Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5649–5652

Polystyrene sulfonic acid catalyzed greener synthesis of hydrazones in aqueous medium using microwaves

Vivek Polshettiwar and Rajender S. Varma*

Sustainable Technology Division, National Risk Management Research Laboratory, US Environmental Protection Agency, 26 W. Martin Luther King Dr., MS 443, Cincinnati, OH 45268, USA

Received 30 May 2007; accepted 6 June 2007
Available online 9 June 2007

Abstract—An environmentally benign aqueous protocol for the synthesis of cyclic, bi-cyclic, and heterocyclic hydrazones using polystyrene sulfonic acid (PSSA) as a catalyst has been developed; the simple reaction proceeds efficiently in water in the absence of any organic solvent under microwave irradiation and involves basic filtration as the product isolation step.

Hydrazones and their derivatives constitute an important class of compounds in organic chemistry. These compounds have interesting biological properties,[1] such as, anti-inflammatory,[3] analgesic,[4] and antipyretic[5] as well as chelating properties towards various metal ions.[2] Savini et al. evaluated heterocyclic hydrazones for anticancer, anti-HIV, and antimicrobial activity.[6] Recently hydrazones have also been found useful as anti-malaria drugs[7] and as inhibitors of macrophage migration inhibitory factor (MIF) tautomerase activity.[8] The synthetic efforts for this class of compounds are very well studied and generally entail the reaction of carbonyl compounds with hydrazine hydrate in organic solvents.[9] Some examples on supported reactions using silica gel/sodium hydroxide[10] and solvent-free synthesis of heterocyclic hydrazones under microwave irradiation conditions are also known.[11]

From an environmental view point, it is desirable to use water instead of organic solvents as a reaction medium, since water is environmentally benign.[12] In addition to the limited aqueous solubility of most organic compounds, a significant drawback of using water as a solvent is its ability to act as both a nucleophile and as an acid, making it incompatible with various organic transformations. In continuation of our green chemistry program,[13] we decided to explore the synthesis of various cyclic, bi-cyclic, and heterocyclic hydrazones in aqueous medium (Scheme 1).

We explored the condensation of acetophenone with phenyl hydrazine in water under microwave (MW) irradiation conditions. After screening a range of usual inorganic and organic acids and exploring their scope at various temperatures, we found that polystyrene sulfonic acid (PSSA) was the most efficient catalyst for hydrazone synthesis in water at 100 °C. Using these optimized reaction conditions,[14] the efficiency of this aqueous approach was studied for the syntheses of a wide variety of hydrazones, and the results are summarized in Table 1.

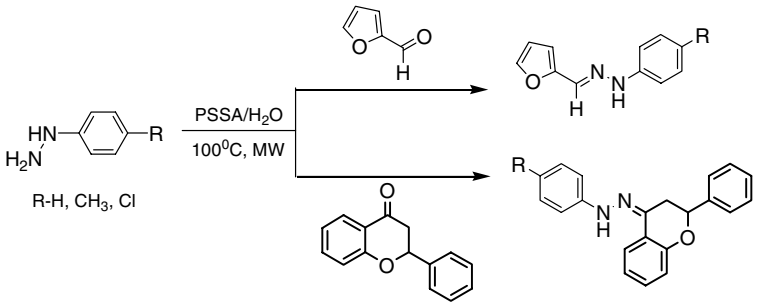
All the described reactions proceeded expeditiously and delivered excellent yields; the friendly isolation procedure simply involved the filtration of the precipitated hydrazones. Aromatic ketones were reacted with phenyl hydrazine (**a**) and 4-methyl phenyl hydrazine (**b**) (entries 1–4) to give hydrazone in excellent yields. 5-Bromoindanone also reacted well with both (**a**) and (**b**) (entries 5 and 6), preserving the bromo-functionality, which can be elaborated further in synthetic sequences. Aliphatic ketones were equally suitable substrates (entries 7–10).

The results of the syntheses of hydrazones from the corresponding aldehydes are summarized in Table 2.

The general reaction worked well for both aromatic (entries 1–4) as well as aliphatic aldehydes (entries 5 and 6). Piperonal also reacted with these hydrazines to yield hydrazones bearing dioxane moiety (entries 7 and 8),

