J. Chem. Sci. Vol. 128, No. 9, September 2016, pp. 1475–1478. © Indian Academy of Sciences.
DOI 10.1007/s12039-016-1130-0

An efficient PEG-400 mediated catalyst free green synthesis of 2-amino-thiazoles from α-diazoketones and thiourea

B HARI BABU[a,*], K VIJAY[b], K BALA MURALI KRISHNA[a], N SHARMILA[a] and M BABY RAMANA[a]

[a]Department of Chemistry, Acharya Nagarjuna University, N Nagar, Andhra Pradesh, 522 510 India
[b]College of Pharmaceutical Sciences, Acharya Nagarjuna University, N Nagar, Andhra Pradesh, 522 510 India
e-mail: dr.b.haribabu@gmail.com

MS received 14 September 2015; revised 13 June 2016; accepted 14 June 2016

Abstract. A simple and efficient method has been developed for the synthesis of 2-aminothiazoles from α-diazoketones using PEG-400 solvent system. This novel synthetic approach involves the reaction between thiourea and α-diazoketones in PEG-400 at 100 °C to yield the corresponding 2-aminothiazoles in good yields. The method is simple, rapid and generates thiazole derivatives in excellent yields without the use of any catalysts. This green protocol can be utilized for fast synthesis of various 2-aminothiazoles in good yields.

Keywords. 2-amino thiazole; α-diazoketone; PEG-400; green synthesis.

1. Introduction

Heterocyclic amines such as 2-amino thiazoles are very interesting compounds as they are found to be useful in the treatment of allergies,[1] hypertension,[2] inflammation,[3] schizophrenia,[4] as antibiotics[5] and for HIV[6] infections. Further, their antitumor[7] properties and *in vivo* bacteriocidal[8] activities make them more useful. There are several methods reported in literature for the preparation of 2-aminothiazoles[9] involving the use of Lewis acids, Bronsted acids or inorganic salts as the catalysts in organic solvent medium. However, many of these methods suffer from lower yields, long reaction times, usage of organic solvents and harsh reaction conditions.

2. Experimental

2.1 *Materials and Methods*

All the chemicals used were of AR grade of Merck manufactures. Reagent grade solvents (E. Merck) were used as such. All the melting points were obtained from Remi melting point apparatus. All reactions were monitored by TLC and all yields refer to isolated products after column chromatography. Proton NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on Bruker 400 MHz and ^{13}C NMR spectra was on Bruker 100 MHz, Mass spectral studies were carried out on LC-MS system equipped with Agilent 1100 series, LC/MSD detector and 1100 series Agilent HPLC pump. The percentage of C, N, S and H were calculated by elemental analysis.

2.2 *General procedure*

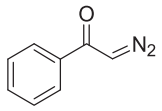
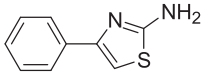
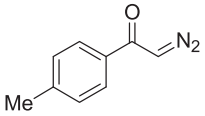
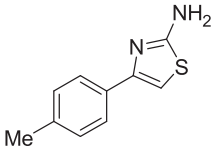
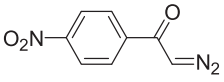
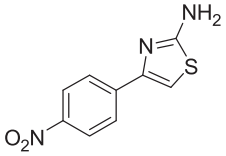
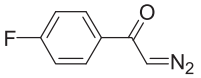
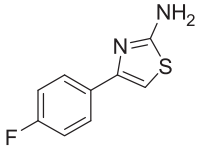
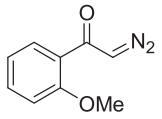
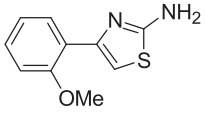
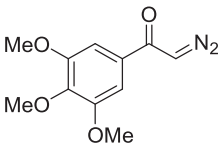
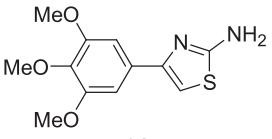
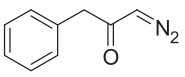
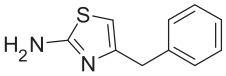
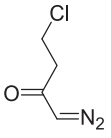
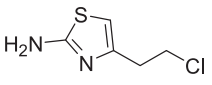
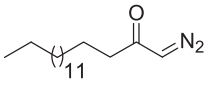
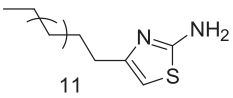
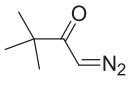
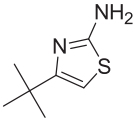
(i) Preparation of α-diazoketones: The starting α-diazoketones were prepared[10] by the condensation of the respective acid chlorides (1 eq) with diazomethane (4 eq) at 0°C in diethyl ether. (ii) Synthesis of thiazoles: A mixture of α-diazoketone (1 mmol), thiourea (1 mmol) in 10 mL of polyethylene glycol was heated at 100°C for the appropriate time (Table 1). After the completion of the reaction as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate (2x15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude residue was purified on silica gel chromatoghraphy (Merck, 100–200 mesh, ethyl acetate–hexane, 3:7) to afford the pure 2-aminothiazole.

