

**FULL PAPER**

# The dual role of ammonium acetate as reagent and catalyst in the synthesis of 2, 4, 5-triaryl-1H-imidazoles

Reza Tayebee<sup>a,\*</sup>  | Ali Gohari<sup>b</sup><sup>a</sup>Department of Chemistry, School of Sciences, Hakim Sabzevari University, Sabzevar, 96179-76487, Iran<sup>b</sup>Department of Biochemistry, School of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran**\*Corresponding Author:**

Reza Tayebee

Email: [rtayebee@hsu.ac.ir](mailto:rtayebee@hsu.ac.ir)

Tel.: +98 (51) 44013212

The new findings concerning synthesis of some 2, 4, 5-triaryl-1H-imidazoles is disclosed in the absence of any catalyst. Results indicated that by enhancing the amount of ammonium acetate, an obvious acceleration can be observed in the reaction progress. It is believed that ammonium acetate should be converted to ammonia and acetic acid during the reaction and the produced acid can catalyze the reaction progress. We believe that the observed efficiency for the previously reported catalytic systems has been mainly due to the presence of high molar ratio of ammonium acetate in the reaction medium and presence of auxiliary catalyst only improved the yield%.

**KEYWORDS**

Tri-aryl-imidazoles; multi-component; green synthesis; catalytic evaluation; ammonium acetate.

**Introduction**

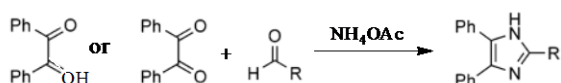
Over this century, the importance of imidazoles in biological systems has attracted a great deal of interest due to their biochemical properties. Compounds containing imidazole ring have many pharmaceutical properties and can play important roles in many natural biochemical processes [1-2]. For example, it is reported that substituted imidazoles can act as inhibitors of P38 MAP kinase [3], glucagon receptor antagonists [4], B-Raf kinase [5], antibacterial [6], plants growth regulators [7], antitumour [8], therapeutic agents [9], and also pesticides [10]. Moreover, the potency and wide application of the imidazole pharmacophores in biological systems can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity to metals which are present in many protein active sites. Because of their wide range of pharmacological activity, industrial and synthetic applications, the synthesis of

imidazoles has received considerable attention in recent years.

Multicomponent reactions (MCRs) have attracted great interest enjoying an outstanding position in modern green organic synthesis and medicinal chemistry because of the one-pot nature of these processes, bringing together three or more components and show high atom economy and high selectivity [11-12]. MCRs have great contribution in the convergent synthesis of complex and important organic medicinal molecules from simple and readily available starting materials, and have been emerged as powerful tools for drug discovery [13]. Various effective methods have been reported for synthesis of 2, 4, 5-triaryl-1H-imidazoles [14-16]. However, these methods may suffer from one or more disadvantages, such as long reaction time, low yields, use of dangerous reagents or expensive instrumentation, and often difficult work-up.

Although there are several methods for the synthesis of 2, 4, 5-triaryl-1H-imidazoles

from benzil/benzoin, aromatic aldehydes, and ammonium acetate using different catalysts such as ammonium chloride [17], poly(AMPS-co-AA) [18], NiFe<sub>2</sub>O<sub>4</sub> [19], Caro's acid-silica gel [20], and ionic liquids [21], development of new strategies for the preparation of 2, 4, 5-triaryl-1*H*-imidazole derivatives is still a demand. Preparation of 2, 4, 5-triaryl-1*H*-imidazoles needs at least 2 moles of ammonium acetate against each mole of benzil (Scheme 1). However, most of reported catalytic procedures had used 4-8 mole of NH<sub>4</sub>OAc per each mole of diketone or benzil. Recently, we have found that this reaction is mainly catalyzed by >8 mol ratio of NH<sub>4</sub>OAc and led to >70% of the corresponding imidazoles.



**SCHEME 1** A general route for the preparation of 2, 4, 5-triaryl-1*H*-imidazoles

## Experimental section

### Materials and methods

All starting materials were purchased commercially and were used as received. All products were characterized by comparison of their spectral and physical data with those reported in the literature. Silica gel 60 (70-230 mesh) was used for column chromatography. Progress of the reactions was monitored by TLC. Infrared spectra were recorded (KBr pellets) on a 8700 Shimadzu Fourier Transform spectrophotometer. <sup>1</sup>HNMR spectra were recorded on a Bruker AVANCE 300-MHz instrument.

