MICROWAVE-INDUCED ONE-POT SYNTHESIS OF 2,4,5-TRIARYLIMIDAZOLES USING GLYOXYLIC ACID AS A CATALYST UNDER SOLVENT-FREE CONDITIONS

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ABSTRACT

A simple and highly efficient method for a three-component condensation of benzil/benzoin, aldehydes and ammonium acetate under microwave irradiation in the presence of Glyoxylic acid (CHOCOOH) in solvent-free condition to afford the corresponding 2,4,5-triarylimidazole derivatives in high yields. The remarkable advantages offered by this method are inexpensive and readily available catalyst, simple procedure, much faster (1-3 min) reactions and high yield of products.

Keywords: *Glyoxylic acid, 2,4,5-triarylimidazoles, one-pot, solvent-free, microwave irradiation.*

INTRODUCTION

The imidazole moiety is an important heterocyclic nucleus due to their widespread biological activities and use in synthetic chemistry. The substituted imidazoles are well known as inhibitors of P38MAP kinase[1] and therapeutic agents[2]. Imidazole chemistry, because of its use in ionic liquids[3] and in N-heterocyclic carbenes (NHCs)[4], gave a new dimension in the area of organometallics and ‘‘Green Chemistry’’. In addition, the imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds such as the hypnotic agent etomidate[5], and the proton pump inhibitor omeprazole[6].

Due to their great importance, many synthesis strategies have been developed. In 1882, Radziszewski and Japp reported the first synthesis of the imidazole from 1,2- dicarbonyl compound, various aldehydes and ammonia, to obtain the 2,4,5-triphenyl imidazoles[7]. Also, Grimmett and et al proposed the synthesis of the imidazole using nitriles and esters[8]. Another method is the four-component one-pot condensation of a glyoxals, aldehydes, amines and ammonium acetate in refluxing acetic acid is the most desirable convenient method[9]. Very recently, literature survey reveals several methods for synthesis of 2,4,5-triaryl imidazoles using $ZrCl_4$[10], zeolite HY/silica gel[11], $NaHSO_3$[12], sulphanilic acid[13], iodine[14], and ionic liquid[15]. However, many of these methodologies suffer from one or more disadvantages, such as low yields, high temperature requirement, prolonged reaction time, highly acidic conditions, requirement of excess of catalysts, use of solvents. Therefore, there is a strong demand for a simple, highly efficient, environmentally benign and versatile method for the one-pot synthesis of 2,4,5-triarylimidazoles derivatives.

The use of microwave for the synthesis of organic compounds under solvent-free conditions proved to be efficient, safe and environmentally benign technique, with shorter reaction time, high yields, and easier manipulation. Additionally, it can also avoid the use of hazardous and expensive solvents and can be environmentally benign to make manipulations much easier[16].

Glyoxylic acid is a strong acid with extreme wide applications such as deportation of oximes[17], Diels’s Alder reaction[18] and very recently, it is used for the synthesis of 1,2 disubstituted

benzimidazoles[19]. However, there are no example of the use of Glyoxylic acid as a catalyst for the synthesis of 2,4,5-triarylimidazoles.

In continuation of our interest in microwave-assisted synthesis[20]**,** here we wish to report a very simple, fast and general method for the synthesis of 2,4,5-triarylimidazoles (**3a-l**) without any solvent in the presence of catalytic amount of Glyoxylic acid under microwave irradiation (Scheme **1,2**).

EXPERIMENTAL

All chemicals were purchased from Merck, Aldrich and Rankem chemical companies and used without further purification. The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. The progresses of the reactions were monitored by TLC (Thin Layer Chromatography). IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on an 80 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. Microwave irradiation was carried out in a microwave oven (BPL, 800T, 2450 MHz) with power output of 800W.

General procedure for the synthesis of 2,4,5-triary-1H-imidazoles (3a-l)

A mixture of benzil/benzoin (1 mmol), aldehyde (1 mmol), ammonium acetate (2.5 mmol) and Glyoxylic acid (5 mol%) was taken in a Borosil beaker (50 mL). The reaction mixture was mixed properly with the help of glass rod and exposed in a microwave oven at the power of 180W and irradiated for a period of 10 sec at a time. After each irradiation the reaction mixture was removed from the microwave oven for shaking. The total period of microwave irradiation was 1-3 min (Table **1**). After TLC (petroleum ether: ethyl acetate = 9:1 as eluent) indicated the starting material of benzil/benzoin and aldehyde had disappeared. The reaction mixture was cooled to room temperature and poured on ice-water (50 ml), a precipitated solid was filtered through Buckner funnel, washed with water, dried and recrystallized from ethanol to get the corresponding 2,4,5-triaryl -1H-imidazoles (**3a-l).** The products (**3a-l**) were confirmed by comparisons with authentic samples, IR, ^{1}H NMR, mass spectra and melting points.

