Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 397–400

Greener and rapid access to bio-active heterocycles: room temperature synthesis of pyrazoles and diazepines in aqueous medium

Vivek Polshettiwar and Rajender S. Varma*

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

Received 10 October 2007; revised 31 October 2007; accepted 1 November 2007
Available online 7 November 2007

Abstract—An expeditious room temperature synthesis of pyrazoles and diazepines by condensation of hydrazines/hydrazides and diamines with various 1,3-diketones is described. This greener protocol was catalyzed by polystyrene supported sulfonic acid (PSSA) and proceeded efficiently in water in the absence of any organic solvent within 1–2 min.

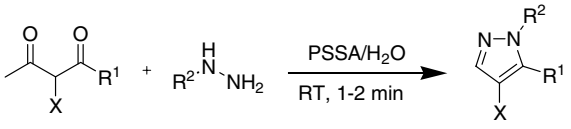
1. Introduction

Pyrazoles are an important class of bio-active drug targets in the pharmaceutical industry, as they are the core structure of numerous biologically active compounds,[1] including blockbuster drugs such as Celebrex[2] and Viagra.[3] They also possess important biological properties such as antitumor cyclin-dependent kinase (CDK) inhibitors,[4] monoamine oxidase-B (MAO-B) inhibitors, and antiinflammatory agents.[5] Recently, they have also emerged as potential atypical antipsychotics.[6]

Several syntheses of pyrazoles have been developed and by far the most prevalent method of choice is the reaction of 1,3-diketones with hydrazines.[7] Other methods for the synthesis of pyrazoles that do not require 1,3-diketones have been reported.[8] Recently, a few efficient methods have been developed,[9] however, most of these utilize a circuitous route, require longer reaction time, and are often carried out in organic solvents. Compared with the reactions in organic solvents, solventless reactions are often rapid, regio- or chemoselective, occur in high yields and have environmental and economic advantages.[10,11]

In our continued quest for greener synthetic pathways,[12] herein, we report an expeditious synthesis of pyrazoles by the reaction of 1,3-diketones with hydrazines and hydrazides catalyzed by polystyrene supported sulfonic acid (PSSA), which proceeded efficiently in water in the absence of any organic solvent at room temperature within 1–2 min (Scheme 1).

To optimize the reaction conditions, we studied the condensation of pentane-2,4-dione with phenyl hydrazine, using various acid catalysts: acetic acid, *p*-toluene sulfonic acid, and PSSA. Although reaction proceeds in each case, the yield and the rate of reaction is superior in the case of PSSA as compared to other catalyst. The general efficiency of this protocol was then studied for the synthesis of a variety of pyrazoles and the results are summarized in Table 1.



R^1 = Me, OEt
R^2 = Ph, 4-ClPh, COPh
CO-furyl, CO-thienyl
X = H, Et, Cl

Scheme 1. PSSA catalyzed pyrazole synthesis in water.

Keywords: Pyrazoles; Diazepines; Polystyrenesulfonic acid (PSSA), Aqueous medium.
* 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.2007.11.017

Table 1. PSSA catalyzed synthesis of pyrazoles at room temperature in aqueous medium[a]

