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Tartaric Acid: An Efficient, Catalyst for the Synthesis of Trisubstituted Imidazole under Microwave Irradiation.

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ABSTRACT
An efficient for synthesis of trisubstituted imidazole from benzil/benzoin, aromatic aldehyde and ammonium acetate in water under microwave irradiation. Tartaric acid is an inexpensive mild catalyst and the remarkable advantages such as mild reaction condition, shorter reaction time, simple procedure and excellent yield.

KEYWORDS
Trisubstituted imidazole, Tartaric acid, Water, Microwave irradiation.

1. INTRODUCTION

Nitrogen containing five membered is an important class in heterocyclic compound. Imidazole and its derivative are in a widespread range of naturally occurring molecules [1-3] and drug molecules [4-5]. Trisubstituted imidazole shows various bioactive effects such as fungicide, herbicidal [6], antitumor [7], anti-inflammatory [8], anti-allergic [9], analgesic [10], antibacterial [11] and used in biosynthesis of interleukin-1 (IL-1) [12].

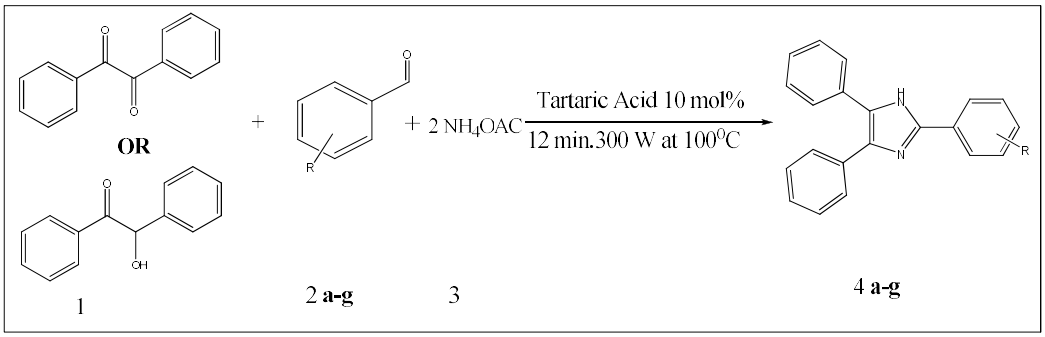
Recently, several method have been developed for synthesis of trisubstituted imidazole by condensation of benzil/benzoin, aromatic aldehyde with ammonium acetate using various catalyst and reagents such as, Ionic liquid [13], Iodine [14], $ZrCl_4$ [15], NH_4OAc [16], $Yb(OTF)_3$ [17], scolecite [18], PEG-400 [19], L-Proline [20], $CuCl_3.2H_2O$ [21], and $SbCl_3$ [22].

However, some disadvantages such as tedious workup procedure, purification, use of hazardous organic solvents, expensive reagents, long reaction time, low yield, occurrence of side reaction and waste materials. The traditional methods for synthesis of trisubstituted imidazole depend upon multicomponent reaction using benzil/benzoin, substituted aromatic aldehyde and a nitrogen source.

There is a strong demand for a simple, environmentally benign, highly efficient and versatile method for one pot synthesis of trisubstituted imidazole. The present study describes synthesis of trisubstituted imidazole on reaction of benzil/benzoin, substituted aromatic aldehyde with ammonium acetate in water in presence of tartaric acid as a catalyst (Scheme-1).

2. MATERIALS AND METHODS

All chemicals, reagents and solvents were used as received from commercial source. Melting points were taken in open capillary and were uncorrected. The reaction was carried out in microwave synthesizer, Mass-II, Sineo. ^1H NMR spectra were recorded on a bucker DRX-300 MHz instrument and IR were recorded as KBr pellets on a Nicolet impact 410.



Scheme 1. Synthesis of trisubstituted imidazoles.

2.1. Synthesis of trisubstituted imidazole (4a-g)

A mixture of benzil/benzoin 1(1 mmol), aromatic aldehyde 2(1 mmol), ammonium acetate 3(2 mmol) and catalyst tartaric acid (10 mol %) was added in 10 ml of distilled water was irradiated under microwave oven for appropriate time (Table 2). Progress of the reaction was monitored by

on TLC completion the reaction mass was poured on cold ice water. Then product was filtered, dried and recrystallized from ethanol.

3. RESULTS AND DISCUSSION

Here, we report a very simple and general method for the synthesis of trisubstituted imidazole using the catalytic amount of tartaric acid under microwave 300W (Scheme-1) as a model reaction. The synthesis of trisubstituted imidazole was carried out by condensation of benzil/benzoin, aromatic aldehyde and ammonium acetate in presence of tartaric acid as a catalyst.