Spectral data of principal compounds

2,4,5-Triphenyl-1H-imidazole (3a)

IR (KBr): 3450 (N-H), 3050 (C-H), 1600 (C=C), 1580 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$, 80 MHz, δ, ppm): 7.15-8.00 (m, 15H, Ph), 9.20 (br s, NH). EIMS (m/z, %): 297 (M+1).

2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (3c)

IR (KBr): 3450 (N-H), 1600 (C=C), 1580 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$, 80 MHz,δ,ppm):7.10-7.60 (m, 10H, Ph), 7.35 (d, 2H, J =10 Hz, Ar), 7.85 (d, 2H, J =10 Hz, Ar). EIMS (m/z, %): 331 (M+1).

2-(4-Methylphenyl)-4,5-diphenyl-1H-imidazole (3d)

IR (KBr): 3450 (N-H), 1600 (C=C), 1585 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$,80 MHz,δ,ppm): 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). EIMS (m/z, %):311 (M+1).

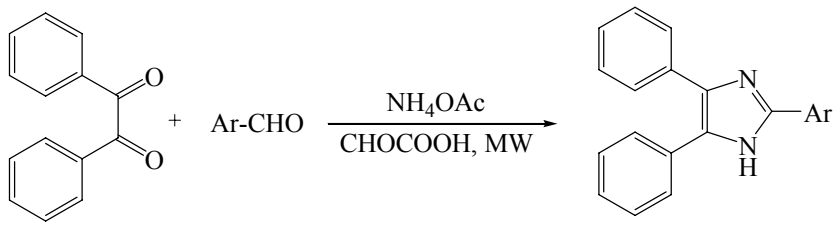
2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (3e)

IR (KBr): 3450 (N-H), 1610 (C=C), 1575 (C=N), 1385 (C-O) cm^{-1}. ^{1}H NMR ($CDCl_3$,80 MHz,δ,ppm): 3.90 (s, OCH_3), 7.05 (d, 2H, J =8.8 Hz, Ar), 7.30-7.80 (m, 10H, Ph), 7.90 (d, 2H, J =8.8 Hz, Ar). EIMS (m/z, %): 327 (M+1).

2-(4-Nitrophenyl)-4,5-diphenyl-1H-imidazole (3g)
IR (KBr): 3400 (N-H), 1580 (C=N), 1515 (NO_2), 1335 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$,80 MHz,δ,ppm): 7.15-7.70 (m, 10H, Ph), 7.90-8.25 (AB, 4H, J .9 Hz, Ar). EIMS (m/z, %): 342 (M+1).
2-(2-Furyl)-4,5-diphenyl-1H-imidazole (3k)
R (KBr): 639, 719, 874, 1169, 1210, 1660, 2470, 2993, 3316 cm-^{1}. ^1H NMR ($CDCl_3$, 200 MHz, δ, ppm): 7.21 (m, 1H, NH), 7.46–7.58 (m, 4H, Ar), 7.60–7.70 (m, 3H, Ar), 7.96–8.02 (m, 6H, Ar). EIMS (m/z, %): 287 (M+1).

