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Ultrasound assisted one pot synthesis of imidazole derivatives using diethyl bromophosphate as an oxidant

Deepak Nagargoje [a,*], Priyanka Mandhane [a], Savita Shingote [b], Pravin Badadhe [a], Charansingh Gill [a]

[a] Dept. of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431 004, India
[b] National Chemical Laboratory, Pune 411 007, India

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ABSTRACT

A one pot, three-component condensation of benzoin/benzyl, an aldehyde, and ammonium acetate using diethyl bromophosphate as a mild oxidant is achieved to form trisubstituted imidazole compounds. Under ultrasound irradiation, a smooth condensation occurs to get the 2, 4, 5-triaryl-1H-imidazole compounds in good to excellent yields. The study explores the scope and limitation of diethyl bromophosphate as an oxidant and suggests advantages, viz., simplicity of operation, reduction in time, and an increase in product yields.

1. Introduction

Imidazole and benzimidazole molecules are important substructures in a number of molecules which exhibit an array of biologic and pharmacological activities. The imidazole ring system is an important constituent of numerous natural products and medicinally important compounds, such as Cimetidine [1], which acts as antiulcerative agent. Omeprazole [2] a proton pump inhibitor, and the benzodiazepine antagonist flumazenil [3]. A platelet coagulation drug in animal and human beings, trifenagrel [4], is a 2, 4, 5 trisubstituted aryl-1H-imidazole derivative.

The development of synthetic protocols for imidazole derivatives has been a subject of concern since the 19th century. Radiziszewski and Japp independently reported a classical method in early 1882 to obtain 2, 4, 5 triphenyl imidazoles by condensing 1, 2 dicarbonyl compounds with different aldehydes and ammonia in acidic medium [5,6]. Afterwards, several new modified procedures were developed over the past two centuries for the synthesis of these biologically important scaffolds starting from benzyl/benzoin, aldehydes and ammonium acetate. These includes acidic, basic and Lewis acid catalysts like AcOH [7], acidic Al_2O_3 [8], HY/silicagel [9], sodium bisulfite [10], $ZrCl_4$ [11], $NiCl_2.6H_2O$ [12], iodine [13] and $Yb(OTf)_3$ [14], and boric acid using ultrasound irradiation [15] and potassium dihydrogen phosphate [16]. A very recent report exploits the use of ionic liquids as an alternative to traditional procedures [17]. Although these methods were developed, every method has its own inadequacies, viz., prolonged reaction time, excess heating, tedious and cumbersome work-up procedures and the use of expensive lanthanide salts. Thus, there is ample scope to develop an efficient and convenient method to construct these scaffolds.

During the last three decades, ultrasound-accelerated organic chemical reactions have been increasingly developed by researchers across the globe for the synthesis of organic molecules. Ultrasound irradiation offers an alternative energy source for organic reactions which are ordinarily accomplished by heating. Ultrasound-assisted reactions proceed by the formation, growth and collapse of acoustic bubbles in the reaction medium. These directly help in shortening the time span of reactions and increasing the yield of products. Many homogeneous and heterogeneous as well as transition metal-catalyzed organic reactions have been conducted efficiently by sonication.

2. Experimental

2.1. Apparatus and analysis

The uncorrected M.P. of compounds were taken in an open capillary in a paraffin bath and compared with those in the literature values. IR spectra were recorded using a Perkin–Elmer FT spectrophotometer with KBr discs. ^1H NMR were recorded on a 200 MHz FT-NMR in $CDCl_3$ as a solvent and TMS as an internal standard. Mass spectra were recorded on a Micromass Quattro II using ESI technique. GC analysis was carried on HP-6890 Instrument using HP-1 column.

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* Corresponding author.
E-mail address: dnagargoje@gmail.com (D. Nagargoje).

