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ORIGINAL ARTICLE

Glycerol as a green solvent for efficient, one-pot and catalyst free synthesis of 2,4,5-triaryl and 1,2,4,5-tetraaryl imidazole derivatives

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Abstract A simple, efficient and catalyst-free method has been developed for the synthesis of 2,4,5-triaryl and 1,2,4,5-tetraaryl imidazole derivatives in glycerol as green solvent at 90 °C. It is noteworthy that in this protocol the yields of products were comparable to or better than, those in conventional media. The use of green reaction media makes this methodology simple, safe and cost-effective.

1. Introduction

The imidazole scaffold is an important heterocyclic nucleus due to its wide spectrum of applications in the field of biology, chemistry as well as in pharmaceutical products. It is found in a large number of pharmacologically active compounds such as Omeprazole (Lindberg et al., 1986), Pimobendan (Mannhold, 1985), Cimetidine and lansoprazole (Beggs et al., 1981; Delgado et al., 1998). Moreover, many of the substituted diaryl imidazoles are known as inhibitors of P38 MAP kinase, fungicides, herbicides and plant growth regulators (Schmierer et al., 1988). Recent advances in green chemistry and organometallic catalysis have extended the application of imidazoles as ionic liquids and *N*-heterocyclic carbenes (Balalaei and Arabanian, 2000; Keim, 2000; Hermann et al., 1997; Hang et al., 1999).

Several methods are reported in the literature for the synthesis of 2,4,5-triaryl-1H-imidazoles and 1,2,4,5-tetraaryl-1H-imidazoles by condensation of benzil/benzoin with a wide variety of aldehydes, aromatic primary amines and ammonium acetate using different catalysts such as N-methyl-2-pyrrolidonium hydrogen sulfate (Shaterian and Ranjbar, 2011), nano-$TiCl_4$–SiO_2 (Mirjalili et al., 2012), zeolite HY/silica gel (Sivakumar et al., 2010), cellulose supported sulfuric acid (Shelke et al., 2010), $NiCl_2{\cdot}6H_2O$ (Heravi et al., 2007), ultrasonic irradiation (Zang et al., 2010), cyclic phosphoric acid (Wang et al., 2012), potassium dihydrogen phosphate (Joshi et al., 2010), Amberlyst A-15 (Sangshetti et al., 2008), L-proline (Samai et al., 2009) and PEG-400 (Wang et al., 2009). Given these proven applications in the field of medicinal, biological and synthetic organic chemistry, there has been tremendous interest in developing an efficient method for the synthesis of imidazoles.

Recently, the trend toward "green chemistry" has gone in to reduce the use of toxic and corrosive reagents and stop the formation of inorganic waste (Sheldon, 1997; Muzart,

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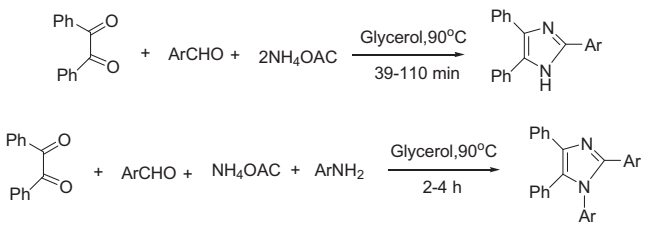
1992). However, it has also been observed that the catalysts employed are not always ecofriendly and because of this, serious environmental pollution often results. Therefore, the design of catalyst-free reactions is a crucial goal for chemists (Anastas and Williamson, 1996). In this regard, the use of glycerol as a promising medium for organic reaction was recently demonstrated (Wolfson et al., 2009; Perin et al., 2010; Radatz et al., 2011; Nandre et al., 2010; Bachhav et al., 2011). Glycerol due to its unique combination of physical and chemical properties such as polarity, low toxicity and flammability, high boiling point, ability to form strong hydrogen bonds and to dissolve both organic and inorganic compounds, and easy availability has recently emerged as a green solvent in organic synthesis. According to our interest in the green protocols (Nemati and Kiani, 2011), we describe in this study the use of glycerol as green solvent in the catalyst-free synthesis of 2,4,5-triaryl-1H-imidazoles and 1,2,4,5-tetraaryl-1H-imidazoles by one-pot condensation of benzil with a wide variety of aldehydes, aromatic primary amines and ammonium acetate.

