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Phosphomolybdic acid accelerated one-pot synthesis of 1-aryl-1H, 3H-thiazolo [3, 4-a] benzimidazoles

Atul Chaskar*

National Taiwan University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received December 03, 2011
Received in Revised form
December 28, 2011
Accepted 28 December 2011
Available online
30 December 2011

Keywords:
Phosphomolybdic acid
Ionic liquid
Multicomponent reaction
Benzimidazoles

ABSTRACT

An efficient and practical, three-component one-pot condensation reaction between 1, 2-phenylenediamine, 2-mercaptoacetic acid and aromatic aldehydes in ionic liquids have been reported for the synthesis of 1-aryl-1H, 3H-thiazolo [3, 4-a] benzimidazoles derivatives in excellent yields.

1. Introduction

On the background of global warming in 21st century, the demand of environmental and eco-friendly multicomponent reactions (MCR) with heterogeneous system have received substantially wide attention. MCRs are one-pot processes in which three or four components react to form a single molecular scaffold without isolation of any intermediate[1]. They showed various applications in organic, medicinal chemistry[2] and in drug discovery as well as 'green chemistry'[3]. On the other hand heteropoly acid (HPA) has been successfully employed as a heterogeneous catalyst in organic synthesis[4]. They are noncorrosive and are environmentally benign, as they can be reused and recycled[5]. Owing to all these characteristic features of multicomponent reaction and heteropoly acid, heterogeneous systems show great potential since the use of toxic solvent is drastically reduced, the chemo selectivity and atom-efficiency are often improved, the product isolation is simplified, and the volume of waste is significantly reduced.

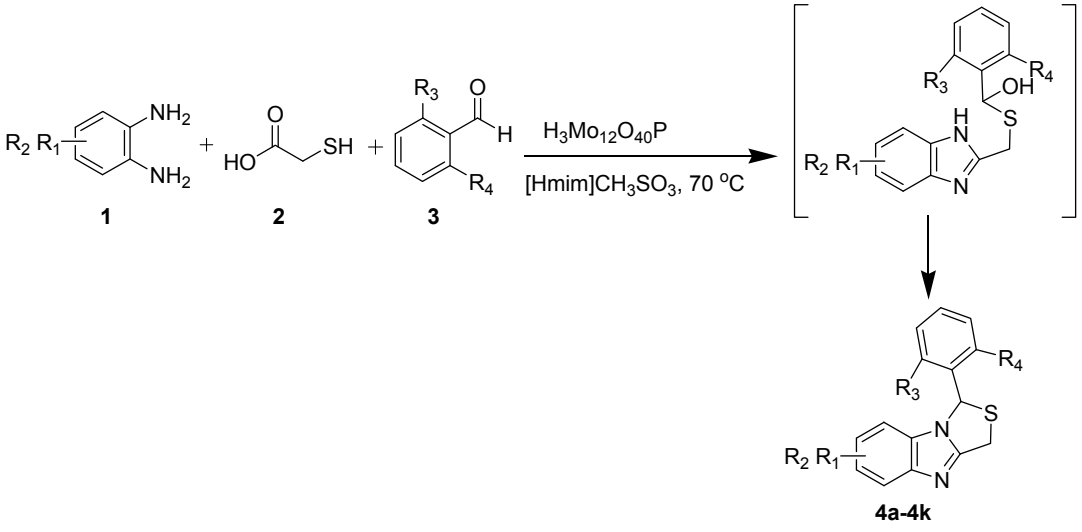
Nitrogen heterocycles containing the benzimidazole moiety are of interest because they show wide pharmacological and biological activities such as anti-microbial[6], anti-fungal[7], antiparkinson[8], anti-

* Corresponding author. Tel.: + 886-917352249
E-mail addresses: achaskar@rediffmail.com (A. Chaskar)

doi: 10.5267/j.ccl.2011.12.003

cancer[9], and anti-biotic[10]. It is intriguing to note that these derivatives have also been used as ligand for the asymmetric transformations[11]. 1*H*, 3*H*-thiazolo [3, 4-*a*] benzimidazoles acts as a potential HIV-1RT inhibitors as well. The usual methods for synthesis of benzimidazole and its derivatives involve condensation of carboxylic acids[12], orthoesters[13], amides[14], nitriles[15], aldehydes[16] and esters with aromatic amines in presences of acid catalyst. Most of the reported synthetic procedures are associated with several shortcomings such as use of harsh reaction conditions, poor yields and environmentally black-listed solvents[17]. Due to their wide range of biological, industrial and synthetic applications, the development of mild and efficient protocols continues to be a challenging endeavor in synthetic organic chemistry.