2.3 *Spectral data for selected products*

2.3a *4-Phenylthiazol-2-amine (entry 1)*: Pink colored solid. M.p. 149–150°C; IR (KBr): 3434, 3254, 3154, 3113, 2924, 2368, 1598, 1517, 1480, 1439, 1332, 1196, 1070, 1023, 909, 843, 770, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO): δ 7.73 (d, J = 7.8 Hz, 2H), 7.36–7.17 (m, 3H), 6.63 (s, 1H) 6.21 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO): d 167.3,

*For correspondence

Table 1. Synthesis of 2-aminothiazoles using polyethylene glycol (PEG-400) medium.

Entry	α-diazoketone	2-aminothiazole	Time (h)	Yield (%)
1	 **2a**	 **3a**	2	96
2	 **2b**	 **3b**	2	91
3	 **2c**	 **3c**	3.5	87
4	 **2d**	 **3d**	3.5	90
5	 **2e**	 **3e**	2.5	93
6	 **2f**	 **3f**	2.5	95
7	 **2g**	 **3g**	3.0	92
8	 **2h**	 **3h**	3.0	90
9	 **2i**	 **3i**	3.0	94
10	 **2j**	 **3j**	4.0	91

[a]All products were characterized by ^{1}H NMR, Mass spectroscopy.
[b]Yield after silica gel column chromatography.

149.1, 133.7, 127.2, 126.0, 124.5, 100.1; ESI-MS (m/z): (M+H) 177; HRMS found for $C_9H_8N_2S$: 177.0488.

2.3b *4-(4-flouro phenyl)-1, 3-thiazol-2-amine (4)*: White Solid, M.p. 178–180°C; IR (KBr): 3425, 2923, 1598, 1505, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.51 (brs, 2H), 6.55 (s, 1H), 7.03(t, 2H), 7.68 (m, 2H); Mass (ESI): 217 $[M+Na]^+$; Anal. found for $C_{10}H_8FNS$: C, 54.53; H, 4.42; N, 14.13; S, 16.38.

2.3c *4-Pentadecylthiazol-2-amine (entry 9)*: Colorless solid. M.p. 65–66°C; IR (KBr): 3430, 3233, 3065, 2920, 2850, 1607, 1541, 1511, 1467, 1377, 1317, 1112, 1021, 967, 847, 720, 698, 632 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 0.91 (t, $J = 7.0$ Hz, 3H), 1.29 (br s, 24H), 1.55–1.65 (m, 2H), 2.43 (t, 2H, $J = 7.0$ Hz), 5.90 (s, 1H), 6.31 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO): d 167.1, 151.5, 99.0, 33.2, 30.5, 30.3, 28.3, 27.4, 23.7, 21.3, 12.9; EIMS (m/z): (M+H): 311.40.

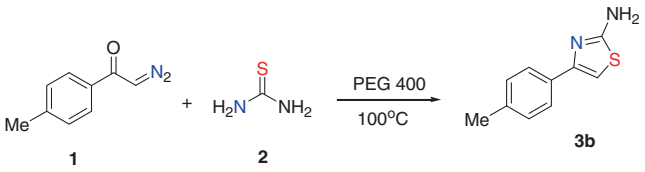
2.3d *4-tert-butylthiazol-2-amine (10)*: Viscous Liquid, IR (KBr) 3438, 3279, 3163, 2961, 1524 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.24 (s, 9H), 5.09 (brs, 2H), 6.02 (s, 1H); EIMS(m/z):156 $[M^+]$; Anal. found for $C_7H_{12}N_2S$: C, 53.62; H, 7.63; N, 17.99; S, 20.61.

3. Results and discussion

The synthesis of 2-aminothiazoles still has great importance. The usage of green reagents and solvents or solvent free conditions has attracted more attention in recent literature due to environmental concerns. The PEG was utilized as a mild, and highly efficient solvent system for the synthesis of benzimidazoles in excellent yields from *o*-phenyldiamine and a wide variety of aryl aldehydes using CAN as catalyst.[11]

In the present investigation, we report a versatile, environmentally friendly green synthesis of 2-aminothiazoles in polyethylene glycol medium. PEG-400 is a more effective and useful medium due to its environmental benign nature, ease of handling and lower cost. The reaction was carried out by heating α-diazoketone (**1**) and thiourea (**2**) in polyethylene glycol (PEG-400) at 100°C for 2 h to afford the corresponding 2-aminothiazole (**3b**) in 91% yield (Scheme 1).

