Asian Journal of Chemistry; Vol. 28, No. 11 (2016), 2517-2520

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2016.20061

Polyethylene Gylcol (PEG-400) as an Efficient and Recyclable Reaction Medium for One-Pot Three-Component Synthesis of Imidazo[1,2-*a*]pyridine Derivatives

P. RAMESH and K. BHASKAR*

Department of Chemistry, Nizam College, Osmania University, Hyderabad-500 001, India

*Corresponding author: E-mail: kuthatibhaskar@gmail.com

Received: 3 May 2016; *Accepted*: 12 July 2016; *Published online*: 10 August 2016; AJC-18030

Polyethylene glycol (PEG) was found to be an inexpensive nontoxic and effective medium for the one-pot three-component synthesis of imidazo[1,2-*a*]pyridine derivatives under catalyst-free conditions in excellent yields. Environmental acceptability, low cost, high yields and recyclability of the polyethylene glycol are the important features of this protocol.

Keywords: Imidazo[1,2-*a*]pyridine, 2-Aminopyridines, Aldehydes, Nitroalkane, Polyethylene glycol, Catalyst-free conditions.

INTRODUCTION

Imidazo[1,2-*a*] pyridines are pharmaceutically important scaffolds widely found in naturally occurring, as well as synthetic biologically active, molecules [1]. Moreover, the pyrimidine ring system have been shown to possess, anti-protozoal [2], antiviral [3] and antiapoptotic [4] activities and have attracted attention to possess a broad range of useful pharmacological properties, including antibacterial, antifungal, anthelmintic, antiviral, antiprotozoal, anti-inflammatory, anticonvulsant, anxiolytic, hypnotic (*e.g.*, zolpidem, Fig. 1), gastrointestinal, antiulcer and immunomodulatory activities [5,6]. Furthermore, several pyrimidines are used in polymer and supramolecular chemistry [7,8].

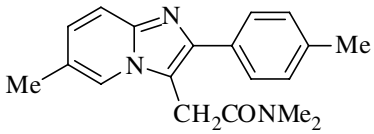
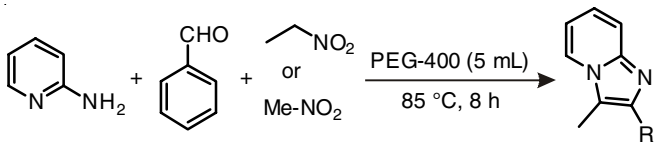


Fig. 1. Zolpidem, a pharmacologically important imidazo[1,2-*a*]pyridine

Several synthetic methods have been reported for the preparation of 2- or 3-substituted imidazo[1,2-*a*]pyridines with the majority relying on the condensation of 2-aminopyridine with α-bromoketones to form the five-membered cyclic system [9,10]. Particularly interesting are those structures that contain an amino group at C-2 or C-3. There are well established methods for the preparation of 3-aminoimidazo[1,2-*a*]pyridines; these include nitration at C-3 of the already formed heterocycle and subsequent reduction [11], preparation from pyridinium fluorides [12], Strecker-Type reaction between 2-amino-pyridines, a cyanide and a limited number of aldehydes [12,13] or by use of benzotriazole as an auxiliary group [14]. Most of these methods involve three or more sequential synthetic steps, the use of harsh reaction conditions that give low yields and in some cases, the use of hazardous or expensive starting materials. Multi-component reactions (MCRs) are useful for the construction of diverse chemical libraries of 'drug-like' molecules. The isocyanide-based multi-component reactions are especially important in this area [15]. New variants of the multi-component reactions were described by Ugi [16] Blackburn [17], Bienaymé [18] and Groebke [19], which enabled simple syntheses of imidazo[1,2-*a*]azines. Reactions of an aldehyde, an isocyanide and 2-aminoazine in methanolic solution containing a catalyst such as $Sc(OTf)_3$ [17], perchloric acid [18] or glacial acetic acid [19] were performed at room temperature. However, these methods required long reaction times and the work-ups were complicated. Imidazo[1,2-*a*]azine syntheses have also been carried out under microwave irradiation in the presence of a solid acid, montmorillonite K10 [20] and $Sc(OTf)_3$ [21] and using a non-polar solvent [22] or in the presence of an ionic liquid [23]. Improved conditions have been reported in recent years [24]. However, most of the reported methodologies still have certain limitations such as expensive and air sensitive nature of catalysts, toxicity of solvents, restrictions for large scale applications, critical product isolation procedures, difficulty in recovery of high boiling solvents, excessive amounts of catalysts and generation of large amounts of toxic wastes in scaling up for industrial applications leading to environmental issues. Thus, the development of a simple

