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Research Article

Efficient Improved Synthesis of 2-Aryl-4,5-diphenylimidazole by Heating

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ABSTRACT

The synthesis of 2-aryl-4,5-diphenylimidazole via the condensation of various aromatic aldehydes, benzil and ammonium acetate in the presence of acetic acid was carried out in 86-95% yields by heating at 140 °C. This method provides several advantages such as simple operation, short reaction time, and high yields.

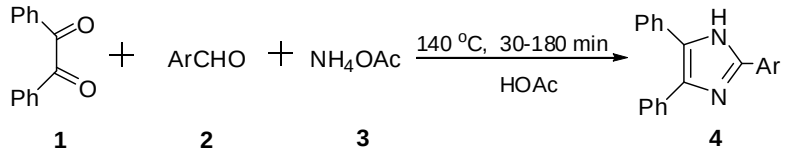
Keywords: 2-Aryl-4,5-diphenylimidazole, Synthesis, Catalysis, Heating, Condensation.

INTRODUCTION

Triarylimidazole derivatives have many biological activities, such as herbicidal[1], fungicidal[2], and anti-inflammatory activities[3]. Besides, they are also used in photography as photosensitive compounds[4]. Due to these properties, the synthesis of imidazole derivatives is still an interesting area in organic synthesis.

Over the years, numerous methods for the synthesis of 2-aryl-4,5-diphenylimidazole have been reported. Synthesis of these compounds *via* three-component condensation of 1,2-diketone, aromatic aldehyde and ammonium acetate can be catalyzed by various catalysts, such as HOAc[5], glyoxylic acid[6], oxalic acid[7], ionic liquids[8], Ytterbium triflate [9] , Ytterbium perfluorooctanesulfonate [10], $InCl_3{\cdot}3H_2O$[11], silica sulfuric acid [12], cellulose sulfuric acid[13] and ceric (IV) ammonium nitrate[14].The three-component condensation of 1,2-diketone, aromatic aldehyde and ammonium acetate can also be completed under microwave[5d, 6, 13, 15] or ultrasound irradiation[14]. Among them, the use of HOAc as the solvent or catalyst is early approach, in which the reaction is carried out under reflux and N_2 atmosphere. The condensation requires long reaction times (1.5–10 h), has low yields, and suffers from tedious and time-consuming workup[5d].

Herein, we wish to report an efficient method for synthesis of 2-aryl-4,5-diphenylimidazole via one-pot condensation of benzil, various aromatic aldehydes and ammonium acetate in the presence of acetic acid by heating at 140 °C (**Scheme 1**).



Scheme 1: Synthesis of 2-aryl-4,5-diphenylimidazole

MATERIALS AND METHODS

Benzil was prepared according to literature[16]. Melting points were uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 600 spectrometer using TMS as internal standard and DMSO-d_6 as solvent. MS were determined on an Agilent Technologies 6310 Lon Trap LC/MS.

General procedure: A 5 mL round-bottomed flask was charged with a mixture of benzil (**1**, 1 mmol), aromatic aldehydes (**2**, 1 mmol), ammonium acetate (**3**, 3 mmol) and HOAc (0.5 mL). The mixture was heated at 140 ^{o}C in oil bath for the appropriate time as indicated in Table 2. The reaction was followed by TLC. After completion of the reaction, the reaction mixture was diluted with water (2 mL). The solid imidazole products were filtered, washed with water and then recrystallized from ethanol to afford pure imidazole.

The authenticity of the products was established by their MS, ^{1}H NMR, ^{13}C NMR and their melting points compared with that reported in literatures.

2,4,5-Triphenyl-1*H*-imidazole (**4a**) , white solid; m.p.276-277 ^{o}C; m/z (ESI): 297 $[M+H]^+$; ^{1}H NMR δ: 7.32-8.10 (m, 15H, Ph-H), 12.10 (s, 1H, N-H); ^{13}C NMR δ: 125.7, 127.0, 127.6, 128.3, 128.6, 128.7, 128.9, 129.1, 129.2, 130.8, 131.5, 135.6, 137.6, 145.8.