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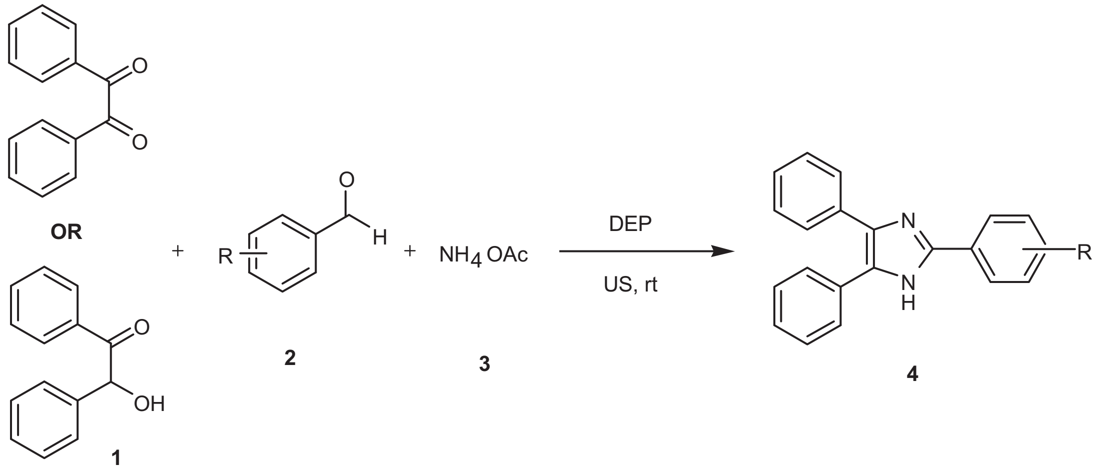

Scheme 1.

2.2. General procedure

To benzil/benzoin (1 mmol) and ammonium acetate (3 mmol) which were dissolved in acetonitrile were added (1 mmol) diethyl bromophosphate. This reaction mixture was then irradiated under ultrasonication at room temperature. The progress of the reaction was monitored using TLC. After completion of the reaction, the solvent was evaporated. The reaction mixture was quenched in water and neutralized by aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (3–10 ml) eluted over silica gel using ether–ethyl acetate as eluting solvent.

Compound (**3a**): IR (KBr): *v* 3450, 3050, 1600, 1580 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.15–8.00 (m, 15H, Ph), 9.20 (s, br, NH); EI-MS: *m/z*, 297 (M^+).

Compound (**3b**): IR (KBr): *v* 3458, 1617, 1581 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.5–7.65 (m, 10H, Ph), 7.42 (d, 1H, *J* = 10 Hz, Ar), 7.33 (d, 1H, *J* = 10 Hz, Ar), 7.20 (t, 1H, *J* = 10 Hz, Ar), 7.10 (t, 1H, *J* = 10 Hz, Ar), 9.4 (s, br, NH); EI-MS: *m/z* 331 (M^+).

Compound (**3c**): IR (KBr): *v* 3399, 1611, 1584 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.10–7.60 (m, 10H, Ph), 7.35 (d, 2H, *J* = 10 Hz, Ar), 7.85 (d, 2H, *J* = 10 Hz, Ar), 9.27(s, br, NH); EI-MS: *m/z*, 331 (M^+).

Compound (**3d**): IR (KBr): *v* 3450, 1600, 1585 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.30 (s, CH_3), 7.10–7.60 (m, 10H, Ph), 7.70 (d, 2H, *J* = 10 Hz, Ar), 7.30 (d, 2H, *J* = 10 Hz, Ar), 9.19 (s, br, NH). EI-MS: *m/z*, 311 (M^+).

3. Results and discussion

In the past few years, our group has become interested in development of new methods for the synthesis of numerous heterocyclic molecules by non-conventional means [18]. As part of our ongoing research, herein we describe the synthesis of 2, 4, 5-triaryl-1H-imidazole by condensing benzyl/benzoin, aldehyde and ammonium acetate in the presence of diethyl bromophosphate as a mild oxidant under ultrasound irradiation (Scheme 1). Diethyl bromophosphate is used for oxidative cyclization reactions, and few reports are available in the literature where it is used as an important oxidant [19]. Its use as an oxidant for the condensation of benzyl/benzoin, aldehyde and ammonium acetate has not been explored until now. For this reason, the reaction of benzaldehyde (1), benzyl or benzoin (2) and ammonium acetate (3) was chosen as a model reaction. By using diethyl bromophosphate under ultrasound irradiation conditions, the condensation reaction occurs very smoothly to afford the 2, 4, 5-triaryl-1H-imidazole products (4) in more than 90% yield (Scheme 1).