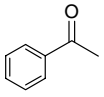
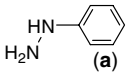
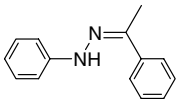
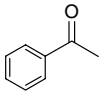
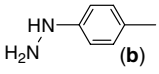
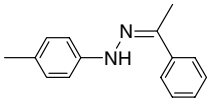
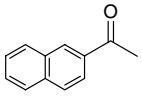
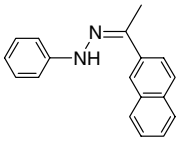
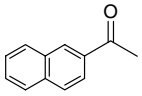
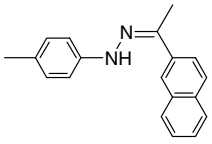
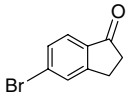
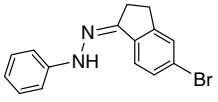
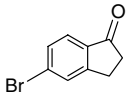
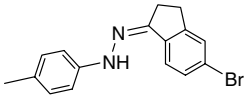
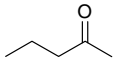
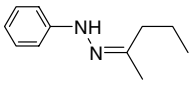
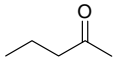
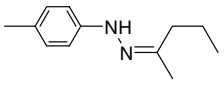
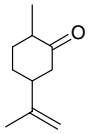
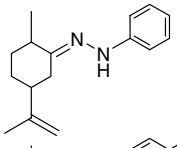
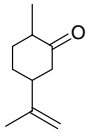
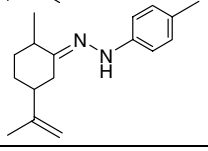
Keywords: Hydrazones; Polystyrene sulfonic acid; Aqueous medium; Microwave irradiation; Green chemistry.
* Corresponding author. Tel.: +1 513 487 2701; fax: +1 513 569 7677; e-mail: varma.rajender@epa.gov

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.06.038



Scheme 1. Hydrazone synthesis of furaldehyde and flavanone in water.

Table 1. PSSA catalyzed hydrazone synthesis from ketones in aqueous medium

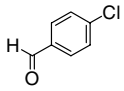
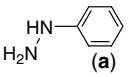
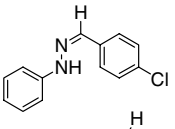
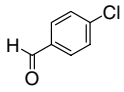
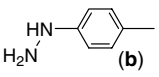
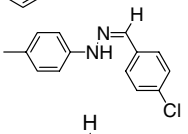
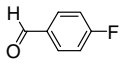
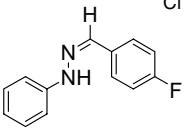
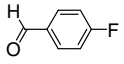
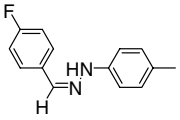
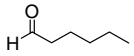
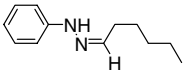
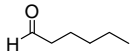
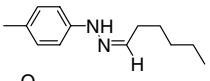
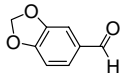
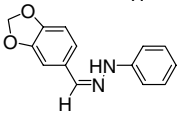
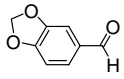
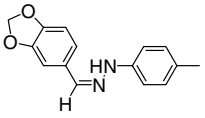
Entry	Ketone	Hydrazine	Product	Yield[a] (%)
1		 (**a**)		90
2		 (**b**)		88
3		(**a**)		91
4		(**b**)		90
5		(**a**)		90
6		(**b**)		88
7		(**a**)		87
8		(**b**)		88
9		(**a**)		89
10		(**b**)		86

[a] Yields were determined by GC. All the compounds are known in the literature and were characterized by GC–MS and NMR.

which may be useful for the synthesis of derivatives containing a dioxane system.

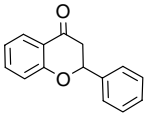
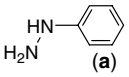
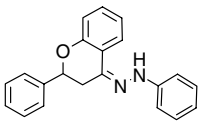
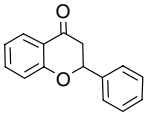
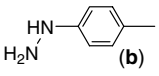
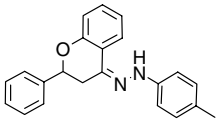
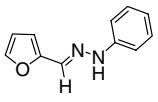
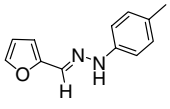
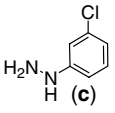
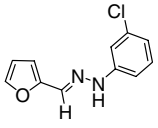
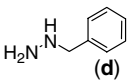
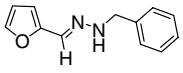
In view of the exceptional biological properties of heterocyclic and bi-cyclic hydrazones,[1] we extended this

Table 2. PSSA catalyzed syntheses of hydrazones from aldehydes in aqueous medium

Entry	Aldehyde	Hydrazine	Product	Yield[a] (%)
1				92
2				91
3		(**a**)		91
4		(**b**)		90
5		(**a**)		87
6		(**b**)		86
7		(**a**)		92
8		(**b**)		92

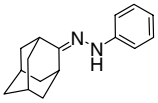
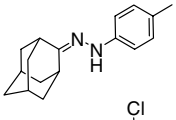
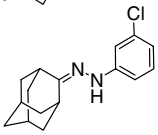
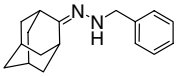
[a] Yields were determined by GC. All the compounds are known in the literature and were characterized by GC–MS and NMR.