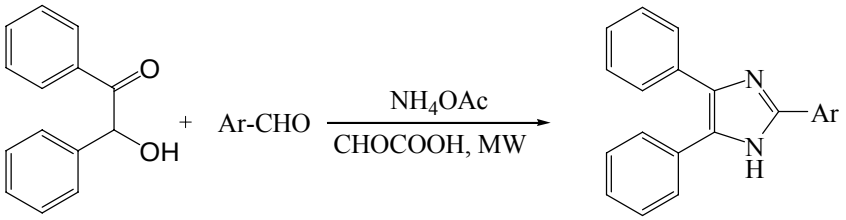
RESULT AND DISCUSSION

In order to find optimum reaction conditions, condensation of benzil, 4-chlorobenzaldehyde and ammonium acetate in the presence catalytic amount of Glyoxylic acid. The optimum molar ratio of benzil: 4-chlorobenzaldehyde: ammonium acetate is 1:1:2.5 and Glyoxylic acid (5 mol%) under solvent-free conditions using microwave irradiation and under this conditions 2-(4-chlorophenyl-4,5-diphenyl-1H-imidazole (**3c**) was obtained in 98% yield after 1.5 min (entry **3c**). We were encouraged by the results obtained with 4-chlorobenzaldehyde. In a similar fashion, a variety of aromatic and heterocyclic aldehydes and benzil/benzoin subjected to this novel procedure to gives the corresponding 2,4,5-triarylimidazole in high yields. The results are summarized in Table **1**. From the results obtained Table **1**, the aldehydes with electron-donating substituents favor the reaction and it was completed within the shorter reaction time with high yields (entry **3a, 3d**) than the aldehydes with electron-withdrawing substituents (entry **3g**). Also, the present method was found to be effective for hetero-aromatic aldehydes for the synthesis of 2-heteroaryl-4,5-diphenyl-1H-imidazoles with better yields (entry **3k,3l**). To determine the role of Glyoxylic acid, the same reaction was carried out in the absence of catalyst at same condition, which resulted in no product formation, after 20 min. These results indicate that Glyoxylic acid exhibits a high catalytic activity in this transformation. The procedure gives the products in high yields and avoids problems associated with solvent use such as cost, handling, specifically safety, because of fire hazard due to occurrence of sparks in microwave oven.
In Table **2**, we have compared our result with results obtained by some other reported procedures for the synthesis of 2-(4-nitrophenyl-4,5-diphenyl-1H-imidazole (**3g**). The data presented in this table show the promising feature of this method in terms of reaction rate and the yield of product compared with those reported in the literature.



1 **2** **3a-l**

Scheme-1: **Synthesis of 2,4,5-triaryl-1H-imdazoles using benzil (1), aldehydes (2), ammonium acetate and Glyoxylic acid as a catalyst under solvent-free conditions**



4 **2** **3a-l**

Scheme-2: Synthesis of 2,4,5-triaryl-1H-imdazoles using benzoin (4), aldehydes (2), ammonium acetate and Glyoxylic acid as a catalyst under solvent-free conditions

CONCLUSIONS

In conclusion, we have investigated that Glyoxylic acid works as an excellent catalyst for the one-pot three component and solvent-free synthesis of 2,4,5-triarylimidazoles. This method is applicable for different substrates including aromatic and heterocyclic aldehydes. The notable merits offered by this method are: the catalyst is inexpensive and readily available, simple procedure, reaction times are short, with high yields and the reaction conditions are environment friendly.

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REFERENCES

1. J. Lee, J. Laydon, P. McDonnell, T. Gallagher, S. Kumar, D. Green, D. McNulty, N. Blumenthal, J. Heys, S. Landvatter, J. Strickler, M. McLaughlin, I. Siemens, S. Fisher, J. Livi, J. White, J. Adams and P. Young, *Nature,* **372**, 739 (1994).
2. J. Heeres, L. Backx, J. Mostmans and J. Vancustem, *J. Med. Chem.,* **22**, 1003 (1979).
3. P, Wasserscheid and W. Keim, *Angew. Chem. Int. Ed. Eng.,* **39,** 3772 (2000).
4. D. Bourissou, O. Guerret, F. Gabbai and G. Bertrand, *Chem. Rev.,* **100,** 39 (2000).
5. A. Wauquier, W. Van Den Broeck, J. Verheyen and P. Janssen, *J. Eur. J. Pharmacol.,* **47,** 367(1978).
6. Y. Tanigawara, N. Aoyama, T. Kita, K. Shirakawa, F. Komada, M. Kasuga and K.Okumura, *Clin Pharmacol Ther.,* **66,** 528 (1999).
7. (a) B. Radziszewski, *Chem. Ber.,* **15,** 1493 (1882); (b) F. Japp and H. Robinson, *Chem. Ber.,* **15,** 1268 (1882).
8. M. Grimmett, A. Katritzky, C. Rees and E. Scriven, *Pergamon: NewYork,* **3,** 77 (1996).
9. B. Krieg and G. Mancke, *Naturforschg,* **226,** 132 (1967).
10. G. Sharma, Y. Jyothi and P. Lakshmi, *Syn. Comm.,* **36** 2991 (2006).
11. S. Balalaie, A. Arabanian and M. Hashtroudi, *Mont. Fur. Chemie.,* **131,** 945 (2000).
12. J. Sangshetti, N. Kokare, A. Kothakar and D. Shinde, *Mont. Fur. Chemie.,* **139,** 125 (2008).