2-(2-Nitro-phenyl)-4,5-diphenyl-1*H*-imidazole (**4b**), brown solid; m.p.231-232 ^{o}C; m/z (ESI): 342 $[M+H]^+$; ^{1}H NMR δ: 7.25-8.01 (m, 14H, Ph-H), 12.98 (s, 1H, N-H); ^{13}C NMR δ: 123.9, 124.5, 127.2, 127.5, 128.5, 128.7, 129.1, 129.2, 130.0, 130.3, 131.0, 132.6, 135.2, 138.0, 141.4, 148.8.

2-(3-Nitro-phenyl)-4,5-diphenyl-1*H*-imidazole (**4c**), yellow solid; m.p.318 ^{o}C; m/z (ESI): 342 $[M+H]^+$; ^{1}H NMR δ: 7.26-8.96 (m, 14H, Ph-H), 13.11 (s, 1H, N-H); ^{13}C NMR δ: 127.3, 127.6, 128.6, 128.7, 128.9, 129.2, 129.6, 130.9, 131.1, 131.7, 132.2, 135.2, 138.2, 143.7, 148.8.

2-(4-Nitro-phenyl)-4,5-diphenyl-1*H*-imidazole (**4d**), brown solid; m.p.236-238 ^{o}C; m/z (ESI): 342 $[M+H]^+$; ^{1}H NMR δ: 7.27-8.37 (m, 14H, Ph-H), 13.15 (s, 1H, N-H); ^{13}C NMR δ: 124.7, 126.2, 127.4, 127.6, 128.8, 129.0, 129.2, 130.4, 135.1 136.5, 138.9, 143.7, 147.1.

2-(2,4-Dichloro-phenyl)-4,5-diphenyl-1*H*-imidazol e (**4e**), white solid; m.p.176-177 ^{o}C; m/z (ESI): 365 $[M+H]^+$; ^{1}H NMR δ: 7.24-7.85 (m, 13H, Ph-H), 12.73 (s, 1H, N-H); ^{13}C NMR δ: 127.1, 127.6, 127.9, 128.3, 128.7, 129.2, 129.3, 130.2, 131.2, 132.9, 133.1, 134.3, 135.4, 137.6, 142.7.

2-(3,4-Dichloro-phenyl)-4,5-diphenyl-1*H*-imidazol e (**4f**), light yellow solid; m.p.255-256 ^{o}C; m/z (ESI): 365 $[M+H]^+$; ^{1}H NMR δ: 7.24-7.55 (m, 13H, Ph-H), 12.89 (s, 1H, N-H); ^{13}C NMR δ: 125.1, 126.5, 126.7, 127.1, 128.0, 128.2, 128.3, 128.7, 129.0, 130.4, 130.7, 130.8, 131.0, 131.6, 134.8, 137.6, 143.1.

2-(3,4-Methylenedioxy-phenyl)-4,5-diphenyl-1*H*-i midazole (**4g**), white solid; m.p.252-253 ^{o}C ; m/z (ESI): 341 $[M+H]^+$; ^{1}H NMR δ: 6.09 (s, 2H, CH_2), 7.03-7.64 (m, 13H, Ph-H), 12.52 (s, 1H, N-H); ^{13}C NMR δ: 101.7, 106.0, 109.0, 119.8, 125.0, 127.0, 127.5, 128.2, 128.6, 128.8, 129.1, 131.5, 135.6, 137.3, 145.7, 147.9, 148.1.

2-(2-Hydroxyl-3-methoxyl-phenyl)-4,5-diphenyl-1 *H*-imidazole (**4h**), white solid; m.p.191-192 ^{o}C; m/z (ESI): 343 $[M+H]^+$; ^{1}H NMR δ: 3.82 (s, 3H, CH_3), 6.87-7.67 (m, 13H, Ph-H), 8.31 (s, 1H, O-H), 13.05 (s, 1H, N-H); ^{13}C NMR δ: 55.7, 112.8, 116.7, 118.4, 126.7, 127.0, 127.2, 128.3, 128.5, 128.8, 130.2, 133.6, 134.0, 146.0, 146.9, 148.4.