2. Results and discussion

As a part of our program to find improved synthetic routes for the preparation of organic compounds (Nemati and Kiani, 2011; Nemati et al., 2011; Nemati and Elhampour, 2012; Nemati et al., 2012), herein we would like to report our investigation into a environmental friendly and highly efficient procedure for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles. This transformation was carried out without a catalyst only in glycerol as a green reaction medium at 90 °C (Scheme 1). To the best of our knowledge the synthesis of imidazoles in glycerol to accomplish such transformation has not been reported in the literature.

In order to investigate the feasibility of the strategy, we selected the one-pot reaction of benzil (1 mmol), benzaldehyde (1 mmol) and ammonium acetate (2 mmol) as a simple model substrate. Different solvents like methanol, ethanol, acetonitrile, DMF and PEG-400 were screened in the catalyst-free model reaction. As could be seen in Table 1, glycerol at room temperature helped obtain the desired product in 52% yield. To increase the yield of the reaction, the same reaction was conducted at different reaction temperatures. It was observed that an optimum yield was obtained in glycerol at 90 °C (Table 1, entry 8). No significant improvement in the yield was obtained beyond that point, so 90 °C was chosen as the reaction temperature for all further studies.

Having these optimal conditions in hand, a number of 2,4,5-trisubstituted imidazoles were synthesized and the results are represented in Table 2. Commercially available aromatic aldehydes bearing electron-withdrawing groups (Table 3, entries 2, 3, 6, 7, 8, 10, 12, 14), electron-donating groups (Table 3, entries 4, 5, 9, 11, 13), heteroaromatic aldehyde (Table 3, entry 15) and high steric hindrance aldehyde (Table 3, entry 16) were all found to be suitable for the reaction and did not show any remarkable difference in the yield of product and duration of the reactions (Table 3). However, aliphatic aldehydes were unable to provide the desired product in an acceptable yield.



Scheme 1 Synthesis of 2,4,5-triaryl and 1,2,4,5-tetra aryl-1H-imidazoles.

Next, in order to explore the applicability of this methodology, we have applied the same reaction conditions for the four-component one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles by condensing benzil (1 mmol), arylaldehydes (1 mmol), aromatic amines (1 mmol) and ammonium acetate (1 mmol) in 6 mL of glycerol at 90 °C. The results are illustrated in Table 4. The yields were good to excellent. Reaction profile is very clean without the formation of any side products such as oxidized products of anilines and aldehydes, which are observed under the influence of acid catalysts.

The role of glycerol in this multi component reaction was established by the fact that in the absence of glycerol, the reaction proceeded sluggishly (Table 1, entry 10). Obviously, glycerol is an essential component of the reaction. In addition, as shown in Table 1 (entries 1 and 2), the reaction did proceed in reflux EtOH or MeOH as protic solvents, but the yield was low even after 5 h. The poor yields in hydroxylic and polar solvents are probably due to the lower solubility of the starting materials in these solvents, coupled with the fact that ammonium acetate is solvated in hydroxylic solvents, thereby reducing its effective reactivity with ammonia. We suggest that the hydrogen of the hydroxyl group of glycerol through the formation of powerful hydrogen bonding activated the carbonyl compounds, while the oxygen of the hydroxyl group of glycerol formed a hydrogen bond with the hydrogen of amine, which makes the N–H bond weaker enhancing the nucleophilicity of nitrogen for addition to the carbonyl group of aldehyde (Scheme 2a). Increasing the reaction temperature has decreased the yield of the products, because the hydrogen bonds have been weak (Table 1, entry 9).

To establish the plausible mechanism, the reaction of benzaldehyde with equimolar 4-methylaniline was performed under the reaction condition, and the imine was isolated as the intermediate of this reaction [^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.44 (s, 1H), 7.90–7.84 (m, 2H), 7.39 (m, 3H), 7.25–7.12 (m, 4H), 2.34 (s, 3H)] (Tang et al., 2012). Then, it was reacted with ammonium acetate and benzil to yield the expected tetra substituted imidazole (Scheme 2b).