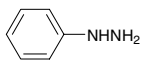
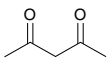
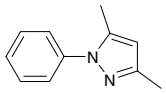
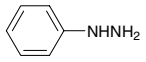
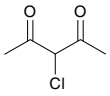
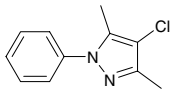
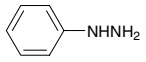
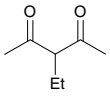
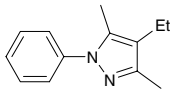
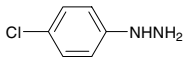
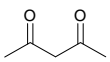
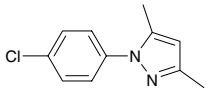
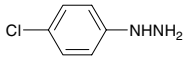
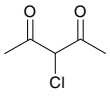
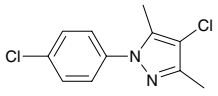
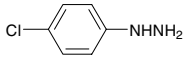
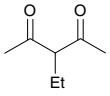
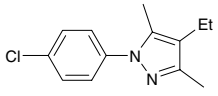
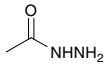
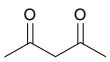
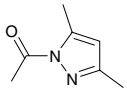
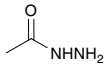
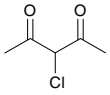
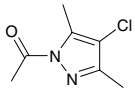
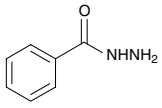
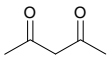
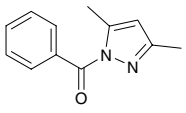
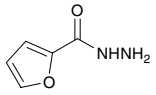
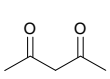
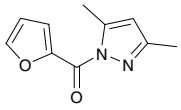
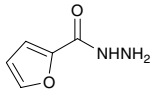
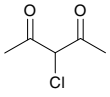
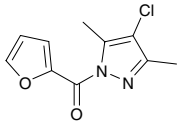
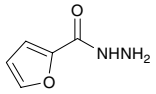
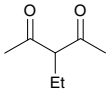
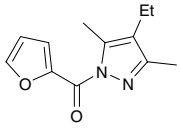
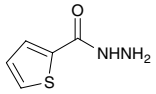
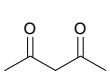
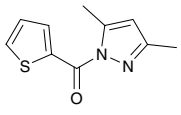
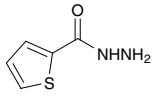
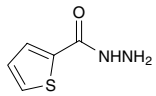
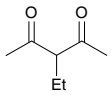
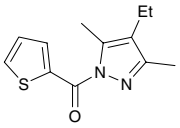
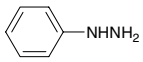
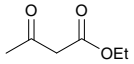
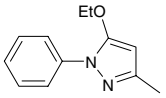
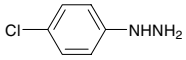
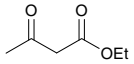
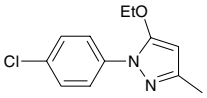
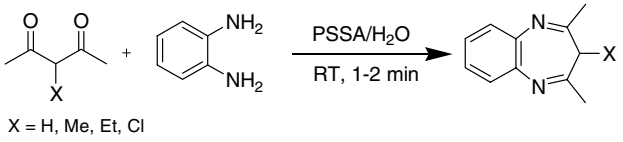
Entry	Hydrazine/hydrazide	Diketone	Product	Yield[b] (%)
1				92
2				75
3				82
4				85
5				72
6				80
7				90
8				78
9				90
10				92
11				85
12				88
13				91
14				85

Table 1 (*continued*)

Entry	Hydrazine/hydrazide	Diketone	Product	Yield[b] (%)
15				90
16				85
17				80

[a] Reactions performed with 1.0 equiv of 1,3-diketone, 1.1 equiv of hydrazines/hydrazides, and 0.1 mL of 20% PSSA solution in water and mixed for 1–2 min at room temperature.
[b] Isolated yields after passing the crude reaction mixture over short silica gel column.

Various hydrazines (entries 1–6) and hydrazides (entries 7–9) reacted efficiently with 1,3-diketones to afford the desired pyrazoles in good yields. In view of the exceptional biological properties of heterocyclic hydrazides, a wide variety of heterocyclic hydrazides (entries 10–15) were evaluated which provide a convenient and flexible method for the synthesis of pyrazoles encompassing heterocycles such as furan, thiophene as a functional arm at the 1-position, which may be useful chemical entities in drug discovery. The β-ketoesters can also be used as a substitute for diketones in this synthesis (entries 16 and 17). All these reactions proceeded efficiently at room temperature in aqueous medium and invariably all the reactions were completed in a minute or less.

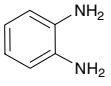
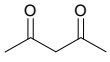
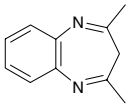
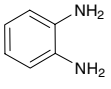
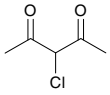
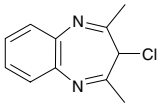
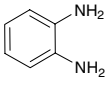
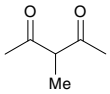
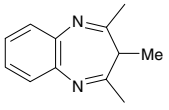
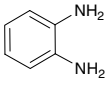
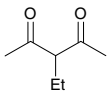
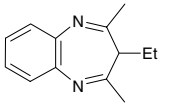
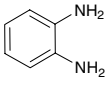
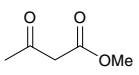
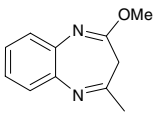


Scheme 2. PSSA catalyzed diazepine synthesis in water.

Finally, this protocol was also extended to the synthesis of various diazepines by the condensation of diamines with various 1,3-diketones in aqueous medium (Scheme 2) and the results are summarized in Table 2.

1,2-Diaminobenzene reacted efficiently with various 1,3-diketones to yield diazepines in a single step. The reaction proceeded at room temperature delivering excellent

Table 2. PSSA catalyzed synthesis of diazepine at room temperature in aqueous medium[a]

Entry	Diamine	Diketone	Product	Yield[b] (%)
1				90
2				85
3				86
4				88
5				NR

[a] Reactions performed with 1.0 equiv of 1,3-diketone, 1.1 equiv of diamines, and 0.1 mL of 20% PSSA solution in water and mixed for 1–2 min at room temperature.
[b] Isolated yields after passing the crude reaction mixture over short silica gel column.

yields within 1–2 min. The reaction of 1,2-diaminobenzene with methylacetoacetate, however, failed to give the desired product (entry 5), but after exposure to microwave irradiation yielded imidazole derivative (not shown) exclusively; more investigations are currently in progress to explore the reaction.