### Synthesis of 2, 4, 5-triaryl-1*H*-imidazoles

A mixture of benzaldehyde (10 mmol, 0.106 g), benzil (10 mmol, 0.210 g), and ammonium acetate was refluxed with stirring in ethanol for 40 min and progress of the reaction was subsequently monitored by TLC. Finally, the

reaction mixture was cooled and poured into ice-water to get the solid precipitate. The obtained precipitate was collected by filtration, washed with water and dried to give the corresponding crude 2, 4, 5-triaryl-1*H*-imidazoles. The crude product can be purified by a simple washing with hot petroleum benzene to afford nearly pure product. Further purity was achieved by recrystallization from ethanol-water mixture or by column chromatography. All products were identified by means of IR and <sup>1</sup>HNMR spectroscopy and/or comparison of their melting points with those reported in the literature.

### Spectral data of some prepared 2, 4, 5-triaryl-1*H*-imidazoles

2, 4, 5-Tripheyl-1*H*-imidazole. IR (KBr): 3452 (N-H), 3050 (C-H), 1602 (C=C), 1583 (C=N) cm<sup>-1</sup>. <sup>1</sup>HNMR (DMSO): δ= 7.53–7.64 (m, 6H), 7.67–7.71 (m, 3H), 7.85–7.92 (m, 6H), 8.9 (bs, 1H).

2, 4, 5-Tri(4-methylphenyl)-1*H*-imidazole. IR (KBr): 3450 (N-H), 1602 (C=C), 1585 (C=N) cm<sup>-1</sup>. <sup>1</sup>HNMR (CDCl<sub>3</sub>): δ= 2.30 (s, CH<sub>3</sub>), 7.11–7.62 (m, 10H, Ph), 7.71 (d, 2H, J= 10 Hz, Ar), 7.33 (d, 2H, J= 10 Hz, Ar).

2,4,5-Tri(4-methoxyphenyl)-1*H*-imidazole. IR (KBr): 3452 (N-H), 1610 (C=C), 1576 (C=N), 1385 (C-O) cm<sup>-1</sup>. <sup>1</sup>HNMR (CDCl<sub>3</sub>): δ= 3.91 (s, OCH<sub>3</sub>), 7.08 (d, 2H, J= 8.8 Hz, Ar), 7.31–7.82 (m, 10H, Ph), 7.93 (d, 2H, J= 8.8 Hz, Ar).

## Results and discussion

In connection with our ongoing work on the synthesis of various heterocyclic compounds [22-29], we wish to report a facile procedure for preparation of imidazole derivatives without addition of any specific catalyst. As mentioned above, several methods are introduced for the synthesis of trisubstitutedimidazoles and their derivatives. In addition, the synthesis of these heterocycles has been usually performed in

polar organic solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to complex isolation and recovery procedures. These processes also generate waste containing catalyst and solvent, which have to be recovered. The toxicity and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in huge amounts for organic reactions have allocated a serious threat to the environment. Thus, design of solvent-free catalytic reaction has received tremendous attention in recent green synthetic approaches.

In continuation of our research program on the use of simple inorganic non-toxic catalysts, we tested the efficacy of  $\text{KH}_2\text{PO}_4$  as catalyst in ethanol under reflux condition (Table 1). Furthermore, preparation of the title compound has been reported with different amounts of ammonium acetate. For example, in the synthesis of this compound with  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  and sodium bisulfite, the mol ratios of benzaldehyde, benzil, and ammonium acetate were 2.4: 2: 8 and with phosphomolybdic acid the ratio of 2.4: 2: 6 had been selected [33]. Table 1 shows some catalytic systems using different amounts of  $\text{NH}_4\text{OAc}$ .

