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Efficient Synthesis of 5-Substituted 2,3-Diphenyl and 5-Substituted 1-Aryl-2,3-diphenyl Imidazoles Using Polyethylene Glycol

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EFFICIENT SYNTHESIS OF 5-SUBSTITUTED 2,3-DIPHENYL AND 5-SUBSTITUTED 1-ARYL-2,3-DIPHENYL IMIDAZOLES USING POLYETHYLENE GLYCOL

Biswanath Das, Chithaluri Sudhakar, and Yallamalla Srinivas
Organic Chemistry Division I, Indian Institute of Chemical Technology, Hyderabad, Andhra Pradesh, India

Treatment of benzoin with an aldehyde and NH_4OAc in polyethylene glycol (PEG-400) under reflux afforded a 5-substituted 2,3-diphenyl imidazole while the same reaction along with an additional aniline produced 5-substituted 1-aryl 2,3-diphenyl imidazole. No any catalyst or solvent was required to carry out this conversion, and the imidazoles were formed in excellent yields.

Keywords: Aldehyde; ammonium acetate; benzoin; imidazole; PEG-400

INTRODUCTION

Imidazole derivatives possess various important biological properties including fungicidal, herbicidal, and plant-growth regulator activities.[1,2] Some of the compounds exhibit antiviral and anticancer properties.[3,4] Substituted imidazoles are in the core portion in many bioactive molecules such as losartan and olmesartan.[5] They have also been employed in the preparation of ionic liquids.[6] Thus, the synthesis of imidazoles is an important task in organic chemistry. Though the preparation of benzimidazoles has recently been studied[7–13] well, the methods for the synthesis of other substituted imidazoles starting from benzoin are limited.[14–17]

RESULTS AND DISCUSSION

In continuation of our work[18–20] on the development of useful synthetic methodologies, we have observed that the treatment of a benzoin with an aldehyde and NH_4OAc in polyethylene glycol (PEG-400) under reflux yielded a 5-substituted

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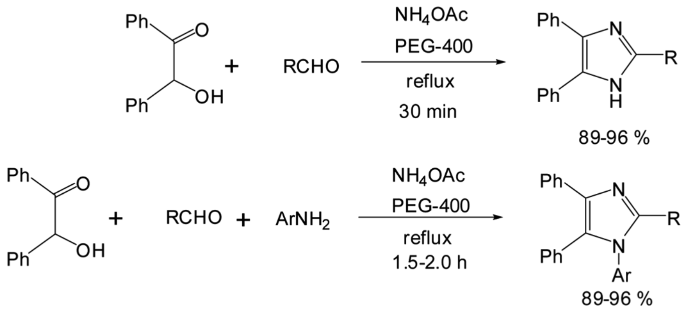

Scheme 1. Synthesis of 5-substituted 2,3-diphenyl and 5-substituted 1-aryl 2,3-diphenyl imidazoles using PEG-400.

2,3-diphenyl imidazole and that the same reaction together with an additional aniline formed 5-substituted 1-aryl 2,3-diphenyl imidazole (Scheme 1).

Various substituted imidazoles were prepared from benzoin, different aldehydes, and anilines (Table 1). For the preparation of 5-substituted 2,3-diphenyl imidazole, the molar ratio of benzoin, aldehyde, and NH_4OAc was 1:1:2, whereas for the preparation of 5-substituted 1-aryl 2,3-diphenyl imidazole, an equimolar ratio of all the substrates (benzoin, aldehydes, aniline, and NH_4OAc) was used. Both the aromatic and aliphatic aldehydes underwent the conversion smoothly. Aromatic aldehydes containing electron-donating as well as electron-withdrawing substituents were applied. 5-Substituted 2,3-diphenyl imidazoles were produced within 20 min, and 5-substituted 1-aryl 2,3-diphenyl imidazoles were produced within 1.5–2 h. The products were formed in excellent yields and with various functionalities such as hydroxyl, ether, halogen, and nitro groups remained unchanged.

When carried out with benzoin, an aldehyde, NH_4OAc, and an aniline, no 1-unsubstituted imidazoles were obtained with the present reaction. Moreover, when heated alone under reflux in PEG, benzoin was converted to benzyl within a few minutes. Aerial oxygen acts as the oxidant as the present conversion could not proceed in the absence of air. Considering all these results, the plausible mechanism of the reaction is proposed[21] in Scheme 2.

