Organic Preparations and Procedures International: The New Journal for Organic Synthesis
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

POLYMER-SUPPORTED 4-(PHENYLSELENO)MORPHOLINE AS A USEFUL α-SELENENYLATING AGENT FOR SATURATED ALDEHYDES. A HIGHLY EFFICIENT ROUTE TO α-HALOALDEHYDES ON SOLID PHASE

Shou-Ri Sheng [a] [b] & Xian Huang [a]
[a] Department of Chemistry, Zhejiang University, Xixi Campus, Hangzhou, 310028, P. R., CHINA
[b] Department of Chemistry, Jiangxi Normal University, Nanchang, 330027, P. R., CHINA

To cite this article: Shou-Ri Sheng & Xian Huang (2003) POLYMER-SUPPORTED 4-(PHENYLSELENO)MORPHOLINE AS A USEFUL α-SELENENYLATING AGENT FOR SATURATED ALDEHYDES. A HIGHLY EFFICIENT ROUTE TO α-HALOALDEHYDES ON SOLID PHASE, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 35:4, 383-387, DOI: 10.1080/00304940309355844

To link to this article: http://dx.doi.org/10.1080/00304940309355844

ORGANIC PREPARATIONS AND PROCEDURES INT., 35 (4), 383-443 (2003)

OPPI BRIEFS

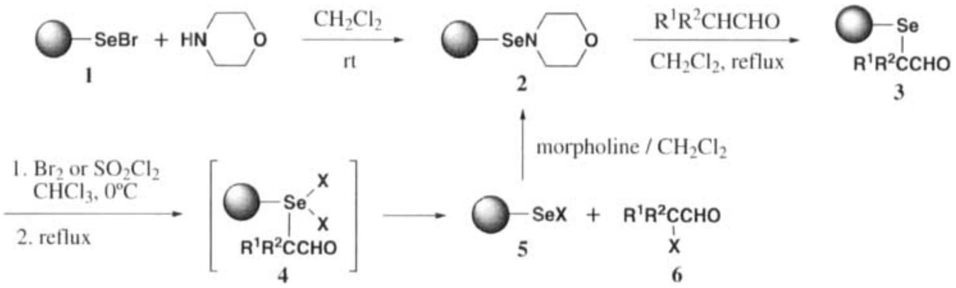
POLYMER-SUPPORTED 4-(PHENYLSELENO)MORPHOLINE AS A USEFUL α-SELENENYLATING AGENT FOR SATURATED ALDEHYDES. A HIGHLY EFFICIENT ROUTE TO α-HALOALDEHYDES ON SOLID PHASE

Submitted by Shou-Ri Sheng[†,††] and Xian Huang*[†]
(09/23/02)

[†] *Department of Chemistry, Zhejiang University*
Xixi Campus, Hangzhou, 310028, P. R. CHINA
[††] *Department of Chemistry, Jiangxi Normal University*
Nanchang, 330027, P. R. CHINA

Polymer-supported reagents are enjoying a renewed popularity in organic synthesis with the emergence of combinatorial chemistry in recent years.[1] One of the important advantages is the ease of separation and recycling of the polymer-resins from the product mixture at the end of reactions. Organoselenium reagents have attracted considerable interest and in particular, 4-(arylseleno)morpholines formed *in situ* are useful for the insertion of arylseleno groups at the α-position of saturated aldehydes.[2a] α-Selenoaldehydes, are important in organic synthesis;[3] for example, α-selenoaldehydes can be converted into α-haloaldehydes by halogenation.[4] However, organoselenium reagents always have a foul smell and are quite toxic. Recently, Nicolaou *et al.* reported the preparation of a polymer-bound selenium bromide and its applications in organic synthesis.[5] We previously described the formation of polymer-supported vinylic selenides, as well as the synthesis of carbonyl compounds on solid-phase.[6] Herein, we report a very simple preparation of polystyrene-supported (4-phenylseleno)morpholine and its application as a powerful reagent for α-selenenylation of saturated aldehydes and deselenenylation reaction by halogenation on solid-phase (*Scheme 1*).

A remarkable advantage of these new polymer-supported selenium reagents is the convenience of handling and their totally odorless nature as compared to the non-polymer-bound reagents. Furthermore, simple work-up procedures are used instead of the time-consuming isolation and purification steps in the corresponding solution-phase synthesis.