**TABLE 1** Synthesis of 2, 4, 5-tripheyl-1*H*-imidazole with different catalysts

Catalyst	Benzil (mmol)	$\text{NH}_4\text{OAc}$ (mmol)	Time (min)	Yield (%)	Ref.
$\text{KH}_2\text{PO}_4$	10	20	40	93	30
$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$	10	40	30	97	31
sodium bisulfite	10	40	30	98	32
phosphomolybdic acid	10	30	45	97	33
Boric acid( $\text{H}_3\text{BO}_3$ )	1	3	30	98	34

Efficiency of this reaction is mainly affected by the amount of ammonium acetate as catalyst. Thus, we performed this reaction with different mmols of ammonium acetate without using any additive to study the role of this initial substrate as catalyst. The results are presented in Table 2.

**TABLE 2** Synthesis of 2, 4, 5-tripheyl-1*H*-imidazole with different amounts of ammonium acetate without any catalyst

Mol ratio of benzil: $\text{NH}_4\text{OAc}$	$\text{NH}_4\text{OAc}$ (mmol)	Yield (%)
1: 2	20	26
1: 3	30	45
1: 4	40	58
1:5	50	77

The reactions were performed with benzaldehyde (10 mmol), benzil (10 mmol) and different amounts of ammonium acetate in ethanol under reflux for 40 min.

Results in Table 2 confirm that an obvious acceleration was observed in the reaction progress by increasing the amount of ammonium acetate. It has been found that

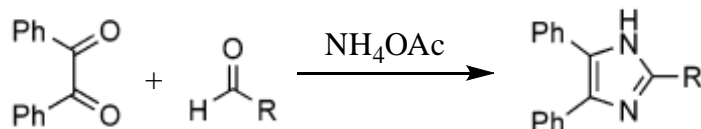
ammonium acetate should be converted to ammonia and acetic acid during the reaction. Therefore, it seems that the produced acid can catalyze the reaction. Thus, the reaction with 1: 4 mol ratio of benzil: ammonium acetate led to ~60% yield. This finding shows that the observed efficiency for the previously reported catalytic systems has been mainly due to the presence of a high molar ratio of ammonium acetate and presence of catalyst only improved the yield%. We repeated the synthesis of 2,4,5-tripheyl-1*H*-imidazole according to Joshi et al. [35]. A mixture of benzaldehyde (10 mmol), benzil (10 mmol), ammonium acetate (20 mmol), and potassium dihydrogen phosphate (5 mol %) was refluxed with stirring in ethanol for 40 min. Despite the reported yield, 93%, we obtained 32% under the same reaction conditions.

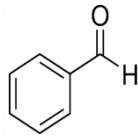
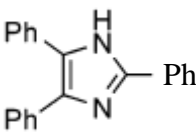
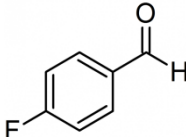
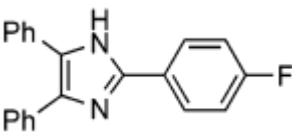
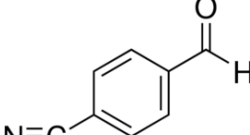
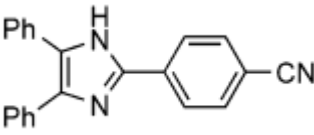
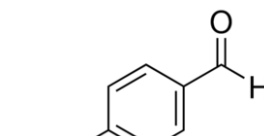
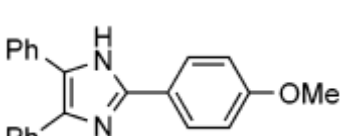
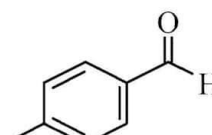
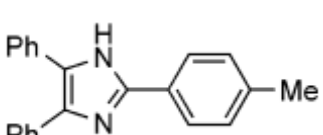
Eventually, to examine the efficiency and applicability of this protocol, the reaction was extended to other substituted aromatic

aldehydes with the new condition in the absence of catalyst and some 2,4,5-triaryl-1*H*-imidazoles are prepared, as shown in Table 3. We examined some *para*-substituted aromatic aldehydes to establish the catalytic

**TABLE 3** Synthesis of some representative 2, 4, 5-triaryl-1*H*-imidazoles in the presence of ammonium acetate

importance of this catalytic system. We found that aldehydes bearing either electron-withdrawing or electron-donating groups performed equally well in the reaction.