2-(4-Hydroxyl-3-methoxyl-phenyl)-4,5-diphenyl-1 *H*-imidazole (**4i**), white solid; m.p.255-256 ^{o}C; m/z

(ESI): 343 $[M+H]^+$; ^1H NMR δ: 3.82 (s, 3H, CH_3), 6.87-7.64 (m, 13H, Ph-H), 8.31 (s, 1H, O-H), 13.04 (s, 1H, N-H); ^{13}C NMR δ: 55.7, 112.8, 112.9, 116.7, 118.4, 126.7, 127.0, 127.2, 128.3, 128.5, 128.7, 128.8, 130.2, 133.6, 134.0, 146.0, 146.9, 148.4.

2-(2-Chloro-phenyl)-4,5-diphenyl-1*H*-imidazole (**4j**), white solid; m.p.197-198 ^oC; m/z (ESI): 331 $[M+H]^+$; ^1H NMR δ: 7.28-7.86 (m, 14H, Ph-H), 12.70 (s, 1H, N-H); ^{13}C NMR δ: 127.1, 127.6, 127.7, 128.2, 128.4, 128.7, 129.2, 130.4, 130.7, 131.3, 132.0, 132.1, 135.5, 137.4, 143.7.

2-(4-Chloro-phenyl)-4,5-diphenyl-1*H*-imidazole (**4k**), white solid; m.p.262-263 ^oC; m/z (ESI): 331 $[M+H]^+$; ^1H NMR δ: 7.24-8.12 (m, 14H, Ph-H), 12.79 (s, 1H, N-H); ^{13}C NMR δ: 127.1, 127.3, 127.6, 128.4, 128.7, 129.1, 129.2, 129.6, 131.3, 133.2, 135.4, 137.8, 144.8.

2-(4-Hydroxy-phenyl)-4,5-diphenyl-1*H*-imidazole (**4l**), white solid; m.p.266-267 ^oC; m/z (ESI): 313 $[M+H]^+$; ^1H NMR δ: 6.86-7.92 (m, 14H, Ph-H), 9.74 (s, 1H, O-H), 12.43 (s, 1H, N-H); ^{13}C NMR δ: 115.8, 115.9, 122.1, 126.8, 127.3, 127.5, 127.7, 127.8, 128.0, 128.6, 128.8, 129.1, 131.7, 131.8, 135.9, 137.1, 146.4, 146.5, 158.1, 158.3.

2-(4-Dimethylamino-phenyl)-4,5-diphenyl-1*H*-imidazole (**4m**), brown solid; m.p.255-256 ^oC; m/z (ESI): 340 $[M+H]^+$; ^1H NMR δ: 2.96 (s, 6H, $2CH_3$), 6.79-7.92 (m, 14H, Ph-H), 12.32 (s, 1H, N-H); ^{13}C NMR δ: 39.5, 39.6, 111.9, 118.3, 126.3, 127.0, 127.4, 128.1, 128.2, 128.5, 131.4, 135.6, 136.5, 146.5, 150.2.

2-(4-Methoxy-phenyl)-4,5-diphenyl-1*H*-imidazole (**4n**), white solid; m.p.231-232 ^oC; m/z (ESI): 327 $[M+H]^+$; ^1H NMR δ: 3.82 (s, 3H, CH_3), 7.04-8.04 (m, 14H, Ph-H), 12.52 (s, 1H, N-H); ^{13}C NMR δ: 55.2, 114.1, 123.1, 126.4, 126.7, 127.0, 127.6, 128.1, 128.3, 128.6, 131.2, 135.3, 136.8, 145.6, 159.4.

RESULTS AND DISCUSSION

In order to improve the yield, the effects of the molar ratio on the condensation of 4-chlorobenzaldehyde (**2k**), benzil with ammonium acetate were examined. The results are summarized in Table 1.

Table 1: The effect of molar ratio on the condensation of 1, 2k and 3

Entry	Molar ratio[a]	Time (min)	Temp. (^oC)[b]	Isolated yield (%)
1	1:1:2	200	140	75
2	1:1:3	110	140	92
3	1:1:4	110	140	93
4	1:1:3	90	140	79[c]

[a] Molar ratio of **1**, **2k** and **3**.

[b] The temperature of oil bath.

[c] Without acetic acid.