Scheme 1

Simple stirring of polymer-supported selenium bromide **1** with morpholine in CH_2Cl_2 resulted in nearly quantitative conversion to the polymer-supported (4-phenylseleno)morpholine (**2**). Treatment of **2** with saturated aldehydes bearing an α-hydrogen gave the corresponding α-phenylselenoaldehyde resins **3**, as indicated by IR spectra showing strong carbonyl absorption at 1700-1710 cm^{-1} and no residual Se-N absorption at 1252 cm^{-1}. The minimum degree of functionalization of resins **3** could be calculated from the nitrogen analysis of the corresponding aldoximes and corresponded to 1.02-1.10 mmol of aldehyde functional group per gram. Resin **2** and **3** are quite stable under the reaction conditions and can be stored in the air at room temperature for several months without loss of reactivity or the liberation of disagreeable odors. Treatment of resins **3** with the equimolar quantity of bromine furnish solid adduct **4** in $CHCl_3$ at 0°C. At more elevated temperatures (70°C), these adducts decompose to give polymer-supported selenium bromide **1** recovered by simple filtration and the α-bromoaldehydes in good yield and high purity by evaporation of the filtrate (*Table 1*). α-Chloroaldehydes are also generated by using sulfuryl chloride in place of bromine. However, we could not obtain the corresponding compounds using iodine under the same conditions. Resin **2** can be recovered by treatment of resin **5** with morpholine and reused several times without significant loss of activity (even after the fourth use). However, resin **2** did not react with saturated ketones, esters, nitriles or amides.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded on a Bruker Avance 400 MHz instrument using $CDCl_3$ as the solvent with TMS as an internal standard. Infrared spectra were obtained on a Bruker Vector-22 instrument. Polystyrene cross-linked with 1% divinylbenzene purchased from Aldrich (H C100-2, 100-200 mesh) was used for the preparation of polymer-supported selenium bromide according to the procedure described in the literature.[5]

Preparation of Polymer-supported 4-(Phenylseleno)morpholine (2).- Polystyrene-supported selenium bromide (1.0 g, 1.18 mmol Br/g) was swelled in CH_2Cl_2 (5 mL) for 30 min, and morpholine (0.21 g, 2.40 mmol) was added. The mixture was stirred at room temperature for 30 min and filtered. After washing successively with THF, H_2O, CH_3OH, CH_2Cl_2 (2 x 3 mL of

Table 1. Yield, Purity and ^{1}H NMR Data of Compounds (**6a-i**) [a]

Cmpd	R^1	R^2	X	Yield (%) [b]	Purity (%) [c]	^{1}H NMR (δ, CDCl$_3$)
6a	CH_3CH_2	H	Br	75	>95	1.01 (t, *J* = 5.9 Hz, 3H) 1.12-1.38 (m, 2H) 4.05 (dt, *J* = 3.1, 7.9 Hz, 1H) 9.43 (d, *J* = 3.0 Hz, 1H)
6b	$CH_3(CH_2)_2$	H	Br	78	>95	0.89 (t, *J* = 6.0 Hz, 3H) 1.10-1.40 (m, 2H) 1.68-1.95 (m, 2H) 4.01 (dt, *J* = 3.0, 8.0 Hz, 1H) 9.28 (d, *J* = 3.1 Hz, 1H)
6c	$(CH_3)_2CH$	H	Br	75	>95	0.85 (d, *J* = 6.1 Hz, 6H) 1.10-1.26 (m, 1H) 4.01 (dd, *J* = 3.1, 8.0 Hz, 1H) 9.33 (d, *J* = 3.1 Hz, 1H)
6d	$CH_3(CH_2)_4$	H	Br	77	>95	0.87 (t, *J* = 7.0 Hz, 3H) 1.07-1.68 (m, 6H) 1.73-2.22 (m, 2H) 4.10 (dt, *J* = 3.1, 8.0 Hz, 1H) 9.30 (d, *J* = 3.1 Hz, 1H)
6e	$C_6H_5CH_2$	H	Br	70	>95	3.31 (d, *J* = 5.7 Hz, 2H) 4.35 (m, 1H) 7.15-7.35 (m, 5H) 9.35 (d, *J* = 3.2 Hz, 1H)
6f	C_6H_5	H	Br	85	>95	3.48 (d, *J* = 3.2 Hz, 1H) 7.62-7.40 (m, 5H) 9.18 (d, *J* = 3.3 Hz, 1H)
6g	C_6H_5	H	Cl	74	>95	3.49 (d, *J* = 3.4 Hz, 1H) 7.61-7.33 (m, 5H) 9.27 (d, *J* = 3.4 Hz, 1H)
6h	C_6H_5	CH_3	Br	92	>95	2.20 (s, 3H) 7.21-7.38 (m, 5H) 9.56 (s, 1H)
6i	C_6H_5	CH_3	Cl	90	>95	2.31 (s, 3H) 7.20-7.40 (m, 5H) 9.50 (s, 1H)
6f	C_6H_5	H	Br	80	90 [d]	----
6g	C_6H_5	H	Cl	70	91 [d]	----

a) All compounds are known and were identified by ^{1}H NMR and IR. b) Overall yields based on polymer-supported 4-(phenylseleno)morpholine (1.12 mmol N/g). c) Determined by ^{1}H NMR (400 MHz) of the crude cleavage product. d) Using recovered resin **2** (4th run).

each) and then drying *in vacuo*, the resin **2** containing 1.12 mmol of nitrogen / g was obtained as yellow beads. IR (KBr): 3058, 3024, 2920, 2849, 1600, 1584, 1492, 1449, 1275, 1252, 1108, 1067, 903, 755, 696 cm^{-1}.