and efficient method under catalyst free conditions for constructing these heterocyclic has been advocated. In recent years, polyethylene glycol (PEG) has emerged as a powerful phase-transfer catalyst and performs many useful organic transformations under mild reaction conditions. Moreover, PEG is inexpensive, easy to handle, thermally stable, nontoxic and recyclable in various organic transformations. In continuation of our interest in the field of the PEG-catalyzed synthesis of heterocyclic compounds under catalyst-free conditions [25]. As a part of our continuing studies into the synthesis of heterocycles, we paid attention to designing a new strategy for straightforward access to imidazo[1,2-*a*]pyridine rings through a de nitration reaction catalyzed by PEG-400 PEG-catalyzed one-pot three-component reaction, involving the assembly of the scaffold from [3+1+1] atom fragments. The method is facile, simple to undertake, uses commercially available starting materials, is environmentally benign and shows functional group tolerance. Herein, we wish to present this simple one pot synthesis of imidazo[1,2-*a*]pyridine derivatives, using PEG-400 as a recyclable medium without additional organic solvent and catalyst (**Scheme-I**).



Scheme-I

EXPERIMENTAL

All the chemicals employed in this study were procured from Sigma Aldrich and Alfaesear. In present study, all the synthetic reactions were monitored by TLC and synthesized compounds were confirmed by various spectroscopic methods. The IR spectra were recorded using KBr pellets on a Perkin Elmer IR spectrophotometer. ^{1}H NMR spectra were recorded on Brucker 300 MHz Avance NMR spectrophotometer using $CdCl_3$ as solvent and TMS as internal standard (chemical shifts in δ ppm). The mass spectra were recorded on Agilent 6300 series ion trap.

General procedure: A mixture of the requisite 2-amino-pyridine (0.5 mmol), benzaldehyde (0.6 mmol), $MeNO_2$ or $EtNO_2$ (15 equiv) was taken in PEG (5 mL) and stirred at 90 °C for the appropriate time. After completion of the reaction, as monitored by TLC, the reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was removed under reduced pressure and the crude product was purified by column chromatography. The recovered PEG could be reused for a number of cycles without significant loss of activity.

Characterization data of imidazo[1,2-*a*]pyridine derivatives

2-Phenylimidazo[1,2-*a*]pyridine (1): Yield: 275 mg (70 %); White solid, m.p. 106–08 °C. IR (neat, cm^{-1}); 3374, 3063, 2920, 2849, 1726, 1676, 1578, 1550, 1523, 1424, 1369, 1309, 1260, 1232, 1145, 1084, 1073, 991. 904, 772, 706, 613, 520. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 6.8 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 2 H), 7.82 (s, 1 H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.34–7.30 (m, 1 H), 7.16–7.12 (m, 1H), 6.74 (t, *J* = 6.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 15105, 147.8, 138.5, 134.2, 132.2, 129.0, 129.9, 128.4, 127.2, 125.9, 119.9, 114.2 ppm. Mass (ESI): *m/z* 193 $[M+H]^+$.

2-(4-Nitrophenyl)imidazo[1,2-*a*]pyridine (2): Yield: 295 mg (90 %); White solid, m.p. 106–08 °C. IR (neat, cm^{-1}); 3134, 2909, 2849, 1726, 1457, 1397, 1369, 1265, 1216, 1063, 1002, 849, 816, 728, 498. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 6.8 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 2 H), 7.82 (s, 1 H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.34–7.30 (m, 1 H), 7.16–7.12 (m, 1H), 6.79 (t, *J* = 6.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 144.7, 132.7, 131.8, 127.5, 125.5, 124.9, 121.9, 117.6, 112.6, 108.1 ppm. Mass (ESI): *m/z* 238 $[M+H]^+$.