In conjunction to our interest to explore the catalytic activities of phosphomolybdic acid in organic transformations[18-21], we hereby report the effective and practical one-pot synthesis of 1*H*, 3*H*-thiazolo [3,4-*a*]benzimidazoles via the simple three-component condensation reaction of 1, 2-phenylenediamine, 2-mercaptoacetic acid and aromatic aldehydes in the presence of a catalytic amount of phosphomolybdic acid in ionic liquid (3-methylimidazolinium methane sulfonated) as solvent at 70 ^{0}C (Scheme 1). Chemical processes often employ large amounts of hazardous and toxic solvents. The choice of pursuing a low-waste route and reusable reaction media to minimize the economic cost and environmental impact of a chemical process is becoming need of future. In this context, here, we have used ionic liquid as a reusable reaction media. Ionic liquids have gained considerable importance as "green solvent" due to their solvating ability, negligible vapour pressure and easy recyclability.



Scheme 1

1.1 Results and Discussion

Preliminary efforts were mainly focused on the evaluation of different solvents. The reaction has been carried out between 1,2-phenylenediamine, 2-mercaptoacetic acid and benzaldehyde in various solvents, ionic liquids, under solvent-free classical heating conditions and results are summarized in **Table 1.** The results demonstrate the effective use of ionic liquid as a solvent for preparation of 1*H*, 3*H*-thiazolo [3, 4-*a*] benzimidazoles derivatives in presence of catalytic amount of phosphomolybdic acid as a solid acid catalyst.

Table 1. Effect of solvents for preparation of 1*H*, 3*H*-thiazolo [3, 4-*a*] benzimidazole (**4b**)[a]

Entry	Solvent	Temp.(°C)	Time (h)	Yield[b] (%)
1	Methanol	55	2	40
2	Ethanol	75	2	53
3	DMF	120	1	45
4	Acetonitrile	75	2	59
5	Solvent Free	100	24	30
6	Ionic Liquid	70	0.45	89
7	Toluene	100	1	73

[a]Reaction condition: 1,2-phenylenediamine (1mmol), benzaldehyde (1mmol),2-mercaptoacetic acid (1mmol), phosphomolybdic acid (0.1mmol), solvent (3 mL.)
[b]Yield: isolated

The aforementioned results encouraged us to generalise this protocol. We have extended the reaction of 1,2-phenylenediamine with a range of aromatic aldehydes and 2-mercaptoacetic acid under similar conditions (ionic liquid and phosphomolybdic acid), furnishing the respective 1*H*, 3*H*-thiazolo [3, 4-*a*]benzimidazoles in high yields. The optimized results are summarized in **Table 2**. Physical and spectral data of known compounds are in agreement with those reported in the literature [16,22].

Table 2. Synthesis of 1*H*, 3*H*-thiazolo [3, 4-*a*] benzimidazoles [a]

Products	R_1	R_2	R_3	R_4	Yield (%)[b]	MP/°C (lit.)
4a	H	H	Cl	Cl	87	133-134 (132-134)
4b	H	H	H	H	89	135-136 (134-135)
4c	H	H	H	NO_2	84	149-151 (150-152)
4d	H	H	H	Cl	88	125-127 (124-126)
4e	H	H	H	OH	82	187-189
4f	H	H	OH	OMe	83	192-195
4g	H	H	F	F	88	140-141 (141-142)
4h	5-Me	H	F	F	89	160-161 (159-161)
4i	6-Me	7-Me	F	F	89	179-180 (178-179)
4j	8-Me	H	F	F	89	147-149 (149-150)
4k	3-NO_2	H	H	H	79	183-184 (182-183)

[a]Reaction condition: 1,2-phenylenediamine (1mmol), aldehydes (1mmol), 2-mercaptoacetic acid (1mmol), phosphomolybdic acid (0.1 mmol), ionic liquid (3 mL), temperature: 70 ^{0}C., time: 45 min.
[b]Yield: isolated

From **Table 2** we conclude that the results were excellent in terms of yields, reaction time and product purity. Electron releasing substituents on 1,2-phenylenediamine favor the formation of compound in the presence of phosphomolybdic acid in ionic liquid.

