</sup> (%)
1	Ph <sub>2</sub> NH	Ph <sub>2</sub> N-NO	3	90	5	90
2	PhNHC <sub>2</sub> H <sub>5</sub>	PhN(NO)C <sub>2</sub> H <sub>5</sub>	2	93	3	91
3	PhNHCH <sub>2</sub> CH <sub>2</sub> OH	PhN(NO)CH <sub>2</sub> CH <sub>2</sub> OH	2	90	3	88
4	(PhCH <sub>2</sub> ) <sub>2</sub> NH	(PhCH <sub>2</sub> ) <sub>2</sub> N-NO	2	98	3	97
5	PhCH <sub>2</sub> NHC <sub>2</sub> H <sub>5</sub>	PhCH <sub>2</sub> N(NO)C <sub>2</sub> H <sub>5</sub>	2	87	3	90
6	PhNHCH <sub>2</sub> Ph	Ph-N(NO)CH <sub>2</sub> Ph	3	93	5	92
7			6	89	8	88
8			2	86	3	88
9			2	88	3	90
10	(C <sub>6</sub> H <sub>13</sub> ) <sub>2</sub> NH	(C <sub>6</sub> H <sub>13</sub> ) <sub>2</sub> N-NO	3	98	5	96
11			3	93	5	94

<sup>a</sup> The structures were confirmed by comparison of the boiling point, melting point, IR, and <sup>1</sup>H-NMR spectra with those of authentic specimen.

<sup>b</sup> Molar ratio of [P<sub>4</sub>-H] Cl : NaNO<sub>2</sub> : amine equal to 3 : 3 : 1 and the reaction take place under solvent-free conditions and at room temperature.

<sup>c</sup> Molar ratio of [P<sub>4</sub>-H] Cl : [P<sub>4</sub>-Me] NO<sub>2</sub> : amine equal to 3 : 3 : 1 and the reaction take place under solvent-free conditions and at room temperature.

<sup>d</sup> Isolated yields.

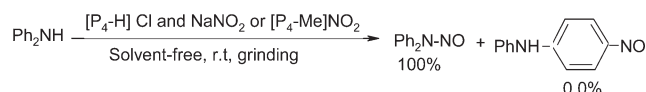
was added and filtered. The filtrate was dried by Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated of the solvent and the pure *N*-nitroso compounds were achieved in excellent to good yields (Table I). Products were characterized by comparison of their IR and <sup>1</sup>H-NMR spectral, physical data, and by comparison of their TLC chromatogram with those of authentic samples. All yields refer to the isolated products. Melting points were determined with a Buchi melting point B-540 B. V. CHI apparatus, IR and <sup>1</sup>H-NMR spectra were recorded on a Perkin-Elmer IR-157-G-or Testscan Shimadzu FTIR 8000 series and a Hitachi R-2413 60 MHz spectrophotometer, respectively. The capacities of the reagents were determined by potentiometric titration with a 0.1*N* solution of silver nitrate and gravimetric methods.

### Cautions

All *N*-nitrosoamines [R<sub>1</sub>R<sub>2</sub>N-NO] should be regarded as potentially powerful carcinogens, since most compounds of these types have been shown to possess high carcinogenic activity in experimental animals.<sup>19</sup>

### General procedure for *N*-nitrosation of secondary amines

In a mortar, a mixture of a secondary amine (1 mmol), [P<sub>4</sub>-H], (II), (0.5 g, 3 mmol) and NaNO<sub>2</sub> (207 mg, 3mmol) or [P<sub>4</sub>-Me] NO<sub>2</sub>, (IV), (1.37 g, 3 mmol) were pulverized for the time specified in Table I (2–6 min). The reaction progress was followed by TLC. After completion of the reaction, CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added and the polymeric support was recovered by filtration, washed with 5 mL of CH<sub>2</sub>Cl<sub>2</sub> and regenerated by, treatment successively with methyl iodide [eq. (10) Scheme 2], and then treatment with a solution of aqueous NaNO<sub>2</sub> [eq. (11) in Scheme 2]. The filtrate was dried by Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated of the solvent and the *N*-nitroso compounds were achieved in excellent to good yields (Table I). If further purification was needed, flash chromatography



Scheme 3 Chemoselectivity.