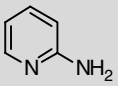
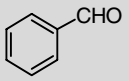
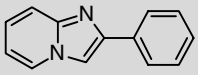
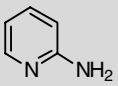
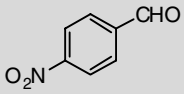
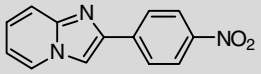
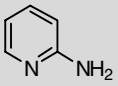
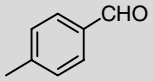
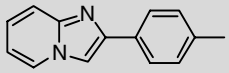
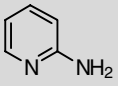
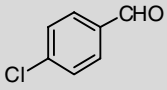
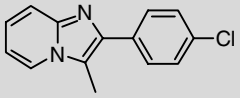
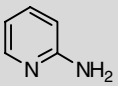
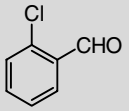
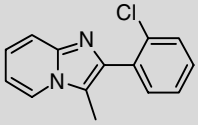
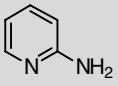
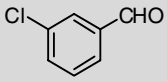
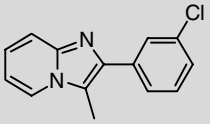
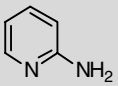
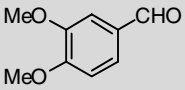
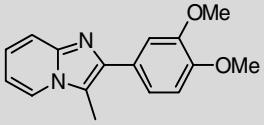
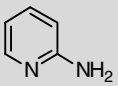
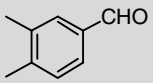
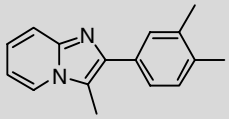
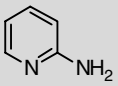
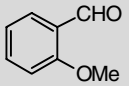
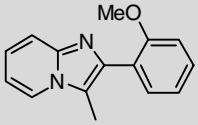
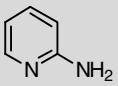
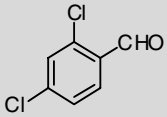
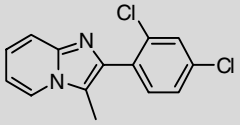
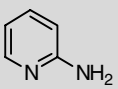
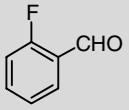
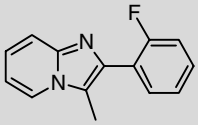
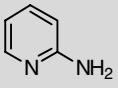
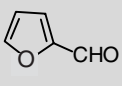
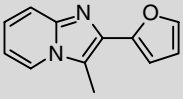
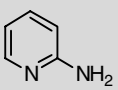
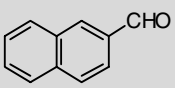
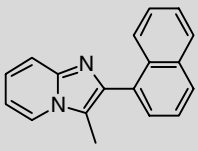
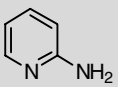
2-(4-Bromophenyl)imidazo[1,2-*a*]pyridine (14): Yield: 285 mg (70 %); Yellow solid, m.p.104–106 °C. IR (neat, cm^{-1}); 3145, 2909, 2849, 2361, 1720, 1457, 1260, 1117, 728, 580, 526. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.12 (m, 2 H), (s, 1 H), 7.86 (s, 1 H), 7.63 (d, *J* = 9.2 Hz, 1 H), 7.45 (dd, *J* = 8.0, *J* = 0.8 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.22–7.18 (m, 1H), 6.81 (td, *J* = 6.8, *J* = 0.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 144.2, 135.8, 130.8, 130.2, 128.9, 125.7, 125.1,124.5, 122.9, 117.6, 112.7, 108.5 ppm. Mass (ESI): *m/z* 270 $[M+H]^+$.

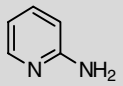
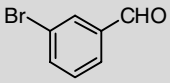
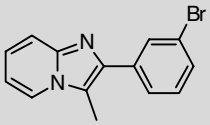
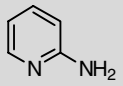
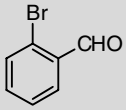
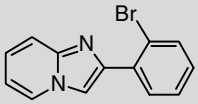
2-(2-Bromophenyl)imidazo[1,2-*a*]pyridine (16): Yield: 280 mg (70 %); Yellow solid, m.p.104–106 °C. IR (neat, cm^{-1}); 3156, 3106, 3057, 2926, 2854, 1928, 1676, 1638, 1561, 1534, 1495, 1457, 1424, 1364, 1315, 1276, 1205, 1019, 942, 915, 739, 641. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.12 (m, 2 H), (s, 1 H), 7.86 (s, 1 H), 7.63 (d, *J* = 9.2 Hz, 1 H), 7.45 (dd, *J* = 8.0, *J* = 0.8 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.22–7.18 (m, 1H), 6.81 (td, *J* = 6.8, *J* = 0.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5, 143.2, 134.4, 133.6, 128.9, 127.5, 125.7, 124.8, 121.5, 117.6, 112.5, 112.0 ppm. Mass (ESI): *m/z* 270 $[M+H]^+$.