In conclusion, we have developed a greener and efficient approach for the synthesis of pyrazoles and diazepines, which gets completed in 1–2 min at room temperature and may provide a useful route for rapid drug discovery. The use of polystyrene supported, relatively low toxic, and inexpensive PSSA as a catalyst and the water as a reaction medium are additional eco-friendly attributes of this synthetic protocol.

2. Experimental

2.1. Typical experimental procedure for pyrazole synthesis

The 1,3-diketone (1 mmol) and hydrazines/hydrazides (1.1 mmol) were placed in a 10 mL glass tube. To this 0.1 mL of 20% PSSA solution in water was added and mixed for 1–2 min on touch mixer. The products were then extracted in to ethyl acetate and washed with dilute sodium bicarbonate solution. After drying the organic layer over sodium sulfate and evaporation of the solvent, the product was isolated by passing the crude reaction mixture over short silica gel column (Silica gel: 20% EtOAc/hexane).

2.2. Typical experimental procedure for diazepine synthesis

The experimental procedure described above was followed using the following mole ratio; 1.0 equiv of 1,3-diketone, 1.1 equiv of diamines, and 0.1 mL of 20% PSSA solution in water (Table 2).

Acknowledgments

Vivek Polshettiwar was supported, in part, by the Postgraduate Research Program at the National Risk Management Research Laboratory administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the US EPA.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.017.

References and notes

1. (a) McDonald, E.; Jones, K.; Brough, P. A.; Drysdale, M. J.; Workman, P. *Curr. Top. Med. Chem.* **2006**, *6*, 1193–1203; (b) Elguero, J. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5; (c) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Targets Heterocycl. Syst.* **2002**, *6*, 52–98.
2. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347–1365.
3. Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819–1824.
4. Lin, R.; Chiu, G.; Yu, Y.; Connolly, P. J.; Li, S.; Lu, Y.; Adams, M.; Fuentes-Pesquera, A. R.; Emanuel, S. L.; Greenberger, L. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4557–4561.
5. Gokhan-Kelekci, N.; Yabanoglu, S.; Kupeli, E.; Salgin, U.; Ozgen, O.; Ucar, G.; Yesilada, E.; Kendi, E.; Yesilada, A.; Bilgin, A. A. *Bioorg. Med. Chem.* **2007**, *15*, 5775–5786.
6. Barceló, M.; Raviña, E.; Masaguer, C. F.; Domínguez, E.; Areias, F. M.; Brea, J.; Loza, M. I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4873–4877.
7. (a) Wang, Z.; Qin, H. *Green Chem.* **2004**, *6*, 90–92, and references cited there in; (b) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon: NewYork, 1985, p 416.
8. (a) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381; (b) Bhat, B. A.; Puri, S. C.; Qurishi, M. A.; Dhar, K. L.; Qazi, G. N. *Synth. Commun.* **2005**, *35*, 1135; (c) Bishop, B. C. *Synthesis* **2004**, *1*, 43; (d) Ahmed, M. S. M.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487.
9. (a) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675–2678; (b) Deng, X.; Mani, N. S. *Org. Lett.* **2006**, *8*, 3505–3508; (c) Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D. *Org. Lett.* **2005**, *7*, 713–716.
10. (a) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *5*, 68; (b) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591; (c) Varma, R. S. *Org. Chem. High.* **2007**, *Clean Chemical Synthesis in Water*, URL: http://www.organic-chemistry.org/Highlights/2007/01February.shtm.
11. (a) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Disc.* **2005**, *5*, 51–63; (b) Polshettiwar, V.; Varma, R. S. *Curr. Opin. Drug Discov. Devel.* **2007**, *10*, 723–737.
12. (a) Polshettiwar, V.; Varma, R. S. *J. Org. Chem.* **2007**, *72*, 7420–7422; (b) Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2007**, *48*, 5649–5652; (c) Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2007**, *48*, 7343–7346; (d) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 6697–6700; (e) Ju, Y.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135–141; (f) Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409–2411; (g) Wei, W.; Keh, C. C. K.; Li, C.-J.; Varma, R. S. *Clean Tech. Environ. Policy* **2005**, *7*, 62–69; (h) Kumar, D.; Chandra Sekhar, K. V. G.; Dhillon, H.; Rao, V. S.; Varma, R. S. *Green Chem.* **2004**, *6*, 156–157; (i) Yang, X.-F.; Wang, M.; Varma, R. S.; Li, C.-J. *Org. Lett.* **2003**, *5*, 657–660; (j) Strauss, C. R.; Varma, R. S. *Top. Curr. Chem.* **2006**, *266*, 199–231.