Table 1
Optimization of molar ratios of reactants and oxidant in synthesis of 2, 4, 5,-triaryl-1H-imidazole.

Sr. No.	Molar ratio 1/2 NH_4OAc	Oxidant DEP (mol)	Time (min)	Yield (%)[a]
a	1:1:3	0.25	30	61
b	1:1:3	0.50	30	79
c	1:1:3	1	30	97

[a] Isolated yield of products.

Table 2
Screening of solvent effect on model reaction.[a]

Entry	Solvent	Time (min)	Yield (%)[b]
1	Ethanol	30	60
2	Methanol	30	58
3	DCM	30	85
4	DMF	30	63
5	THF	30	86
6	Acetonitrile	30	97

[a] Reaction of benzil, benzaldehyde and ammonium acetate (1:1:3) in presence of DEP (1 mol) under ultrasonic waves (45 KHz).
[b] Yields based on GC analysis after 30 min.

To study the efficacy of diethyl bromophosphate, the ratios of the reactants and catalyst were optimized. On optimization of catalyst to substrate ratio, it was found that the molar ratio of 1:1:3:1 works well for all the reactions (Table 1). Different solvents were also screened for the model reaction. Among the different solvents screened, including ethanol, methanol, DCM, DMF, THF and acetonitrile, only acetonitrile was found to be the solvent of choice under ultrasound irradiation condition (Table 2). In order to gauge the effect of different irradiation frequencies, the model reaction was performed under three different frequencies of 35, 45 and 60 kHz. The product yield for these frequencies was 97%, 89% and 75% respectively. It seems that the lower frequency of ultrasound irradiation can improve the yield of imidazole derivatives. These results are consistence with the literature, because as the ultrasonic frequency is increased, the production of cavitation in liquids

Table 3
Syntheses of 2, 4, 5-triaryl-1H-imidazoles using DEP under ultrasonication at room temperature.

Entry	Aldehyde	Reaction time (min)		Yield (%)		M. P. (°C)	
		Benzil	Benzoin	Benzil	Benzoin	Found	Lit.
3a	Benzaldehyde	40	50	95	93	275–276	276–277
3b	*o*-Chlorobenzaldehyde	35	45	96	91	195–197	195–196
3c	*p*-Chlorobenzaldehyde	30	50	95	94	262–264	260–262
3d	*p*-Toluldehyde	45	65	92	90	230–232	231–232
3e	4-Methoxy benzaldehyde	35	70	98	94	233–234	227–228
3f	2,4-Dimethoxy benzaldehyde	30	50	93	94	215–217	219–220
3g	4-Nitrobenzaldehyde	40	80	96	93	232	232–233
3h	4-*N*, *N*-Dimethyl benzaldehyde	45	60	98	97	260–261	257–258
3i	4-Hydroxy benzaldehyde	35	40	90	92	269–270	268–270
3j	4-Fluorobenzaldehyde	25	35	97	95	191	190
3k	Furfuraldehyde	45	50	94	91	201–202	199–201
3i	2-Formyl thiophene	35	45	97	95	261–263	260–261

decreases [20]. From the results above, the optimum reaction conditions were chosen as: benzoin/benzyl (**1**, 1 mmol), aldehyde (**2**, 1 mmol), sodium acetate (**3**, 3 mmol).

Using the optimized reaction conditions, various aromatic and heterocyclic aldehydes were condensed with benzil/benzoin in the presence of diethyl bromophosphate under ultrasonication. It was observed that aromatic aldehydes containing different functional groups (electron donating as well as withdrawing) worked well and did not show any remarkable electronic field effects on the reactivity of aldehydes. Also, hetero-aromatic aldehydes also reacted quickly, and the general method worked well for them also. The results are summarized in Table 3. The synthesized compounds were analyzed with the help of various analytical techniques and their physical constants were compared with literature values.