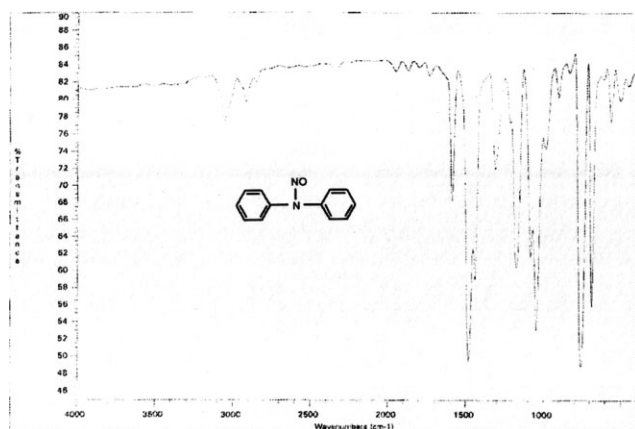


Figure 1 FTIR spectrum of *N*-nitrosodiphenylamine.

on silica gel [eluent : acetone-petroleum ether (10 : 90)] provides highly pure products.

#### *N*-nitrosation of diphenylamine with NaNO<sub>2</sub> and [P<sub>4</sub>-H] Cl (II): a typical procedure

In a mortar, a mixture of diphenylamine (169 mg, 1 mmol), [P<sub>4</sub>-H] Cl (II) (0.5 g, 3 mmol) and NaNO<sub>2</sub> (207 mg, 3 mmol) were pulverized for 3 min (entry 1 in Table I). The reaction progress was followed by TLC. After completion of the reaction, CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added and the polymeric support was recovered by filtration, washed with 5 mL of CH<sub>2</sub>Cl<sub>2</sub> and regenerated by, treatment successively with methyl iodide, and then treatment with a solution of aqueous NaNO<sub>2</sub> (Scheme 3). The filtrate was dried by Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated of the solvent and the crystalline yellow solid of *N*-nitrosodiphenylamine was achieved in 90% yield [188 mg; mp: 65–66 °C (Ref. 8 mp: 67°C); IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3050 (C–H, aromatic), 1450, 1600 (C=C, aromatic), 1490–1500, (N=O, stretch), 1050 (N–N, stretch) (Fig. 1); <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.0–7.2 ppm (10 H, aromatic)].

### CONCLUSIONS

Polymer-supported nitrite is an efficient and chemoselective nitrosating agent for *N*-nitrosation of secondary amines under solvent-free conditions at room temperature. This simple procedure is highly selective, and contamination by C-nitrosation side-products is avoided. In conclusion, easy and clean work-up, chemoselectivity and high isolated yields make this method attractive for large-scale operation.

### References

- Garcia-Rio, L.; Leis, J. R.; Issglesias, E. *J Org Chem* 1997, 62, 4712.
- Nudelman, N. S.; Bonatti, A. E. *Synlett* 2000, 1825, and references cited therein.