Polyethylene glycol (PEG-400)[22,23] is a biologically acceptable polymer that is inexpensive and ecofriendly. Its applications in organic synthesis have not yet been fully explored. In the present conversion, it possibly activates the carbonyl and hydroxyl groups of the substrates and intermediates through hydrogen bonding. The experimental procedure is convenient, and no any additional catalyst was required. The structures of the imidazoles were settled from their spectral [infrared (IR), ^{1}H NMR, and mass (MS)] and analytical data.

CONCLUSION

In conclusion, we have described how 5-substituted 2,3-diphenyl and 5-substituted 1-aryl 2,3-diphenyl imidazoles can be prepared efficiently in PEG-400 medium starting from benzoin in short reaction times and in impressive yields.

Table 1. Synthesis of 5-substituted 2,3-diphenyl imidazoles[a]

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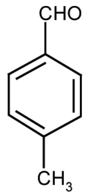
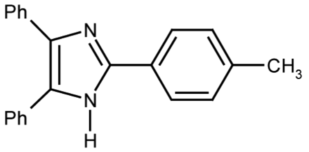
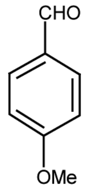
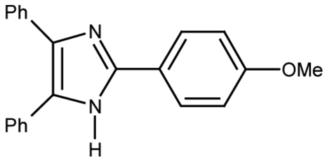
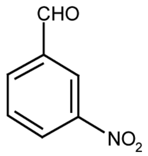
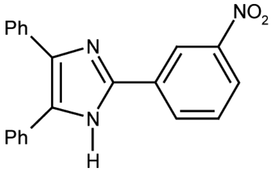
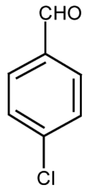
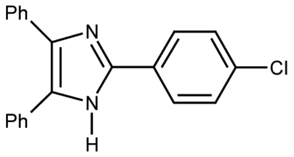
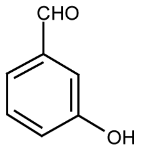
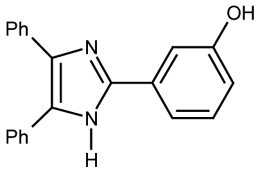
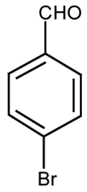
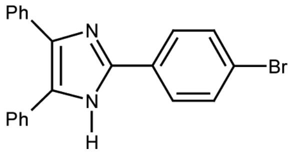
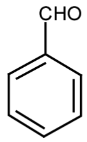
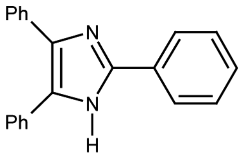
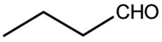
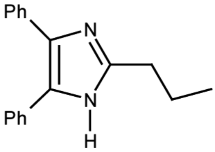
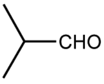
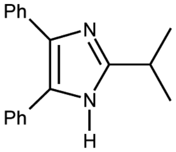
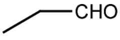
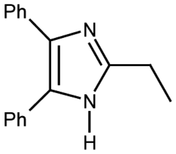
1a			94
1b			96
1c			89
1d			92
1e			92
1f			91
1g			93

(*Continued*)

Table 1. Continued

Entry	Aldehyde	Product	Isolated yield (%)
1h			92
1i			94
1j			91

[a] The structures of the products were settled from their spectral (IR, ^{1}H NMR, and MS) and analytical data.