In view of the green chemistry, the catalyst and reaction media were further explored for the reusability. After completion of reaction, the heteropolyacid acid and ionic liquid were easily recovered. In a reaction mixture diethyl ether was added to separate the ionic liquid from the mixture of product and heteropolyacid acid. Diethyl ether was further washed with water and the aqueous layer was evaporated under reduced pressure to get the heteropolyacid, while the combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to isolate the product. Heteropolyacid acid and ionic liquid were reused for two more processes (**Table 3**). It should be noted that the yields in second and even third runs are comparable to that of the first run. Hence, this procedure is advantageous over conventional reaction media.

Table 3. Recyclability of the phosphomolybdic acid and ionic liquid system for preparation 1*H*, 3*H*-thiazolo [3,4-*a*]benzimidazoles

Run	Yield(%)
1	89
2	89
3	87

2. Conclusions

In summary, we have demonstrated here a new, efficient and practical one pot procedure for the synthesis of 1*H*, 3*H*- thiazolo [3, 4-*a*] benzimidazoles derivatives via cyclocondensation reaction of 1, 2-phenylenediamine, 2-mercaptoacetic acid and aromatic aldehydes catalyzed by phosphomolybdic acid in ionic liquid. The advantages of our protocol are easy workup, fast reaction rates, mild reaction conditions, good yields, and reusability of catalyst as well as reaction media, which make the method an attractive and a useful contribution to the present methodologies.

3. Experimental

All commercial reagents were used as received without purification and all solvents were of reagent grade. The reaction was monitored by TLC using 0.25 mm E-Merck silica gel 60 F254 precoated plates, which were visualized with UV light. Melting points were taken in open capillaries. The IR spectra were recorded on a PerkinElmer 257 spectrometer using KBr discs. ^{1}H NMR and ^{13}C NMR spectra were recorded on a VXR-300 MHz instrument using TMS as an internal standard.

3.1 General experimental Procedure

A mixture 1, 2-phenylenediamine (1mmol), aldehyde (1mmol), 2-mercaptoacetic acid (1 mmol), phosphomolybdic acid (0.1 mmol) and ionic liquid (3 mL) was stirred at 70 ^{0}C for 45 min. After completion of reaction (checked by TLC) diethyl ether was added to reaction of mixture to separate the ionic liquid from the reaction mass. Diethyl ether was further washed with water and the aqueous layer was evaporated under reduced pressure to get the heteropolyacid acid, while the combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to isolate the product and catalyst was recycled. The crude product was crystallized by using ethanol to afford the pure product.

3.2 Representative spectral data

1–(2′, 6′-Dichlorophenyl)-1H, 3H-thiazolo [3, 4-a] benzimidazole (4a):

Mp: 132-134 $^{\circ}$C; IR (KBr):1617, 772, 707 cm^{-1}; ^{1}H NMR (DMSO-d_6): 4.21 (d, J = 14.1 Hz, 1H, H_3), 4.54 (dd, J = 1.75 and 14.2 Hz, 1H, H_3), 6.65 (s, 1H, H_1), 6.8–7.79 (m, 7H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6): 162, 159.8, 159, 158.6, 156.2, 152, 149, 137.4, 135.1, 133, 126.5, 125, 123.3, 76, 70 ppm; MS: (M+2): 323.2.

References

1. Menendez J. C. (2006) Multicomponent Reactions. *Synthesis*, 15, 2624-2624.

2. Dax S. L., McNally J. J., and Youngman M. A. (1999) Multi-component methodologies in solid-phase organic synthesis. Curr**.** Med**.** Chem**.** *6***,** *255-270.*

3. Domling A., and Ugi I. (2000) Multicomponent Reactions with Isocyanide. *Angew. Chem. Int. Ed.* 39, 3168-3210.

4. Okuhara T., Mizuno N., and Misono M. (1996) Catalytic Chemistry of Heteropolyacids. *Adv. Catal.* 41, 113-252.

5. Schwegler M. A., Van Bekkum H., and Munck N. (1991) Heteropolyacids as catalysts for the production of phthalate diesters. *Appl. Catal.* 74, 191-204.

6. Yildiz-Oren I., Yalcin I., Aki-Sener E., and Carturk N. **(**2004) Synthesis and structure–activity relationships of new antimicrobial active multisubstituted benzazole derivatives. *Eur. J. Med. Chem.* 39, 291-298.