RESULTS AND DISCUSSION

To the best of our knowledge there are no previous reports for the synthesis of imidazo[1,2-*a*]pyridine derivatives by using PEG-400 as a reaction medium under catalyst-free conditions. In general, all the reactions were very clean and the imidazo-[1,2-*a*]pyridine derivatives were obtained in high yields. We pleased to note that the transformation is very general for a wide range of aldehydes. Aryl and alkyl aldehydes revealed good reactivity in this reaction. A variety of electron-donating (Me, OMe; Table-1, entries 3, 7) and electron-withdrawing substituents (Cl, Br, F, NO_2; Table-1, entries 2, 4, 11 and 14) at the aromatic ring of the aldehyde were tolerated. In addition, a bulky naphthyl substituent did not hamper the process and also gave desired product albeit in lower yields (Table-1, entry 13). Heteroaryl-substituted substrate furan-2-carbaldehyde could be converted into target product in 57 % yield (Table-1, entry 12). The structures of all the products were determined from their analytical and spectroscopic (IR, ^{1}H NMR and ^{13}C NMR) data and by direct comparison with authentic samples [26,27].

TABLE-1
PEG-400 MEDIATED SYNTHESIS OF IMIDAZO[1,2-*a*]PYRIDINE DERIVATIVES

Entry	Aminopyridine	Aldehyde	Product	Yield (%)
1				70
2				90
3				50
4				55
5				50
6				40
7				55
8				60
9				70
10				70
11				85
12				50
13				50
14				70

Entry	Aminopyridine	Aldehyde	Product	Yield (%)
15				70
16				60

[a]The reaction was carried out by using 2-aminopyridine (0.5 mmol), benzeldehyde (0.6 mmol) and nitro methane (10 equiv.) with catalyst, PEG (5 mL), 85 °C. [b]Yield of isolated product.

Conclusion

We have developed an efficient and facile method for the synthesis of imidazo[1,2-*a*]pyridine derivatives by treatment of 2-aminopyridine, benzaldehyde and $EtNO_2$ using PEG as a recyclable medium without the addition of any additive or organic co-solvent. Mild reaction conditions, inexpensive reaction medium, operational simplicity and high yields are the advantages of the protocol.

ACKNOWLEDGEMENTS

The authors are thankful to UGC-CSIR, India and Indian Institute of Chemical Technology (IICT) Hyderabad, India for their constant support and encouragement.