To optimize the reaction conditions, all catalytic effects on the condensation reaction. The reaction was carried out in same conditions. When using PEG-400 and glycerol as catalyst, we got 4a in low yield product and prolong reaction time 86% and 92% (Table 1, Entry 1-2). Such as another catalyst $[Hbim]BF_4$, SSA, CAN, $Yb(OTF)_3$, L-Proline and they give low yield and more reaction time 91%, 73%, 75%, 90%, 91% yield respectively (Table 1, Entry 3-7).Hence, using Tartaric acid gives an excellent catalytic activity, which gave product in a yield of 96% (Table 1, Entry 8).

We determined the synthesis of trisubstituted imidazole derivatives using Tartaric acid at 10 mol percentage gave excellent yield of product (Table 1, entry 8). These are diprotic aldaric acid and it found naturally in plants such as bananas and grapes. It is used an antioxidant. These catalysts soluble in water, cheaper, easily available and non-hazardous. The reaction mixture was irradiated in microwave at an appropriate time (10-15 min.) the corresponding product was obtained in excellent yield.

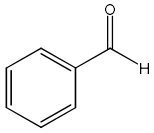
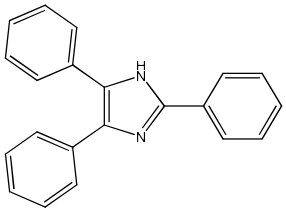
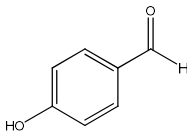
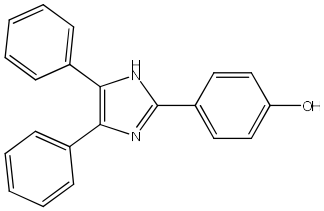
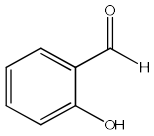
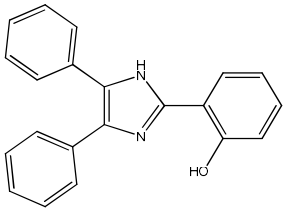
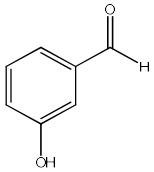
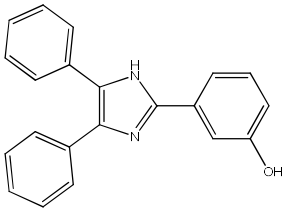
Table 1. Comparison of different catalyst in the synthesis of Trisubstituted imidazole.

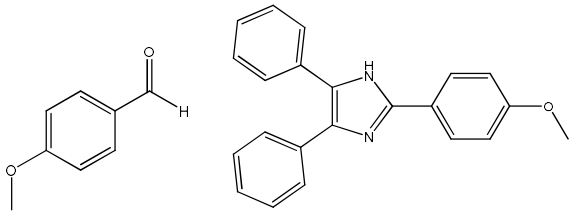
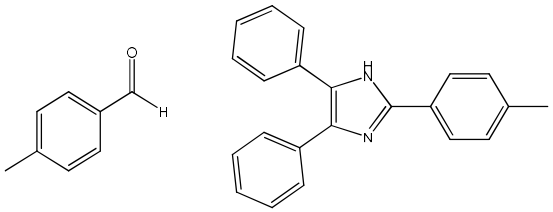
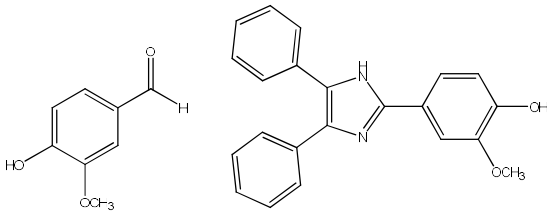
Entry	Catalyst	Time (min.)	Yield[a] (%)
1	PEG-400	360	86
2	Glycerol	180	92
3	$[Hbim]BF_4$	25	91
4	SSA	240	73
5	CAN	360	75
6	$Yb(OTF)_3$	120	90
7	L-Proline	540	91
8	**Tartaric acid**	**12**	**96**

[a]Reaction condition: Benzil/Benzoin(1 mmol), ammonium acetate (2 mmol), aldehyde (1 mmol) and Tartaric acid (10 mol%) at 300 W, [b]Isolated yields.

To examined the efficiency and applicability of this protocol. The reaction was carried out various substituted aromatic aldehyde are shown in Table 2. These result shows the reactions are facile electron donating and electron withdrawing substituent present on the substituted aromatic aldehyde resulting in high yields of corresponding imidazoles.