Table 4 compares the efficiency of our method for the synthesis of 2,4,5-triphenyl-1H-imidazole with other published works. Each of these methods has its own advantages, but some of them often suffer from disadvantages such as use of organic solvents (entries 1 and 3), long reaction times (entries 4 and 7) and employment of catalyst or reagent (entry 6), so the present method could be economical than the other methods.

3. Experimental

Chemicals were purchased from the Fluka, Merck and Aldrich chemical companies. Melting points were determined on Electro thermal 9100 without further corrections. TLC on commercial aluminum-backed plates of silica gel 60 F254 was

Table 1 Reaction conditions evaluation for imidazole synthesis.

Entry	Solvent	Condition (°C)	Time	Yield (%)
1	MeOH	63	5 h	25
2	EtOH	75	5 h	47
3	Acetonitrile	78	5 h	40
4	DMF	110	5 h	43
5	PEG-400	120	1.5 h	88 (Wang et al., 2009)
6	Glycerol	RT	1.5 h	52
7	Glycerol	70	1.5 h	69
8	Glycerol	90	43 min	94
9	Glycerol	110	43 min	83
10	Solvent-free	90	43 min	Trace

Table 2 Catalyst-free synthesis of 2,4,5-trisubstituted imidazoles in glycerol at 90 °C.

Entry	Ar–CHO	Time (min)	Yield (%)[a]	Mp (Lit.) °C
1	Ph	43	94	267–269 (267–269) (Samai et al., 2009)
2	4-Br–C_6H_4	62	96	267–268 (261–263) (Wang et al., 2009)
3	3-Br–C_6H_4	63	91	> 300
4	4-MeO–C_6H_4	81	93	220–222 (220–223) (Samai et al., 2009)
5	2-MeO–C_6H_4	50	93	213–214 (210–211) (Samai et al., 2009)
6	2-NO_2–C_6H_4	60	96	233–235 (230–231) (Samai et al., 2009)
7	3-NO_2–C_6H_4	51	96	319–321 (> 300) (Samai et al., 2009)
8	4-NO_2–C_6H_4	88	92	236–238 (235–238) (Heravi et al., 2007)
9	4-Me–C_6H_4	42	94	236–238 (233–235) (Samai et al., 2009)
10	2-Cl–C_6H_4	108	87	192–193 (190–191) (Samai et al., 2009)
11	2-OH–C_6H_4	30	81	204–205 (202–205) (Samai et al., 2009)
12	4-F–C_6H_4	39	89	190–191 (189–191) (Shaterian and Ranjbar, 2011)
13	3-OEt-4-OH–C_6H_3	79	93	268–269
14	4-CO_2H–C_6H_4	53	92	> 300
15	2-Thiophen	110	89	260–261 (260–261) (Shaterian and Ranjbar, 2011)
16	2-Naphthyl	80	90	241–243 (241–242) (Shaterian and Ranjbar, 2011)

[a] The products were characterized from their spectral data especially IR, ^{1}H NMR or mp by comparison with reported samples and the yields refer to isolated products.