Aromatic aldehyde	product	Yield (%)	m.p. (°C)
		77	275-277
		68	261-263
		73	236-237
		75	227-229
		79	230-232

The reactions were carried out with aldehyde (10 mmol), benzil (10 mmol) and ammonium acetate (50 mmol) in ethanol under reflux for 40 min.

## Conclusion

In summary, this paper describes a convenient and efficient method for the synthesis of biologically active trisubstitutedimidazoles through the three-component coupling of benzil, aromatic aldehydes, and ammonium acetate, acting as both reagent and catalyst. Reaction profile is very clean and no side products are formed. All the synthesized imidazoles have been characterized based on the spectral studies. We believe that this procedure is convenient and economic, and uses an eco-friendly mediator for the synthesis of trisubstitutedimidazole. This report also illustrated the new findings on the synthesis of some 2,4,5-triaryl-1H-imidazoles in the absence of any additive as catalyst.

## Acknowledgements

Partial financial support from the Research Council of Hakim Sabzevari University is greatly appreciated.

## Orcid:

Reza Tayebee: <https://www.orcid.org/0000-0003-1211-1472>

## References

- [1] J.G. Lambardino, E.H. Wiseman, *J. Med. Chem.*, **1974**, *17*, 1182-1188.
- [2] A. Chawla, A. Sharma, A.K. Sharma, *Der Pharm. Chem.*, **2012**, *4*, 116-140.
- [3] J.C. Lee, J.T. Laydon, P.C. McDonnell, T.F. Gallagher, S. Kumar, D. Green, D. McNulty, M.J. Blumenthal, J.R. Keys, S.W.R. Vatter, J.E. Strickler, M.M. McLaughlin, I.R. Siemens, S.M. Fisher, G.P. Livi, J.R. White, J.L. Adams, P.R. Young, *Nature*, **1994**, *372*, 739-746.
- [4] L.L. Chang, K.L. Sidler, M.A. Cascieri, S. Laszlo, G. Koch, B. Li, M. Maccoss, N. Mantlo, S. Okeefe, M. Pang, A. Rolando, W.K. Hangmann, *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 2549-2553.
- [5] A.K. Takle, M.J.B. Brown, S. Davies, D.K. Dean, G. Francis, A. Gaiba, A.W. Hird, F.D. King, P.J. Lovell, A. Naylor, A.D. Reith, J.G. Steadman, D.M. Wilson, *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 378-381.
- [6] M. Antolini, A. Bozzoli, C. Ghiron, G. Kennedy, T. Rossi, A. Ursini, *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 1023-1028.
- [7] R. Schmierer, H. Mildenberger, H. Buerstell, *German Patent*, **1987**, *3*, 61464; *Chem. Abstr.*, **1988**, *108*, 37838.
- [8] M. Antolini, A. Bozzoli, C. Ghiron, G. Kennedy, T. Rossi, A. Ursini, *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 1023-1028.
- [9] J. Heeres, L.J.J. Backx, J.H. Mostmans, J. Van Custem, *J. Med. Chem.*, **1979**, *22*, 1003-1005.
- [10] T. Maier, R. Schmierer, K. Bauer, H. Bieringer, H. Buerstell, B. Sachse, *U.S. Patent* **1989**, 4820335; *Chem. Abstr.*, **1989**, *111*, 19494w.
- [11] A.R. Moosavi-Zare, H. Goudarziafshar, Z. Jalilian, *Prog. Chem. Biochem. Res.*, **2019**, *2*, 59-63.
- [12] M. Aghazadeh, *Prog. Chem. Biochem. Res.*, **2019**, *2*, 34-39.
- [13] M. Asif, I. Mohd, *Prog. Chem. Biochem. Res.*, **2019**, *2*, 192-210.
- [14] B. Maleki, S. Sedigh Ashrafi, *J. Mexican Chem. Soc.*, **2014**, *58*, 76-81.
- [15] B. Maleki, H.K. Shirvan, F. Taimazi, E. Akbarzadeh, *Inter. J. Org. Chem.*, **2012**, *2*, 93-99.
- [16] M.M. Heravi, N. Karimi, S. Pooremami, *Adv. J. Chem. A*, **2019**, *2*, 73-78.
- [17] B. Maleki, H. Keshvari, A. Mohammadi, *Orient. J. Chem. A*, **2012**, *28*, 1207-1212.
- [18] A. Mohammadi, H. Keshvari, R. Sandaroos, B. Maleki, H. Rouhi, H. Moradi, Z. Sepehr, S. Damavandi, *Appl. Catal. A: Gen.*, **2012**, *429*, 73-78.
- [19] B. Maleki, H. Eshghi, A. Khojastehnezhad, R. Tayebee, S.S. Ashrafi, G.E. Kahoo, F. Moeinpour, *RSC Advances*, **2015**, *5*, 64850-64857.
- [20] M.M. Heravi, H. Hamidi, N. Karimi, A. Amouchi, *Adv. J. Chem. A*, **2018**, *1*, 1-6.
- [21] B. Maleki, G.E. Kahoo, R. Tayebee, *Org. Prep. Proced. Int.*, **2015**, *47*, 461-472.