As shown in Table I, the yield of **4k** increased from 75% to 92% by changing the molar ratio from 1:1:2 to 1:1:3, and the reaction time was shorted from 220 min to 110 min (Entries **1** and **2**). By increasing the molar ratio from 1:1:3 to 1:1:4, the yield of **4k** increased from 92% to 93% (Entry **3**). The results show that changing the molar ratio of substrates from 1:1:3 to 1:1:4 had not a significant effect on the yield of **4k**. Considering the atomic economic benefits, the optimum molar ratio of **1**, **2**, and **3** was 1:1:3.

A comparison experiment in the absence of acetic acid was also carried out, and **4k** was obtained in 79% yield (Entry **4**), while in the presence of acetic acid the yield was 92%, it indicated that acetic acid can improve the yield.

From the result above, the reaction conditions we

chose were as follow: the molar ratio of **1**, **2** and **3** was 1:1:3, the temperature was 140 ^{o}C, HOAc was 0.5 mL. Using this reaction system, a series of 2-aryl-4,5-diphenylimidazoles were prepared. The results are summarized in Table 2.

From these results listed in Table 2, we can deduce that the yields are in general, similar or higher than those described in literatures. Compared with some other reported methods which use acetic acid as solvent, the main advantages of the procedure are less acetic acid used, short reaction times. For example, the condensation of benzil, aldehyde and ammonium acetate was carried out in 65%-88% yield in refluxing acetic acid for 5-6 h[5e], whereas present procedure offered 2-aryl-4,5-diphenylimidazole in 86-95% yield by heating at 140 ^{o}C within 30-180 min. In the reaction catalyzed by Ytterbium perfluorooctanesulfonate [10], the condensation of benzil, aldehyde

Table 2: Synthesis of 2-aryl-4,5-diphenylimidazoles catalyzed by HOAc [a]

Entry	Ar	Product	Time (min)	Yield (%)	m.p. (^{o}C) (Lit).
a	C_6H_5	**4a**	160	94	276-277 (276-277) [7]
b	2-$NO_2C_6H_4$	**4b**	180	95	231-232 (230) [17]
c	3-$NO_2C_6H_4$	**4c**	160	92	318 (>300) [5d]
d	4-$NO_2C_6H_4$	**4d**	40	91	236-238(236-237) [15c]
e	2,4-$Cl_2C_6H_3$	**4e**	95	93	176-177 (176.5-177) [5c]
f	3,4-$Cl_2C_6H_3$	**4f**	83	87	255-256
g	3,4-$(OCH_2O)C_6H_3$	**4g**	45	90	252-253 (254) [15a]
h	2-HO-3-$CH_3OC_6H_3$	**4h**	30	92	191-192 (170) [8]
i	4-HO-3-$CH_3OC_6H_3$	**4i**	40	93	255-256 (197) [8]
j	2-ClC_6H_4	**4j**	150	86	197-198 (197.3-197.8) [15c]
k	4-ClC_6H_4	**4k**	110	92	262-263 (262-264) [15c]
l	4-HOC_6H_4	**4l**	80	94	266-267 (268-268.5) [15c]
m	4-$(Me)_2NC_6H_4$	**4m**	120	91	255-256 (257-258) [9]
n	4-$CH_3OC_6H_4$	**4n**	45	91	231-232 (230-232) [15c]

[a] Reaction temperature, 140 ^{o}C, HOAc, 0.5 mL.

and ammonium acetate was carried out in 75-97% yield at 80 ^{o}C using acetic acid as solvent for 6 h, while present procedure offered products in 86-95% yield by heating. Besides, this method did not need additional catalyst except acetic acid, and the amount of acetic acid was greatly decreased, it was one quarter of reported in the literatures[5e, 11].

CONCLUSION

In conclusion, we have found a simple, efficient and practical procedure for the synthesis of 2-aryl-4,5-diphenylimidazoles via the condensation of aromatic aldehyde, benzil and ammonium acetate catalyzed by acetic acid, which make it a useful and attractive process for the synthesis of these compounds. In both cases, the reaction was very tolerant of aromatic aldehydes carrying either electron-withdrawing or electron-donating substituent groups.

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