- Olszewska, T.; Milewska, M. J.; Gdaniec, M.; Matuszynska, H.; Potonski, T. *J Org Chem* 2001, 66, 501.
- Williams, D. L. H. *Nitrosation*; Cambridge University Press: Cambridge, UK, 1988; pp 77–149.
- Williams, D. L. H. *Chemistry of Functional Groups*; Patai, S., Ed.; Wiley: New York, 1996; Vol 2, pp 665–682.
- Keefer, L. K.; Williams, D. L. H. *Methods in Nitric Oxide Research*; Feelisch, M.; Stamler, J. S., Eds.; Wiley: New York, 1996; p 509, and references cited therein
- Garica-Rio, L.; Leis, J. R.; Moreira, J. A.; Norberto, F. *J Org Chem* 2001, 66, 81.
- Zolfigol, M. A.; Shirini, F.; Ghorbani-Choghamarani, A.; Taqian-nasab, A.; Keypour, H.; Salehzadeh, S. *J Chem Res Synop* 2000, 420.
- Rivvera, A.; Gallo, G. I.; Joseph-Nathan, P. *Synth Commun* 1997, 27, 163.
- Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogels Text Book of Practical Organic Chemistry*, 5th ed.; Longman: London, 1989.
- Sheriner, R. L.; Reynold, T. L.; Fuson, C.; Curtin, D. Y.; Morrill, T. C. *Systematic Identification of Organic Compounds*, 6th ed.; Wiley: New York, 1980; pp 220–223.
- Castedos, L.; Riguera, R.; Vezquez, M. P. *J Chem Soc Chem Commun* 1983, 301.
- Nakajima, M.; Warner, J. C.; Anselme, J. P. *Tetrahedron Lett* 1984, 25, 2619.
- Chang, S. K.; Harrington, G. W.; Rothstein, M.; Shergalis, W. A.; Swern, D.; Vohra, S. K. *Cancer Res* 1979, 39, 3871.
- Makhova, N. N.; Karpov, G. A. N.; Mikhailiuk, A. N.; Bova, A. E.; Khmel nitskii, L. I.; Novikov, S. S. *Izv Akad Nauk SSSR Ser Khim* 1978, 1, 226.
- Zolfigol, M. A. *Synth Commun* 1999, 29, 905.
- Zolfigol, M. A.; Ghorbani-Chghamarani, A.; Hazarkhani, H. *Synlett* 2002, 1002.
- Sherrington, D. C.; Hodge, P. *Synthesis and Separations Using Functional Polymers*; Wiley: New York, 1988.
- Sherrington, D. C.; Hodge, P. *Polymer Supported Reactions in Organic Synthesis*; Wiley: New York, 1980.
- Karimi Zarchi, M. A.; Zarei, A. *J Chin Chem Soc* 2005, 52, 309.
- Riego, J. M.; Sedin, Z.; Zaldivar, J. M.; Marziano, N. C.; Tortato, C. *Tetrahedron Lett* 1996, 37, 513.
- Turro, N. J. *Tetrahedron* 1987, 43, 1589.
- Olah, G. A.; Molhotra, R.; Narang, S. C. *J Org Chem* 1978, 43, 4628.
- Takemoto, K.; Inaki, Y.; Ottenbrite, R. M. *Functional Monomers and Polymers*; Marcel Dekker: New York, 1987.
- Akelah, A.; Sherrington, D. C. *Chem Rev* 1981, 81, 577.
- Akelah, A.; Sherrington, D. C. *Polymer* 1984, 24, 1369.
- Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J Chem Soc Perkin Trans 1* 2000, 3815.
- Tamami, B.; Iranpoor, N.; Karimi Zarchi, M. A. *Polymer* 1993, 34, 2011.
- Tamami, B.; Karimi Zarchi, M. A. *Eur Polym J* 1995, 13, 715.
- Karimi Zarchi, M. A.; Noei, J. *J Appl Polym Sci* 2007, 104, 1064.
- Karimi Zarchi, M. A. *J Chin Chem Soc* 2007, 54, 1299.
- Karimi Zarchi, M. A.; Mirjalili, B. F.; Ebrahimi, N. *Bull Korean Chem Soc* 2008, 29, 1079.
- Caddick, S. *Tetrahedron* 1995, 51, 10403.
- Michael, D.; Mingos, P.; Baghurst, D. R. *Chem Soc Rev* 1991, 20, 1.
- Gedy, R. J.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett* 1986, 27, 279.
- Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett* 1986, 27, 4945.
- Abramovitch, A. *Org Prep Proc Int* 1991, 23, 685.

38. Loupy, A.; Petit, A.; Ramdiani, M.; Yvanaeff, C.; Majdoud, M.; Labiad, B.; Villemin, D. *Can J Chem* 1993, 71, 90.
39. Varma, R. S.; Chatterjee, A. K.; Varma, M. *Tetrahedron Lett* 1993, 34, 3207.
40. Smith, K. *Solid Supports and Catalysts in Organic Synthesis*; Perntice Hall: New York, 1992.
41. Hajipour, A. R.; Mallakpour, S. E.; Imanzadeh, G. *J Chem Res* 1999, 228.
42. Hajipour, A. R.; Mallakpour, S. E.; Adibi, H. *Chem Lett* 2000, 460.
43. Hajipour, A. R.; Mallakpour, E.; Mallakpour, A. *Tetrahedron* 1999, 55, 2311.
44. Hajipour, A. R.; Islami, F. *Ind J Chem* 1999, 38, 461.
45. Hajipour, A. R.; Mallakpour, S. E.; Imanzadeh, G. *Chem Lett* 1999, 99.
46. Hajipour, A. R.; Mallakpour, S. E.; Hantehzadeh, M. *J Org Chem* 1999, 64, 8475.
47. Hajipour, A. R.; Mallakpour, S. E.; Backnejad, H. *Synth Commun* 2000, 30, 3855.
48. Hajipour, A. R.; Mallakpour, S. E.; Afrousheh, A. *Phosphorus, Sulfur Silicon Relat Elem* 2000, 160, 67.
49. Hajipour, A. R.; Mallakpour, S. E.; Khoee, S. *Synlett* 2000, 740.
50. Hajipour, A. R.; Mallakpour, S. E.; Khoee, S. *Chem Lett* 2000, 120.
51. Hajipour, A. R.; Baltork, I. M.; Nikbaght, K.; Imanzadeh, G. *h Synth Commun* 1999, 29, 1697.