Table 2. Synthesis of Trisubstituted imidazole (4a-g) using (10 mol %) of Tartaric acid[a].

Entry	Ar-CHO	Products	Benzil Time(min.)/ Yield[b]	Benzoin Time(min.)/ Yield[b]
a			15 min./89	20 min./75
b			12 min./96	18 min./80
c			13 min./90	25 min./70
d			15 min./94	30 min./75

e		11 min./95	20 min./82
f		14 min./91	25 min./71
g		11 min./95	20 min./74

[a]Reaction condition: Benzil/Benzoin(1 mmol), ammonium acetate (2 mmol), aldehyde (1 mmol) and Tartaric acid (10 mol%) at 300 W, [b]Isolated yields.

3.2. Characterization data

Synthesis of 2-(4-Hydroxyphenyl)-4, 5-diphenylimidazole Entry-4b**:** MP 266-268^{o}C. IR(KBr, cm^{-1}): 3591, 3453, 3283, 3065, 1702, 1284; ^{1}HNMR (300 MHz, DMSO-d_6): 12.22 (s, 1H, NH), 9.41 (s, 1H, OH), 7.91 (d, J=8.4 Hz, 2H), 7.53-7.28 (m, 10H, Ar-H), 6.79 (d, J=8.4 Hz, 2H), ^{13}C NMR (300 MHz, DMSO-d_6): 157.5, 146.66, 127.11, 125.6, 124.4, 124.8, 114.7, 112.84, 98.56, 95.45 ppm.

Synthesis of 2-(4-Methoxyphenyl)-4, 5-diphenylimidazole Entry-4e**:** MP 229-231^{0}C IR (KBr, cm^{-1}): 3401, 3061, 1612, 1492, 1178, 1029, 831, 760; ^{1}HNMR (300 MHz, DMSO-d_6): 12.53 (s, 1H, NH), 8.02 (d, J=8.80 Hz,2.0 Hz, 2H), 7.71-7.11 (m, 10H,Ar-H), 7.04 (dt, J=8.8Hz, 2.0 Hz, 2H), 9.82 (s, 3H, CH_3) ^{13}C NMR (300 MHz, DMSO-d_6): 158.31, 145.08, 136, 134.63, 131.39, 121.31, 127.5, 126.02, 123.08, 113.08, 54.61 ppm.

4. CONCLUSION

In summary, we have developed a simple and environmentally benign procedure for synthesis of trisubstituted imidazole using tartaric acid as a highly effective. The advantages of this method such as reduced time, mild reaction condition, desired products in excellent yield and easy workup.

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6. REFERENCES

1. Shalini, K., Sharma, P., Kumar, N. (2010) Imidazole and its biological activities: A review. *Der Chemica Sinica*, 1(3), 36-47.
2. Luca, L. D. (2006). Naturally occurring and synthetic imidazoles: Their chemistry and their biological activities. *Current medicinal chemistry*, *13*(1), 1-23.
3. Ho, J. Z., Mohareb, R. M., Ahn, J. H., Sim, T. B., Rapoport, H. (2003) Enantio specific synthesis of carbapentostatins, *J. Org. Chem.68(10),*109-114.
4. Wong, K. K. (2009). Recent developments in anti-cancer agents targeting the Ras/Raf/ MEK/ERK pathway.*Recent pat. Anticancer Drug Discovery*, *4*(2), 28-35.
5. Wolkenberg, S. E., Wisnoski, D. D., Leister, W. H., Wang, Y., Zhao, Z., &Lindsley, C. W. (2004). Efficient synthesis of imidazoles from aldehydes and 1, 2-diketones using microwave irradiation. *Organic Letters*, *6*(9), 1453-1456.
6. Maier, T., Schmierer, R., Bauer, K., Bieringer, H., Buerstell, H., Sachse, B. (2014) Substituted imidazole-5-carboxylic acid derivatives, their preparation and their use as biocides. U.S. Patent 4820335.
7. Wang, L., Woods, K. W., Li, Q., Barr, K. J., McCroskey, R. W., Hannick, S. M., ... & Warner, R. (2002). Potent, orally active heterocycle-based combretastatin A-4 analogues: synthesis, structure-activity relationship, pharmacokinetics, and in vivo antitumor activity evaluation. *Journal of medicinal chemistry*, *45*(8), 1697-1711.
8. Lombardino, J. G. (1973) Anti-inflammatory imidazole. DE Patent 2155558, 1972. U.S. 3772441.
9. Black, J. W., Durant, G. J., Emmett, J. C., & Ganellin, C. R. (1974). Sulphur-methylene isosterism in the development of metiamide, a new histamine H2-receptor antagonist. *Nature*, *248*(5443), 65.
10. Uçucu, Ü., Karaburun, N. G., & Işikdağ, İ. (2001). Synthesis and analgesic activity of some 1-benzyl-2-substituted-4, 5-diphenyl-1H-imidazole derivatives. IL *Farmaco*, *56*(4), 285-290.
11. Khan, M. S., Siddiqui, S. A., Siddiqui, M. S. R. A., Goswami, U., Srinivasan, K. V., & Khan, M. I. (2008). Antibacterial activity of synthesized 2, 4, 5-trisubstituted imidazole derivatives. *Chemical biology & drug design*, *72*(3), 197-204.
12. Gallagher, T. F., Fier-Thompson, S. M., Garigipati, R. S., Sorenson, M. E., Smietana, J. M., Lee, D., Bender P E, Lee J C, Laydon J T, Griswold D E, Chabot-Fletcher M C, Breton J J, Adams J L, & Chabot-Fletcher, M. C. (1995). 2, 4, 5-Triarylimidazole inhibitors of IL-1 biosynthesis. *Bioorganic & Medicinal Chemistry Letters*, *5*(11), 1171-1176.