EXPERIMENTAL

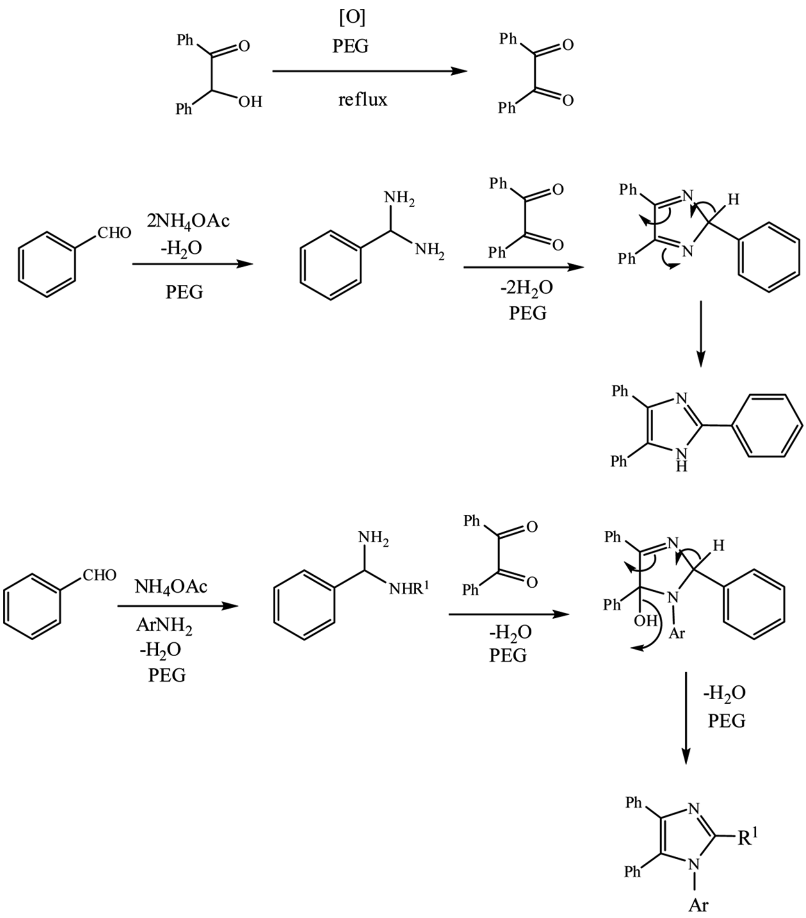
General Procedure for the Synthesis of 5-Substituted 2,3-Diphenyl and 5-Substituted 1-Aryl 2,3-Diphenyl Imidazols

A mixture of benzoin (0.5 mmol), an aldehyde (0.5 mmol), and NH$_4$OAc (1 mmol) was suspended in PEG-400 (5 mL). The mixture was heated under reflux, and the reaction was monitored by thin-layer chromatography (TLC). After completion, water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The extract was dried over anhydrous Na$_2$SO$_4$ and concentrated. The residue was purified by column chromatography (silica gel, n-hexane–EtOAc) to obtain pure 5-substituted 2,3-diphenyl imidazole.

For the preparation of 5-substituted 1-aryl 2,3-diphenyl imidazoles, this experimental procedure was followed using a mixture of benzoin (0.5 mmol), aldehyde (0.5 mmol), aniline (0.5 mmol), and NH$_4$OAc (0.5 mmol) suspended in PEG-400 (5 mL).

Spectral Data for Selected Compounds

Product 1e (Table 1). Mp 272–274 °C (EtOH); IR (KBr): 3231, 1653, 1586, 1484, 1408, 1224 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 9.02 (1H, brs), 7.62–7.50 (6H, m), 7.31–7.16 (6H, m), 6.75 (2H, d, $J = 8.0$ Hz); ESIMS: m/z 313 $[M+H]^+$. Anal. calcd. for $C_{21}H_{16}N_2O$: C, 80.77; H, 5.13; N, 8.97%. Found: C, 80.88; H, 5.18; N, 8.91%.



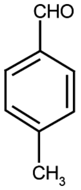
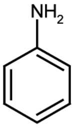
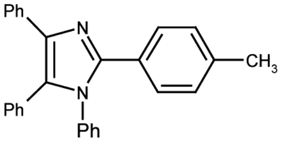
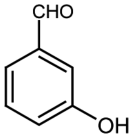
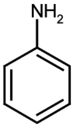
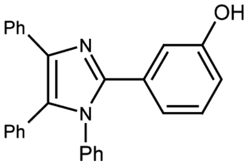
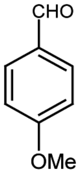
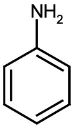
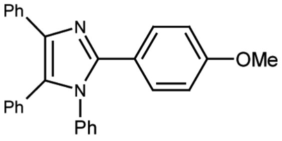
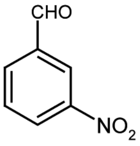
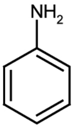
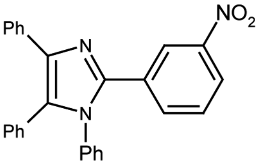
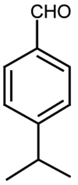
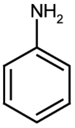
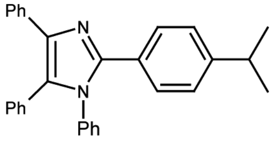
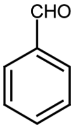
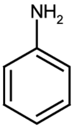
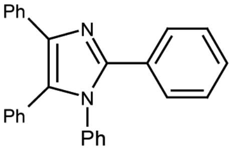
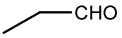
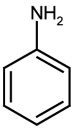
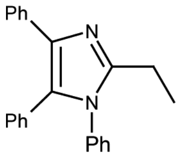
Scheme 2. Mechanism of 5-substituted 2,3-diphenyl and 5-substituted 1-aryl 2,3-diphenyl imidazoles using PEG-400.