Table 3. PSSA catalyzed synthesis of heterocyclic and bi-cyclic hydrazones in aqueous medium

Entry	Aldehyde/ketone	Hydrazine	Product	Yield[a] (%)
1				86
2				84
3		(**a**)		85
4		(**b**)		85
5				84
6				85

(*continued on next page*)

Table 3 (*continued*)

Entry	Aldehyde/ketone	Hydrazine	Product	Yield[a] (%)
7		(**a**)		88
8		(**b**)		87
9		(**c**)		88
10		(**d**)		88

[a] Yields were determined by GC. All the compounds are known in the literature and were characterized by GC–MS and NMR.

aqueous protocol for their synthesis and the results are described in Table 3.

Phenyl hydrazine (**a**) and 4-methyl phenyl hydrazine (**b**) reacted efficiently with flavanone (entries 1 and 2) to yield the respective hydrazone in high yield. Hydrazines (**a**), (**b**), (**c**) and (**d**) also react with furaldehyde (entries 3–6) and bi-cyclic ketones (entries 7–10).

Thus, we have demonstrated an efficient and general MW protocol for the synthesis of hydrazones from cyclic, bi-cyclic, and heterocyclic carbonyl compounds using PSSA as a catalyst in aqueous medium. The simple product isolation via filtration precludes the use of a organic solvent thus culminating in an environmentally benign aqueous protocol for the synthesis of hydrazones.

Acknowledgment

V.P. is a postgraduate research participant at the National Risk Management Research Laboratory administered by the Oak Ridge Institute for Science and Education.

References and notes

1. Savini, L.; Massarelli, P.; Chiasserini, L.; Sega, A.; Pellerano, C.; Barzi, A.; Nocentini, G. *Eur. J. Med. Chem.* **1995**, *30*, 547.
2. Maurya, M. R.; Agarwal, S.; Abid, M.; Azam, A.; Bader, C.; Ebel, M.; Rehder, D. *Dalton Trans.* **2006**, 937.
3. Sondhi, S. M.; Dinodia, M.; Kumar, A. *Bioorg. Med. Chem.* **2006**, *14*, 4657.
4. Cunha, A. C.; Tributino, J. L. M.; Miranda, A. L. P.; Fraga, C. A. M.; Barreiro, E. J. *Il Farmaco* **2002**, *57*, 999.
5. Sridhar, S. K.; Ramesh, A. *Biol. Pharm. Bull.* **2001**, *24*, 1149.
6. Savini, L.; Massarelli, P.; Travagli, V.; Pellerano, C.; Novellino, E.; Cosentino, S.; Pisano, M. B. *Eur. J. Med. Chem.* **2004**, *39*, 113.
7. Melnyk, P.; Leroux, V.; Sergheraert, C.; Grellier, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 31.
8. Dabideen, D. R.; Cheng, K. F.; Aljabari, B.; Miller, E. J.; Pavlov, V. A.; Al-Abed, Y. *J. Med. Chem.* **2007**, *50*, 1993.
9. (a) Banik, B. K.; Barakat, K. J.; Wagle, W. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1999**, *64*, 5746; (b) Gadhwal, S.; Baruah, M.; Sandhu, J. S. *Synlett* **1999**, 1573.
10. Hajipour, A. R.; Mohammadpoor-Baltork, I.; Bigdeli, M. *J. Chem. Res. (S)* **1999**, 570.
11. (a) Ješelnik, M.; Varma, R. S.; Polanc, S.; Kočevar, M. *Chem. Commun.* **2001**, 1716; (b) Ješelnik, M.; Varma, R. S.; Polanc, S.; Kočevar, M. *Green. Chem.* **2002**, *4*, 35.
12. (a) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *5*, 68; (b) Varma, R. S. *Org. Chem. Highlights* **2007**, February 1, *Clean Chemical Synthesis in Water*, Feb. 1, **2007**, URL: http://www.organic-chemistry.org/Highlights/2007/01February.shtm.
13. (a) Varma, R. S. In *Green Chemistry: Challenging Perspectives*; Tundo, P., Anastas, P. T., Eds.; Oxford University Press: Oxford, 2000; p 221; (b) Kumar, D.; Chandra Sekhar, K. V. G.; Dhillon, H.; Rao, V. S.; Varma, R. S. *Green Chem.* **2004**, *6*, 156; (c) Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409; (d) Yang, X.-F.; Wang, M.; Varma, R. S.; Li, C. -J. *Org. Lett.* **2003**, *5*, 657; (e) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 7665; (f) Wei, W.; Keh, C. C. K.; Li, C.- J.; Varma, R. S. *Clean Technol. Environ. Policy* **2005**, *7*, 62; (g) Ju, Y.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135; (h) Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409; (i) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 6697.
14. *Typical experimental procedure*: All the reactions were carried out in CEM discover MW reactor. Typically, the carbonyl compound (1 mmol) and hydrazine (1.2 mmol) were dissolved in 20% PSSA solution in water (three times the weight of ketone/aldehyde). This homogeneous reaction mixture was then exposed to microwaves at 100 °C in a closed system for 8 min and 5 min for ketone and aldehyde, respectively. After completion of the reaction, products were isolated with simple filtration (1–2 mL of water was added to facilitate easy filtration) and washed with methanol to afford pure hydrazones.