4. Conclusion

In conclusion, a simple and practical method was developed using diethyl bromophosphate as a mild oxidant under ultrasound irradiation for the synthesis of 2, 4, 5-triaryl-1H-imidazole derivatives. The method offer several advantages, including a simple experimental process, easy work up and improved yields under ultrasonic conditions.

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References

[1] R.W. Brimlecombe, W.A. Duncan, G.J. Durant, J.C. Emmett, C.R. Ganellin, M.E. Parons, J. Int. Med. Res. 3 (1975) 86.
[2] Y. Tangiwara, N. Aoyama, T. Kita, K. Shirakawa, F. Komada, M.K. Kasuga, Clin. Pharmacol. Ther. 66 (1999) 528.
[3] W. Hunkeler, H. Mohler, L. Pieri, P. Polc, E.P. Bonetti, R. Cumin, R.W. Schaffner, Nature 290 (1981) 514.
[4] S.L. Abrahams, R.J. Hazen, A.G. Batson, A.P. Phillips, J. Pharmacol. Exp. Ther. 249 (1989) 359.
[5] B. Radziszewski, Chem. Ber. 15 (1882) 1493.
[6] F.R. Japp, H.H. Robinson, Chem. Ber. 15 (1882) 1268.
[7] S.E. Wolkenberg, D.D. Winoski, W.H. Leister, Y. Wang, Z. Zhao, C.W. Lindsley, Org. Lett. 6 (2004) 1453.
[8] A.Y. Usyantinsky, Y.L. Khemelnitsky, Tetrahedron Lett. 41 (2000) 5031.
[9] S. Balalaie, A. Arabanian, M.S. Hashtroudi, Mont. Fur. Chem. 131 (2000) 945.
[10] J.N. Sangshetti, N.D. Kokare, S.A. Kotharkar, D.B. Shinde, Mont. Fur. Chem. 139 (2008) 125.
[11] G.V.M. Sharma, Y. Jyothi, P.S. Lakshmi, Syn. Commun. 36 (2006) 2991.
[12] M.M. Heravi, K. Bakhtiari, H.A. Oskooie, S.J. Taheri, Mol. Cat. A: Chem. 263 (2007) 279.
[13] M. Kidwai, P. Mothsra, V. Bansal, R. Goyal, Mont. Fur. Chem. 137 (2006) 1189.
[14] L.M. Wang, Y.H. Wang, H. Tian, Y.F. Yao, J.H. Shao, B. Liu, J. Fluorine Chem. 127 (2006) 1570.
[15] K.F. Shelke, S.B. Sapkal, S.S. Sonar, B.R. Madje, B.B. Shingate, M.S. Shingare, Bull. Korean Chem. Soc. 30 (2009) 1057.
[16] R.S. Joshi, P.G. Mandhane, M.U. Shaikh, R.P. Kale, C.H. Gill, Chin. Chem. Lett. 21 (2010) 429.
[17] H. Zang, Q. Su, Y. Mo, B. Cheng, S. Jun, Ultrason. Sonochem. 17 (2010) 749.
[18] (a) R.S. Joshi, P.G. Mandhane, S.D. Diwakar, C.H. Gill, Ultrason. Sonochem. 17 (2010) 298;
(b) P.G. Mandhane, R.S. Joshi, D.R. Nagargoje, C.H. Gill, Tetrahedron Lett. 51 (2010) 1490;
(c) P.G. Mandhane, R.S. Joshi, D.R. Nagargoje, C.H. Gill, Tetrahedron Lett. 51 (2010) 1490;
(d) C.H. Gill, G.R. Jadav, M.U. Shaikh, R.P. Kale, A.R. Ghawalkar, D.R. Nagargoje, M.G. Shiradkar, Bioorg. Med. Chem. Lett. 18 (2008) 6244.
[19] S.S. Patil, V.D. Bobade, Syn. Commun. 40 (2010) 206.
[20] J. Li, X. Zhang, Z. Lin, Beilstein J. Org. Chem. 3 (2007) 13.