Product 1f (Table 1). Mp 247–249 °C (EtOH); IR (KBr): 3420, 1651, 1601, 1482, 1432, 1203 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 8.02 (2H, d, $J = 8.0$ Hz), 7.77 (1H, brs), 7.60–7.52 (6H, m), 7.38–7.21 (6H, m); ESIMS: m/z 375, 377 $[M+H]^+$. Anal. calcd. for $C_{21}H_{15}BrN_2$: C, 67.20; H, 4.00; N, 7.47%. Found: C, 67.31; H, 4.09; N, 7.42%.

Product 2e (Table 2). Mp 184–186 °C (EtOH); IR (KBr): 1670, 1600, 1495, 1450, 1235 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.54 (2H, d, $J = 8.0$ Hz), 7.32–7.01 (17H, m), 2.85 (1H, m), 1.22 (6H, d, $J = 7.0$ Hz); ESIMS: m/z 415 $[M+H]^+$. Anal. calcd. for $C_{30}H_{26}N_2$: C, 86.96; H, 6.28; N, 6.76%. Found: C, 86.82; H, 6.33; N, 6.68%.

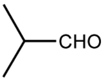
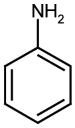
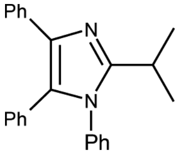
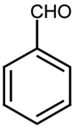
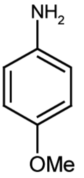
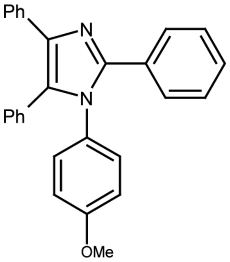
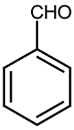
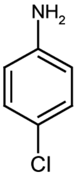
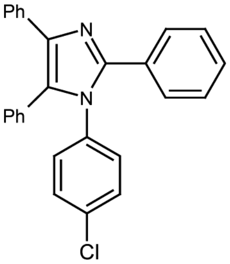
Product 2h (Table 2). Mp 197–199 °C (EtOH); IR (KBr): 1674, 1599, 1498, 1456, 1279 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.49 (2H, d, $J = 8.0$ Hz),

Table 2. Synthesis of 5-substituted 1-aryl 2,3-diphenyl imidazoles[a]

Entry	Aldehyde	Amine	Product	Time (h)	Isolated yield (%)
2a				1.5	94
2b				2	91
2c				1.5	96
2d				2.0	89
2e				1.5	94
2f				1.5	92
2g				1.5	92

(*Continued*)

Table 2. Continued

Entry	Aldehyde	Amine	Product	Time (h)	Isolated yield (%)
2h				1.5	94
2i				1.5	94
2j				2	92

[a]The structures of the products were settled from their spectral (IR, ^{1}H NMR, and MS) and analytical data.

7.38–7.02 (13H, m), 2.84 (1H, m), 1.31 (6H, d, $J = 7.0$ Hz); ESIMS: m/z 339 $[M + H]^+$. Anal. calcd. for $C_{24}H_{22}N_2$: C, 85.21; H, 6.51; N, 8.28%. Found: C, 85.13; H, 6.62; N, 8.34%.

Product 2i (Table 2). Mp 171–173 °C (EtOH); IR (KBr): 1649, 1602, 1508, 1444, 1247 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.54 (2H, d, $J = 8.0$ Hz), 7.48–7.39 (2H, m), 7.30–7.04 (11H, m), 6.99 (2H, d, $J = 8.0$ Hz), 6.72 (2H, d, $J = 8.0$ Hz), 3.80 (3H, s); ESIMS: m/z 403 $[M + H]^+$. Anal. calcd. for $C_{28}H_{22}N_2O$: C, 83.58; H, 5.47; N, 6.97%. Found: C, 83.67; H, 5.42, N, 6.89%.

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