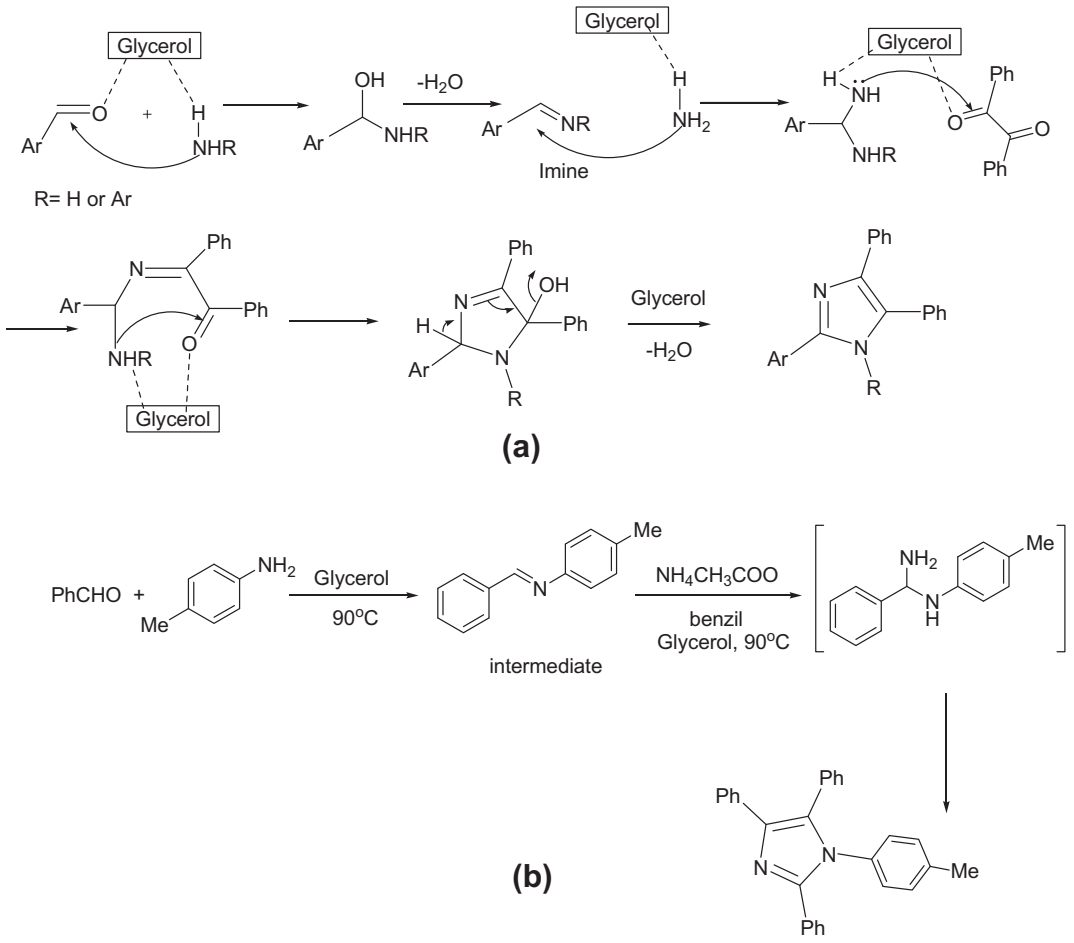
Table 3 Catalyst-free synthesis of 1,2,4,5-tetrasubstituted imidazoles in glycerol at 90 °C.

Entry	Ar–CHO	Ar–NH_2	Time(h)	Yield (%)	Mp (Lit.) °C
1	Ph	Ph	3	96	218–219 (220–221) (Shaterian and Ranjbar, 2011)
2	4-MeO–C_6H_4	Ph	3	91	185–188 (183–185) (Wang et al., 2012)
3	3-OEt-4-OH–C_6H_3	Ph	3.15	95	206–207
4	Ph	4-Cl–C_6H_4	4	91	190–193
5	Ph	4-Me–C_6H_4	2.4	92	173–175
6	3-OEt-4-OH–C_6H_3	4-Me–C_6H_4	2.15	93	199–201

Table 4 Comparison of results using glycerol with results of other works for synthesis of 2,4,5-triphenyl-1H-imidazole.

Entry	Reagents	Conditions	Time (min)	Yield (%)	Ref.
1	Ionic liquid/EtOH	Ultrasonic/rt	45	87	(Zang et al., 2010)
2	–	PEG-400/110 °C	90	88	(Wang et al., 2009)
3	KH_2PO_4	EtOH/Reflux	40	93	(Joshi et al., 2010)
4	L-Proline	MeOH/60 °C	540	78	(Samai et al., 2009)
5	$Cu(NO_3)_2$–Zeolite	Solvent free/80 °C	30	96	(Sivakumar et al., 2010)
6	Amberlyst A-15	MW	15	87	(Sangshetti et al., 2008)
7	SSA[a]	Water/Reflux	240	70	(Shaabani and Rahmati, 2006)
8	–	Glycerol/90 °C	43	94	This work

[a] Silica sulfuric acid.