REFERENCES

1. J.P. Michael, *Nat. Prod. Rep.*, **16**, 675 (1999).
2. (a) T. Biftu, D. Feng, M. Fisher, G.-B. Liang, X. Qian, A. Scribner, R. Dennis, S. Lee, P.A. Liberator, C. Brown, A. Gurnett, P.S. Leavitt, D. Thompson, J. Mathew, A. Misura, S. Samaras, T. Tamas, J.F. Sina, K.A. McNulty, C.G. McKnight, D.M. Schmatz and M. Wyvratt, *Bioorg. Med. Chem. Lett.*, **16**, 2479 (2006); (b) A. Scribner, R. Dennis, S. Lee, G. Ouvry, D. Perrey, M. Fisher, M. Wyvratt, P. Leavitt, P. Liberator, A. Gurnett, C. Brown, J. Mathew, D. Thompson, D. Schmatz and T. Biftu, *Eur. J. Med. Chem.*, **43**, 1123 (2008).
3. K.S. Gudmundsson and B.A. Johns, *Bioorg. Med. Chem. Lett.*, **17**, 2735 (2007).
4. C. Enguehard-Gueiffier, F. Fauvelle, J.C. Debouzy, A. Peinnequin, I. Thery, V. Dabouis and A. Gueiffier, *Eur. J. Pharm. Sci.*, **24**, 219 (2005).
5. A.S. Howard, in eds.: A.R. Katritzky, C.W. Rees and E.V.F. Scriven, In Comprehensive Heterocyclic Chemistry II; Pergamon Press: London, Chap. 10, p. 262 (1996).
6. F. Couty and G. Evano, in eds.: A.R. Katritzky, C.A. Ramsden, E.V.F. Scriven and R.J.K. Taylor, In Comprehensive Heterocyclic Chemistry III; Elsevier Science: Oxford, vol. 11, Chap. 11, p. 409 (2008).
7. R. Gompper, H.J. Mair and K. Polborn, *Synthesis*, 696 (1997); T. Kanbara, T. Kushida, N. Saito, I. Kuwajima, K. Kubota and T. Yamamoto, *Chem. Lett.*, 583 (1992).
8. G.S. Hanan, D. Volkmer, U.S. Schubert, J.-M. Lehn, G. Baum and D. Fenske, *Angew. Chem. Int. Ed. Engl.*, **36**, 1842 (1997); A. Semenov, J.P. Spatz, M. Möller, J.-M. Lehn, B. Sell, D. Schubert, C.H. Weidl and U.S. Schubert, *Angew. Chem. Int. Ed.*, **38**, 2547 (1999).
9. A.S. Howard, in eds.: A.R. Katritzky, C.W. Rees and E.V.F. Scriven, In Comprehensive Heterocyclic Chemistry II; Pergamon Press: London, vol. 8, Chap. 10, pp 262 (1996).
10. R. Goel, V. Luxami and K. Paul, *RSC Adv*., **5**, 81608 (2015).
11. C. Blackburn, B. Guan, P. Fleming, K. Shiosaki and S. Tsai, *Tetrahedron Lett*., **39**, 3635 (1998)
12. C. Roubaud, P. Vanelle, J. Maldonado and M.P. Crozet, *Tetrahedron*, **51**, 9643 (1995).
13. A. Kiselyov, *Tetrahedron Lett.*, **46**, 4487 (2005).
14. N.W. Bristow, P.T. Charlton, D.A. Peak and W.F. Short, *J. Chem. Soc.*, 616 (1954).
15. A.R. Katritzky, Y.-J. Xu and H. Tu, *J. Org. Chem.*, **68**, 4935 (2003).
16. (a) A. Dömling, *Chem. Rev.*, **106**, 17 (2006); (b) A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, **39**, 3168 (2000).
17. I. Ugi and R. Meyr, *Chem. Ber.*, **94**, 2229 (1961).
18. C. Blackburn, *Tetrahedron Lett.*, **39**, 5469 (1998).
19. H. Bienaymé and K. Bouzid, *Angew. Chem. Int. Ed.*, **37**, 2234 (1998).
20. K. Groebke, L. Weber and F. Mehlin, *Synlett*, 661 (1998).
21. R.S. Varma and D. Kumar, *Tetrahedron Lett.*, **40**, 7665 (1999).
22. S.M. Ireland, H. Tye and M. Whittaker, *Tetrahedron Lett.*, **44**, 4369 (2003).
23. V.Z. Parchinsky, O. Shuvalova, O. Ushakova, D.V. Kravchenko and M. Krasavin, *Tetrahedron Lett.*, **47**, 947 (2006).
24. A. Shaabani, E. Soleimani and A. Maleki, *Tetrahedron Lett.*, **47**, 3031 (2006).
25. (a) L.R. Odell, M.T. Nilsson, J. Gising, O. Lagerlund, D. Muthas, A. Nordqvist, A. Karlen and M. Larhed, *Bioorg. Med. Chem. Lett.*, **19**, 4790 (2009); (b) M.C. Pirrung, S. Ghorai and T.R. Ibarra-Rivera, *J. Org. Chem.*, **74**, 4110 (2009); (c) S.K. Guchhait and C. Madaan, *Synlett*, 628 (2009); (d) M. Nayak, S. Batra and S. Kanojiya, *Synthesis*, 431 (2009); (e) A. Shaabani, E. Soleimani, A. Maleki and J. Moghimi-Rad, *Synth. Commun.*, **38**, 1090 (2008); (f) F. Mert-Balci, J. Conrad, U. Beifuss, K. Meindl, T. Schulz and D. Stalke, *Synthesis*, 3649 (2008); (g) A.L. Rousseau, P. Matlaba and C.J. Parkinson, *Tetrahedron Lett.*, **48**, 4079 (2007); (h) A. Shaabani, A. Maleki, J. Moghimi Rad and E. Soleimani, *Chem. Pharm. Bull. (Tokyo)*, **55**, 957 (2007); (i) V.G. Nenajdenko, A. Reznichenko, L. Balenkova and E.S. Russ, *Chem. Bull*, **56**, 560 (2007).
26. L. Nagarapu, R. Mallepalli, L. Yeramanchi and R. Bantu, *Tetrahedron Lett.*, **52**, 3401 (2011).
27. H. Yan, Y. Wang, C. Pan, H. Zhang, S. Yang, X. Ren, J. Li and G. Huang, *Eur. J. Org. Chem.*, **2014**, 2754 (2014).