Encouraged by the results of clean product formation, various α-diazoketones were treated further with thiourea in a similar fashion to synthesize the corresponding 2-aminothiazoles. In all these cases, reactants were completely converted into the corresponding 2-aminothiazoles with excellent yields (Table 1).



Scheme 1. PEG-400 mediated synthesis of 2-amino-4-tolylthiazole **3b**.

Various substituents on α-diazoketones, such as electron donating and electron withdrawing groups did not affect the efficiency of the reaction and the reactions proceeded smoothly to afford the corresponding aminothiazoles in excellent yield. The reaction yields were not affected even when halogen substituents were present on diazoketone. All resulting compounds were confirmed by their ^1H NMR and mass spectroscopic data.

4. Conclusions

In conclusion, we report an inexpensive, fast and efficient synthesis of 2-aminothiazoles from α-diazoketones using polyethylene glycol (PEG-400)as an efficient solvent medium. This procedure is a very attractive and useful alternative method to the other existing methods for the synthesis of 2-aminothiazoles.

Supplementary Information (SI)

Figures S1–S11 are provided in the supporting information available at www.ias.ac.in/chemsci.

Acknowledgements

Authors are thankful to Acharya Nagarjuna University, Guntur for constant encouragement and CSIR, New Delhi (EMR-II, 02/198) for financial assistance.

References

1. Hargrave K D, Hess F K and Oliver J T 1983 *J. Med. Chem.* **26** 1158
2. Patt W C, Hamilton H W, Taylor M D, Ryan M J, Taylor D G Jr., Cnnolly C J C, Dr. Ioherty A M, Klutchko S R, Sircar I, Steinbaugh B A, Batley B L, Painchaud C A, Rapundalo S T, Michniewicz B M and Olson S C 1992 *J. Med. Chem.* **35** 1562
3. (a) Haviv F, Ratajczyk J D, DeNet R W, Kerdesky F A, Walters R L, Schmidt S P, Holms J H, Young P R and Carter G W 1998 *J. Med. Chem*. **31** 1719; (b) Clemence F, Martret O L, Delevallee F, Benzoni J, Joianen A, Jouquey S, Mouren M and Deraedt R 1998 *J. Med. Chem*. **31** 1453

4. Jaen J C, Wise L D, Caprathe B W, Tecle H, Berggmeier S, Humblet C C, Heffner T G, Meltzner L T and Pugsley T A 1990 *J. Med. Chem.* **33** 1453
5. Tsuji K and Ishikawa H 1994 *Bioorg. Med. Chem. Lett.* **4** 1601
6. Bell F W, Cantrell A S, Ho'berg M, Jaskunas S R, Johansson N G, Jordon C L, Kinnick M D, Lind P, Morin J M Jr., Nore'en R, Berg B, Palkowitz J A, Parrish C A, Pranc P, Sahlberg C, Ternansky R J, Vasileff R T, Vrang L, West S J, Zhang H and Zhou X X 1995 *J. Med. Chem.* **38** 4929
7. Komar Y, Green R, Wise D and Worting L L 1988 *J. Med. Chem.* **23** 501
8. Yang-I Lin C M, Seifert S M, Kang J P and Lang S A 1979 *J. Heterocycl. Chem.* **16** 1377
9. (a) Pradip K S, Chandrasekhar S, Sridhar S and Javed Iqbal 2008 *Tetrahedron* **64** 11074; (b) Thompson M J and Beining C 2008 *Tetrahedron Lett*. **49** 5324; (c) Yadav J S, Reddy B V S, Gopala Rao Y and Narsaiah A V 2008 *Tetrahedron Lett*. **49** 2381; (d) Potewar T M, Ingale S A and Srinivasan K V 2008 *Tetrahedron* **64** 5019; (e) Aoyama T, Murata S, Takido T and Kodomari M 2007 *Tetrahedron* **63** 11933; (f) Kabalka G W and Mereddy A R 2007 *Tetrahedron Lett*. **47** 5171; (g) Sreejalekshmi K G, Devi S K C and Rajasekharan K N 2006 *Tetrahedron Lett*. **46** 6179
10. Pace V, Verniest G, Sinisterra J -V, Alcántara A R and Kimpe N De 2010 *J. Org. Chem.* **75** 5760
11. Mazaahir K, Anwar J and Divya B 2010 *J. Chem. Sci.* **122** 607