7. Yamato M. (1992) Study on the Development of Biological- Active Compounds after the Model of Natural Products. *J. Pharm. Soc. Jpn.* 112(2), 81-99.

8. Benazzouz A., Boraud T., Dubedat P., Boireu A., Stutzmann J. M., and Gross C. (1995) Riluzole prevents MPTP-induced parkinsonism in the rhesus monkey: a pilot study. *Eur. J. Pharmacol.* 284, 299-307.

9. Kumar D., Jacob M. R., Reynolds M. B., and Kerwin S. M. (2002) Synthesis and evaluation of anticancer benzoxazoles and benzimidazoles related to UK-1. *Bioorg. Med. Chem.* 10(12), 3997-4004.

10. Evans D. A., Sacks C. E., Kleschick W. A., and Taber T. R. (1979) Polyether antibiotics synthesis. Total synthesis and absolute configuration of the ionophore A-23187. *J. Am. Chem. Soc.* 101(22), 6789-6791.

11. Figge A., Altenbach H. J., Brauer D. J., and Tielmann P. (2002) Synthesis and resolution of 2-(2-diphenylphosphinyl-naphthalen-1-yl)-1-isopropyl-1*H*-benzoimidazole; a new atropisomeric *P*,*N*-chelating ligand for asymmetric catalysis. *Tetrahedron: Asymmetry* 13(2), 137-144.

12. So Y. H., and Heeschem J. P. (1997) Mechanism of Polyphosphoric Acid and Phosphorus Pentoxide−Methanesulfonic Acid as Synthetic Reagents for Benzoxazole Formation. *J. Org. Chem.*, 62(11), 3552–3561.

13. Villemin D., Hammadi M., and Martin B. (1996) Clay Catalysis: Condensation of Orthoesters with O-Substituted Aminoaromatics into Heterocycles. *Synth. Commun.*, 26 (15), 2895-2899.

14. Masanao T., Masako I., and Yuichi K. (1982) A Facile Synthesis of 2-Substituted Benzoxazoles. *Synthesis*, 6, 484-485.

15. Hein D. W., Alheim R. J., and Leavitt J. J. (1957) The Use of Polyphosphoric Acid in the Synthesis of 2-Aryl- and 2-Alkyl-substituted Benzimidazoles, Benzoxazoles and Benzothiazoles. *J. Am. Chem. Soc.*, 79(2), 427–429.

16. Salehi P., Dabiri M., Zolfigol M. A., Otokesh S., and Baghbanzadeh M. (2006) Selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in water at ambient temperature. *Tetrahedron Lett.* 47(15), 2557-2560.

17. Chimirri A., Monforte P., Musumeci L., Rao A., Zappala M., and Monforte A. (2001) Synthesis and Antitumour Activity of 1**H**,3**H**-Thiazolo[3,4-**a**]benzimidazole Derivatives. *Arch. Pharm.* 334(6), 203-208.

18. Chaskar A., Padalkar V., Phatangare K., Patil K., and Langi B. (2009) Heteropoly acids as useful recyclable heterogeneous catalysts for the facile and highly efficient aza-cope rearrangement of *N*-allylanilines. *Applied Catalysis A: Gen.* 359 (1-2), 84-87.

19. Phatangare K., Padalkar V., Mhatre D., Patil K., and Chaskar A. (2009) Highly efficient and novel method for synthesis of 1,3,5-triarylbenzenes from acetophenones. *Synth. Commun.* 39, 4117-4121.

20. Gawand P., Deokar H., Langi B., Yadav A., and Chaskar A. (2009) $H_3Mo_{12}O_{40}P$-catalyzed one-pot synthesis of amidoalkyl naphthols. *Synth. Commun.* 39, 4171-4179.

21. Chaskar A., Phatangare K., Padalkar V., Langi B., and Naik P. (2009) Phosphomolybdic acid-catalyzed highly efficient and simple one-pot synthesis of quinoxaline. *J. Korean Chem. Soc.* 53, 727-730.

22. Yadav A. K., Kumar M., Yadav T., and Jain R. (2009) An ionic liquid mediated one-pot synthesis of substituted thiazolidinones and benzimidazoles. *Tetrahedron Lett.*, 50(35), 5031-5034.