- [22] H. Ramshini, R. Tayebee, A. Bigi, F. Bemporad, C. Cecchi, F. Chiti, *Int. J. Mol. Sci.*, **2019**, *20*, 5558-5576.
- [23] R. Tayebee, M. FattahiAbdizadeh, N. Erfaninia, A. Amiri, M. Baghayeri, R.M. Kakhki, B. Maleki, E. Esmaili, *Appl. Organomet. Chem.*, **2019**, *33*, e4959.
- [24] R. Tayebee, A.F. Lee, L. Frattini, S. Rostami, *Catalysts*, **2019**, *9*, 409-416.
- [25] N. Erfaninia, R. Tayebee, E.L. Foletto, M.M. Amini, M. Dusek, F.M. Zonoz, *Appl. Organomet. Chem.*, **2018**, *32*, e4047.
- [26] N. Erfaninia, R. Tayebee, M. Dusek, M.M. Amini, *Appl. Organomet. Chem.*, **2018**, *32*, e4307.
- [27] R. Tayebee, A. Pejhan, H. Ramshini, B. Maleki, N. Erfaninia, Z. Tabatabaie, E. Esmaeili, *Appl. Organomet. Chem.*, **2018**, *32*, e3924.
- [28] F. Javadi, R. Tayebee, B. Bahramian, *Appl. Organomet. Chem.*, **2017**, *31*, e3779.
- [29] F. Javadi, R. Tayebee, *Iran. J. Catal.*, **2017**, *7*, 283-292.
- [30] B. Mirjalili, A. Bamoniri, N. Mohaghegh, *Curr. Chem. Lett.*, **2013**, *2*, 35-42.
- [31] J.N. Sangshetti, N.D. Kokare, S.A. Kotharkar, D.B. Shinde, *Chin. Chem. Lett.*, **2008**, *19*, 762-766.
- [32] J.N. Sangshetti, N.D. Kokare, S.A. Kotharkar, D.B. Shinde, *Monat. für Chem.-Chem. Mon.*, **2008**, *139*, 125-127.
- [33] S.D. Jadhav, N.D. Kokare, S.D. Jadhav, *J. Heterocycl. Chem.*, **2008**, *45*, 1461-1464.
- [34] K.F. Shelke, S. Sapkal, S. Sonal, B.R. Madje, B.B. Shingate, M.S. Shingare, *Bull. Kor. Chem. Soc.*, **2009**, *30*, 1057-1060.
- [35] R.S. Joshi, P.G. Mandhan, M.U. Shaikh, R.P. Kale, C.H. Gill, *Chin. Chem. Lett.*, **2010**, *21*, 429-432.

**How to cite this article:** Reza Tayebee\*, Ali Gohari. The dual role of ammonium acetate as reagent and catalyst in the synthesis of 2,4,5-triaryl-1H-imidazoles. *Eurasian Chemical Communications*, 2020, 2(5), 581-586. **Link:** [http://www.echemcom.com/article\\_101526.html](http://www.echemcom.com/article_101526.html)