Scheme 2 The proposed mechanism.

used to monitor the progress of reactions. Infrared spectra were recorded on a Shimadzu 8400s spectrometer with KBr plates. Only representative absorptions are given. NMR spectra were taken in $CDCl_3$ on a Bruker Avance 3–400 MHz instrument at 20–25 °C.

3.1. Typical procedure for the synthesis of 2,4,5-triphenyl-1H-imidazole

A mixture of benzil (0.21, 1 mmol), benzaldehyde (0.154 g, 1.1 mmol) and NH_4OAc (0.154, 2 mmol) was poured into 6 ml of glycerol, and stirred at 90 °C for the appropriate time under ambient conditions (Table 2). After completion of the reaction (monitored by TLC) the reaction mixture was poured into water. The separated solid was filtered and the product was crystallized with ethanol or 2-propanol to afford the pure product. The yield was 0.27 g (94%), m.p. 267–269 °C (Ref. Muzart, 1992 m.p. 267–269 °C).

3.2. Glycerol could be recycled according to this procedure

After the completion of the reaction, the reaction mixture was extracted with n-hexane and the retained glycerol phase was reused. The hexane layer was washed with water (2 mL) and dried over $MgSO_4$. The organic solvent was removed under reduced pressure to give the crude product. Crystallization from EtOH or 2-propanol provided the pure product.

Other products were characterized by comparison of their spectral (IR, ^{1}H NMR), TLC and melting point data with authentic samples.

The spectral (IR, ^{1}H NMR, ^{13}C NMR) and analytical data of new compounds:

2-(3-Bromophenyl)-4,5-diphenyl-1H-imidazole (entry 3, Table 2): m.p. > 300 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23–7.59 (m, 12H), 8.1 (d, J = 7.6 Hz, 1H), 8.30 (s, 1H), 12.97 (s, br); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 123.33, 126.41, 127.00, 127.45, 125.52, 129.30, 129.97, 133.11, 131.42, 131.64, 132.97, 146.36; IR (KBr) v: 3031, 2962, 1581, 1134 cm^{-1}; Anal. calcd for $C_{21}H_{15}N_2Br$: C 67.21, H 4.00, N 7.46; found: C 67.17, H 4.15, N 7.39.

2-Ethoxy-4-(4,5-diphenyl-1H-imidazol-2-yl)phenol (entry 13, Table 2): m.p. 268–269 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.39 (t, J = 7.2 Hz, 3H), 4.11 (q, J = 6.8 Hz, 2H), 6.87 (d, J = 8.4 Hz, 1H), 7.22–7.55 (m, 11H), 7.63 (d, J = 1.6 Hz, 1H), 9.23 (s, br), 12.43 (s, br); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 14.81, 64.01, 112.51, 114.03, 122.55, 126.52, 127.04, 127.94, 128.15, 128.24, 128.30, 129.99, 130.84, 131.26, 134.56, 138.19, 145.27, 146.05, 147.21; IR (KBr) v: 3224 (br.), 1589, 1473, 1180 cm^{-1}; Anal. calcd for $C_{23}H_{20}N_2O_2$: C 77.52, H 5.61, N 7.86; found: C 77.55, H 5.68, N 7.81.

4-(4,5-diphenyl-1H-imidazol-2-yl)benzoic acid (entry 14, Table 2): m.p. >300 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35–7.54 (m, 5H), 8.05 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 12.97 (s, br); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 125.50, 127.62, 128.95, 130.00, 130.09, 130.32, 130.40, 134.52, 144.85, 167.45; IR (KBr) v: 3400–2545 (br.), 1689, 1434, 1180 cm^{-1}; Anal. calcd for $C_{22}H_{16}N_2O_2$: C 77.64, H 4.70, N 8.23; found: C 77.59, H 4.75, N 8.19.