Table-1: Microwave-induced Glyoxylic acid catalyzed one-pot synthesis of 2,4,5-triarylimidazole derivatives under solvent-free conditions

Entry	Ar-CHO	Reaction time(min)		Yield (%)[a]		M.P. (^{0}C)	
		Benzil	Benzoin	Benzil	Benzoin	Found	Lit.
3a	C_6H_5	1	1.5	98	96	274-276	276-277[11]
3b	2-ClC_6H_4	1.5	2	97	94	195-196	195-196[12]
3c	4-ClC_6H_4	1.5	2	98	95	258-260	260-262[12]
3d	4-MeC_6H_4	2	2.5	97	93	230-232	231-232[11]
3e	4-$OMeC_6H_4$	1	2	96	93	227-228	228-230[11]
3f	3,4-$(OMe)_2C_6H_3$	2	2.5	95	91	220-221	220-221[11]
3g	4-$NO_2C_6H_4$	2	3	97	93	230-232	232-233[12]
3h	4-$N(Me)_2C_6H_4$	2	2	95	90	257-258	257-258[11]
3i	4-OHC_6H_4	2	2.5	96	92	268-269	268-270[12]
3j	4-FC_6H_4	1	2	97	95	190-191	190[10]
3k	2-furyl	2	2.5	97	93	199-200	199-201[12]
3l	2-thienyl	2	2.5	96	92	259-260	260-261[14]

[a]All yield are of isolated products

Table-2: Comparisons of some other reported procedures with the present method for the synthesis of 2-(4-nitrophenyl-4,5-diphenyl-1H-imidazole (Table 1,entry 3g)

Entry[a]	[Lit.]	Catalyst	Solvent	Reaction condition	Time	Yield (%)[b]
1	Present	Glyoxylic acid	-	MW	2min	97
2	[10]	$ZrCl_4$	CH_3CN	r.t., stirring	7 h	89
3	[11]	Zeolite/silica gel	-	MW	6min	94/89
4	[12]	$NaHSO_3$	EtOH:H_2O	80^{0}C	40min	90
5	[13]	Sulphanilic acid	EtOH:H_2O	80^{0}C	70min	87

[a]All reactions carried out in benzil:4-nitrobenzaldehyde:ammonium acetate (1:1:2.5) under different reaction conditions

[b]All yield are of isolated products

13. A. Mohammed, N. Kokare, J. Sangshetti and D. Shinde, *J. Korean Chem. Soci.,* **51,** 418 (2007).
14. M. Kidwai, P. Mothsra, V. Bansal and R. Goyal, *Mont. Fur. Chemie.,* **137,** 1189 (2006).
15. S. Siddiqui, U. Narkhede, S. Palimkar, T. Daniel, R. Lahoti and K. Srinivasan, *Tetrahedron,* **61,** 3539 (2005).
16. (a) S. Caddick, *Tetrahedron Let.,* **51,** 10403 (1995); (b) A. Katritzky, K. Sandeep, *Arkivoc,* **xiii,** 68 (2003); (c) C. Khour, C. Darth, A. Lalnger and M. Daves, *J. Catal.,* **149,** 195 (1994).
17. S. Chavan and P.Soni, *Tetrahedron Lett*., **45**, 3161 (2004).
18. A.Jacques and L. Nadege, *J.Chem. edu.,* **75**, 1285 (1998).
19. S.Pawar, V. Dekhane, M. Shingare and S. Thore, *Chin. Chem. Lett.,* **19**, 1055 (2008).
20. (a) B. Karale, V. Chavan, A. Mane, R. Hangarge, C. Gill and M. Shingare, *Syn. Comm.,* **32,** 497 (2002).; (b) B. Madje, S. Shindalkar, M. Ware and M. Shingare, *Chem: An Ind. J.,* **2,** 95 (2005); (c) S. Shindalkar, B. Madje and M. Shingare, *Mendeleev Commun.,* **17,** 43 (2007); (d) K. Shelke, V. Markhele, A. Kategaonkar and M. Shingare, *Bulle. Cata. Soc. Ind.,* **6,** 136 (2007).

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Delight at having understood a very abstract and obscure system leads most people to believe in the truth of what it demonstrates.
-Georg C. Lichtenberg