Anal. Calcd for resin **2**: N, 1.64. Found: N, 1.57

General Procedure for Preparation of Polymer-supported α-Selenoaldehyde Resin (3).- Resin **2** (1.0 g, 1.12 mmol) was swelled in CH_2Cl_2 (5 mL) for 30 min. The aldehyde (1.25 mmol) was then added, and the suspension was refluxed for 5 h, cooled and filtered. The resin **3** was washed with CH_2Cl_2 (4 x 3 mL) and dried under vacuum. The minimum capacity of this resin was calculated by the nitrogen elemental analysis of its corresponding aldoxime prepared according to the method described in literature.[7]

General Procedure for Preparation of α-Haloaldehydes (6).- Resin **3** (1.0 g) was swelled as above in $CHCl_3$ (5 mL) at room temperature overnight, and treated with equimolar quantity of bromine or sulfuryl chloride. The mixture was stirred at 0°C for 1 h, then refluxed for 1 h and filtered. The resin **5** was collected by filtration and washed with $CHCl_3$ (4 x 3 mL), and its FT-IR spectrum did not exhibit the characteristic carbonyl absorption of resin **3**. The filtrate was washed with brine, dried over $MgSO_4$, evaporated to afford α-haloaldehyde **6a-i** with greater than 90% purity determined by ^1H NMR.

The ^1H NMR spectra of **6a**,[8] **6b**,[4] **6c**,[8] **6d**,[8] **6e**,[4] **6f**,[4] **6g**,[4] **6h**,[9] and **6i**[4]were identical to those reported in the references cited.

Acknowledgement.- We are grateful to the National Nature Science Foundation of China (Project No. 29932020) for financial support.

REFERENCES

1. For recent reviews on solid-phase organic synthesis, see: (a) R. C. D. Brown, *J. Chem. Soc. Perkin Trans. 1*, 3293 (**1998**); (b) B. A. Lorsbach and M. J. Kurth, *Chem. Rev.*, **99**, 1549 (1999); (c) F. Guillier, D. Orain and M. Bradley, *Chem. Rev.*, **100**, 2091 (2000).

2. (a) P. Lerouge and C. Paulmier, *Bull. Soc. Chim. Fr.*, 1219 (**1985**). For related α-selenenylating agent for aldehydes, see: (b) H. J. Reich and J. M. Renga, *J. Org. Chem.*, **40**, 3313 (1975); (c) M. Jefson and J. Meinwald, *Tetrahedron Lett.*, **22**, 3561 (1981).

3. C. Paulmier, Ed., *"Selenium Reagents and Intermediates in Organic Synthesis"*, Pergamon Press, Oxford, **1986**.

4. C. Paulmier and F. Outurquin, *Tetrahedron Lett.*, **29**, 5893 (1988).

5. K. C. Nicolaou, J. Pastor, S. Barluenga and N. Winssinger, *Chem. Commun.*, 1947 (**1998**).

6. X. Huang and S.-R. Sheng, *Tetrahedron Lett.*, **42**, 9035 (2001).

7. M. J. Farrall and J. M. J. Fréchet, *J. Org. Chem.*, **41**, 3877 (1976).

8. Y. Satoh, T. Tayano, H. Koskino, S. Hara and A. Suzuki, *Synthesis*, 4068 (**1985**).

9. R. H. Reuss and A. Hassner, *J. Org. Chem.*, **39**, 1785 (1974).

****

EFFICIENT SYNTHESIS
OF 4-ISOCYANO-2,2,6,6-TETRAMETHYLPIPERIDINE-1-OXYL

Submitted by
(07/18/02)

Jerzy Zakrzewski* and Jaroslaw Hupko

Institute of Industrial Organic Chemistry
6 Annopol, 03-236 Warsaw, POLAND
e-mail: zakrzewski@ipo.waw.pl

Isocyanides have a wide range of synthetic potential[1-5] as starting compounds for the multicomponent reactions (MCRs) such as the Passerini and Ugi reactions, which are powerful tools for the creation of combinatorial libraries.[3,4,6-8] Isocyanides are also versatile building blocks for the synthesis of heterocycles.[5,8,9] Aryl, benzyl, cyclohexyl and *t*-butyl isocyanides[3,6] (the last three are commercially available) are most commonly used in these reactions. Herein we report an efficient and high yield synthesis of 4-isocyano-2,2,6,6-tetramethylpiperidine-1-oxyl. This compound will enrich the set of available isocyanides and allow the insertion of a spin label fragment into MCRs products, libraries created in MCRs reactions and heterocycles built from isocyanides.

The two most important routes to isocyanides involve the dehydration of *N*-substituted formamides using phosgene, phosphorus oxychloride, thionyl chloride or other dehydrating systems,[1,3] and by the reaction of primary amines with chloroform in the presence of strong bases.[1,10] Both routes have been reported for the synthesis of the title isocyanide **3**. The reaction of the amine **1** with chloroform[11,12] in the presence of solid potassium hydroxide gave **3** in only 9% yield,[11] while the dehydration of the formamide **2** with $POCl_3$/pyridine reagent in petroleum ether is reported to afford a 67% yield of **3**.[13]