2-Ethoxy-4-(1,4,5-triphenyl-1H-imidazol-2-yl)phenol (entry 3, Table 3) m.p. 206–207 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (dd, J = 7.8 Hz, J = 1.2 Hz, 2H), 7.31–7.19 (m, 7H), 7.16–7.066 (m, 4H), 7.02 (d, J = 1.6 Hz, 1H), 6.88 (dd, J = 82 Hz, J = 1.6 Hz), 6.78 (d, J = 8.4 Hz, 1H), 5.85 (s, br, 0.85 H), 3.92 (q, J = 6.8 Hz, 2H), 1.36 (t, J = 6.8 Hz, 3H); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 14.57, 64.36, 112.36, 114.03, 122.36, 122.57, 126.58, 127.44, 127.84, 128.05, 128.14, 128.22, 129.31, 130.75, 130.84, 131.61, 133.56, 134.31, 137.83, 138.10, 145.74, 146.01, 147.0; IR (KBr) v: 3517, 1596, 1496, 1272 cm^{-1}; Anal. calcd for $C_{29}H_{24}N_2O_2$: C 80.55, H 5.55, N 6.48; found: C 80.61, H 5.49, N 6.42.

1-(4-chlorophenyl)-2,4,5-triphenyl-1H-imidazole (entry 4, Table 3) m.p. 190–193 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, J = 7.2 Hz, 2H), 7.55–7.24 (m, 13H), 7.15 (dd, J = 7.6 Hz, J = 1.2 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 123.31, 123.74, 127.49, 127.53, 128.11, 128.91, 129.24, 129.31, 129.82, 130.64, 131.97, 133.15, 133.76, 135.53, 144.92; IR (KBr) v: 3035, 1596, 1396, 1087 cm^{-1}; Anal. calcd for $C_{27}H_{19}N_2Cl$: C 79.70, H 4.67, N 6.88; found: C 79.63, H 4.61, N 6.92.

2,4,5-Triphenyl-1-p-tolyl-1H-imidazole (entry 5, Table 3) m.p. 173–175 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 8 Hz, 2H), 7.49–7.36 (m, 6H), 7.30–7.08 (m, 8H), 2.31 (s, 3H); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 24.1, 121.31, 123.45, 127.32, 127.54, 127.81, 128.45, 129.32, 129.46, 129.53, 130.02, 130.71, 131.89, 133.09, 133.21, 134.45, 137.94, IR (KBr) v: 3031, 1512, 1396 cm^{-1}; Anal. calcd for $C_{28}H_{22}N_2$: C 87.04, H 5.69, N 7.25; found: C 86.99, H 5.63, N 7.31.

2-Ethoxy-4-(4,5-diphenyl-1-p-tolyl-1H-imidazol-2-yl)phenol (entry 6, Table 3): m.p. 199–201 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (t, J = 6.8 Hz, 3H), 2.34 (s, 3H), 3.94 (q, J = 6.8 Hz, 2H), 5.91 (s, br, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.87 (dd, J = 8.2 Hz, J = 1.6 Hz, 1H), 6.95 (d, J = 9.6 Hz, 2H), 7.04–7.19 (m, 5H), 7.22–7.29 (m, 5H), 7.61 (d, J = 7.6 Hz, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.82, 21.16, 64.31, 112.57, 114.03, 122.36, 122.70, 126.52, 127.44, 127.84, 128.15, 128.24, 128.32, 129.71, 130.55, 130.84, 131.16, 134.56, 134.74, 137.83, 138.10, 145.31, 146.00, 147.05; IR (KBr) v: 3525, 3047, 2977, 1596, 1188 cm^{-1}; Anal. calcd for $C_{30}H_{26}N_2O_2$: C 80.71, H 5.82, N 6.27; found: C 80.69, H 5.85, N 6.31.

4. Conclusion

In conclusion, we have developed a green and efficient multi component reaction of benzil, arylaldehydes and ammonium acetate or primary aromatic amines for the synthesis of trisubstituted and tetrasubstituted imidazole derivatives under catalyst-free conditions in glycerol at 90 °C. The present reaction showed the following salient characteristics: (1) avoiding the use of any catalyst, (2) suitable reaction rates which enable the reaction to be completed within 40–110 min for trisubstituted imidazoles and 2–4 h for tetrasubstituted imidazoles, (3) convenient workup requiring only simple filtration since the products precipitate upon dilution of the reaction mixture with water. Further investigation into the application of glycerol for other reactions is underway in our laboratory.

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