13. Siddiqui, S. A., Narkhede, U. C., Palimkar, S. S., Daniel, T., Lahoti, R. J., & Srinivasan, K. V. (2005). Room temperature ionic liquid promoted improved and rapid synthesis of 2, 4, 5-triaryl imidazoles from aryl aldehydes and 1, 2-diketones or α-hydroxyketone. *Tetrahedron*, *61*(14), 3539-3546.

14. Kidwai, M., Mothsra, P., Bansal, V., & Goyal, R. (2006). Efficient elemental iodine catalyzed one-pot synthesis of 2, 4, 5-triarylimidazoles. *Chemical Monthly*, *137*(9), 1189-1194.

15. Sharma, G. V. M., Jyothi, Y., & Lakshmi, P. S. (2006). Efficient room-temperature synthesis of tri-and tetra substituted imidazoles catalyzed by ZrCl4. *Synthetic communications*, *36*(20), 2991-3000.

16. Kidwai, M., Saxena, S., & Rastogi, S. (2005). An Efficient Synthesis of 2, 4, 5-Trisubstituted and 1, 2, 4, 5-Tetrasubstituted-1H-imidazoles. *Bulletin of the Korean Chemical Society*, *26*(12), 2051-2053.

17. Wang, L. M., Wang, Y. H., Tian, H., Yao, Y. F., Shao, J. H., & Liu, B. (2006). Ytterbium triflate as an efficient catalyst for one-pot synthesis of substituted imidazoles through three-component condensation of benzil, aldehydes and ammonium acetate. *Journal of Fluorine chemistry*, *127*(12), 1570-1573.

18. Gadekar, L., Mane, S., Katkar, S., Arbad, B., & Lande, M. (2009). Scolecite as an efficient heterogeneous catalyst for the synthesis of 2, 4, 5-triarylimidazoles. *Open Chemistry*, *7*(3), 550-554.

19. Wang, X. C., Gong, H. P., Quan, Z. J., Li, L., & Ye, H. L. (2009). PEG-400 as an efficient reaction medium for the synthesis of 2, 4, 5-triaryl-1H-imidazoles and 1, 2, 4, 5-tetraaryl-1H-imidazoles. *Chinese Chemical Letters*, *20*(1), 44-47.

20. Shitole, N. V., Shelke, K. F., Sonar, S. S., Sadaphal, S. A., Shingate, B. B., &Shingare, M. S. (2009). L-Proline as an efficient catalyst for the synthesis of 2, 4, 5-triaryl-1H-imidazoles. *Bulletin of the Korean Chemical Society*, *30*(9), 1963-1966.

21. Hangirgekar, S. P., Kumbhar, V.V., Shaikh, A. L., Bhairuba, I. A. (2014) One-pot synthesis of 2,4,5- trisubstituted imidazoles using cupric chloride as a catalyst under solvent free conditions. *Der Pharma Chemica*, 6, 164-168.

22. Safari, J., Naseh, S., Zarnegar, Z., & Akbari, Z. (2014). Applications of microwave technology to rapid synthesis of substituted imidazoles on silica-supported $SbCl_3$ as an efficient heterogeneous catalyst. *Journal of Taibah University for Science*, *8*(4), 323-330.