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Original Scientific Article

Facile and Rapid Synthesis of Polysubstituted Imidazoles by Employing $Y(NO_3)_3 \times 6H_2O$ as Catalyst

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Abstract. An efficient and environmentally adapted synthesis of polysubstituted imidazoles in one-pot and multicomponent reaction of various aldehydes, benzil, aliphatic and aromatic primary amines and ammonium acetate under solvent-free condition is reported. Highly efficient role of $Y(NO_3)_3 \times 6H_2O$ as catalyst in this synthesis was shown. By this advantage, several polysubstituted imidazoles as pharmaceutical important molecules can be prepared in high yield and high purity. This method is very easy and rapid for the synthesis of imidazole derivatives. All products were deduced from their IR and NMR spectroscopic and elemental analysis data. The catalyst exhibited remarkable reusable activity. (doi: 10.5562/cca1979)

Keywords: catalyst, $Y(NO_3)_3 \times 6H_2O$, benzil, polysubstituted imidazoles

INTRODUCTION

Multicomponent reactions (MCRs) are the special type of organic reactions which afford complex products from reaction of three or more simple starting materials in one pot. Because of atom-economy, convergent character, operational simplicity, structural diversity and complexity of the molecules in these reactions, they have attracted much attention.[1,2]

The imidazoles and their derivatives are very important molecules because many applications in chemical processes, especially in pharmaceuticals.[3,4] Various substituted imidazoles act as inhibitors of p38 MAP kinase,[5] B-Raf kinase,[6] glucagon receptors,[7] plant growth regulators,[8] antitumor[9] and pesticides.[10]

There are many methods for the synthesis of polysubstituted imidazoles such as condensation of diones, aldehydes, primary amines and ammonia in the presence of various acid catalysts,[11–13] *N*-alkylation of trisubstituted imidazoles,[14] condensation of benzil or benzoin acetate with aldehydes, primary amines and ammonia in the presence of copper acetate[15,16] *etc.* The first mention method is the most well-known and classical method.

However, some of these methods, involved long reaction times, and unsatisfactory yields. Therefore, improvements in these syntheses have been sought continuously. In this work, high activation, and reusability of $Y(NO_3)_3 \times 6H_2O$ as a catalyst in the synthesis of polysubstituted imidazoles have been shown.

A new method for the synthesis of polysubstituted imidazoles was obtained by condensation of benzil with aldehydes, primary amines and ammonium acetate in the presence of $Y(NO_3)_3 \times 6H_2O$ as an effective catalyst in solvent free condition (Scheme 1).

Herein, we report a simple, rapid and one-pot procedure for the synthesis of three and four substituted imidazoles by using $Y(NO_3)_3 \times 6H_2O$ with high yields and short reaction times. While using benzil **1**, aromatic aldehydes **2**, aromatic and aliphatic amine **3**, ammonium acetate **4** and $Y(NO_3)_3 \times 6H_2O$ as catalyst under solvent-free condition lead to tetrasubstituted imidazoles **5**, that in the absence of aromatic and aliphatic amine **3**, trisubstituted imidazoles **6** were obtained (Scheme 1).

EXPERIMENTAL SECTION

Melting points were measured on an elecrtothermal KSB1N apparatus. IR spectra were recorded in the matrix of KBr with JASCO FT-IR-680 plus spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a FT-NMR Bruker Avance Ultra Shield Spectrometer at 400.13 and 100.62 MHz in $CDCl_3$ and DMSO-d_6 as solvent in the presence of tetramethylsilane as internal standard. TLC was performed on TLC-Grade silica gel-G/UV 254 nm plates. The products were isolated and characterized by physical and spectral data and they were compared with authentic samples (Table 1).

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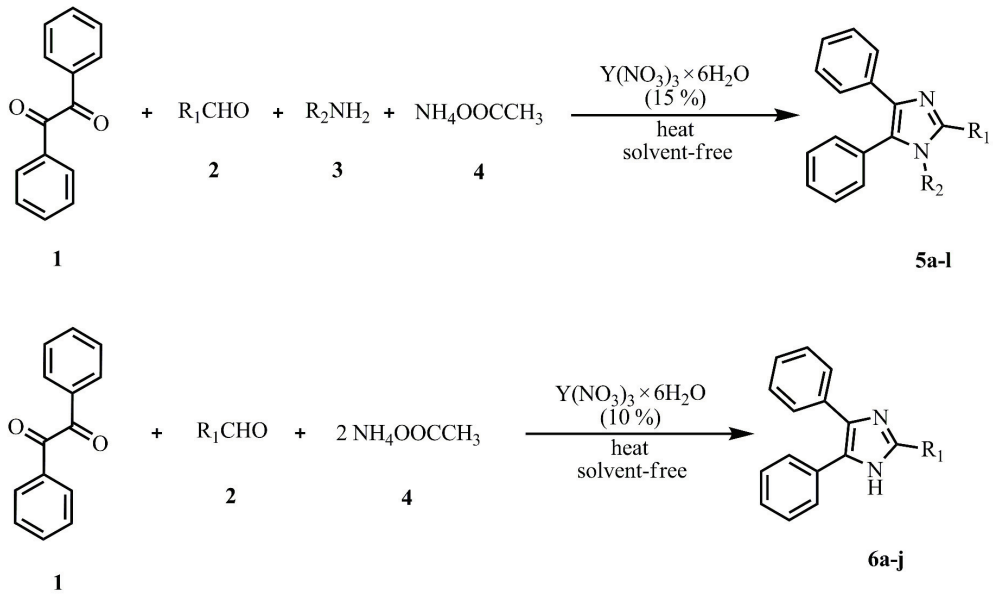


Scheme 1. Synthesis of polysubstituted imidazoles in the presence of $Y(NO_3)_3 \times 6H_2O$ as catalyst.

Table 1. Synthesis of polysubstituted imidazoles catalyzed by $Y(NO_3)_3 \times 6H_2O$

Compound	R^1	R^2	*t* / min	Yield[(a)] / %	M.p. / °C (from literature)
5a	C_6H_5	$C_6H_5CH_2$	30	96	162–164 (Ref. 13)
5b	4-BrC_6H_4	$C_6H_5CH_2$	25	90	169–170 (Ref. 13)
5c	4-$CH_3C_6H_4$	$C_6H_5CH_2$	55	98	156–158 (Ref. 17)
5d	4-ClC_6H_4	$C_6H_5CH_2$	60	85	160–162 (Ref. 17)
5e	2-ClC_6H_4	$C_6H_5CH_2$	25	85	193–195 (Ref. 18)
5f	3-$NO_2C_6H_4$	$C_6H_5CH_2$	20	80	150–152[(b)]
5g	4-$CH_3C_6H_4$	Cyclohexyl	40	75	160–161 (Refs. 19,20)
5h	4-$OCH_3C_6H_4$	$C_6H_5CH_2$	50	90	148–151 (Ref. 21)
5i	2-OH-5-BrC_6H_3	4-ClC_6H_4	25	98	156–158[(b)]
5j	4-Benzyloxyphenyl	$C_6H_5CH_2$	95	96	138–139[(b)]
5k	2,4-Dichlorophenyl	$C_6H_5CH_2$	45	95	216–219[(b)]
5l	4-$CH_3C_6H_4$	C_6H_5	25	93	182–184 (Ref. 20)
6a	C_6H_5	–	50	90	272–273 (Ref. 22)
6b	3-BrC_6H_4	–	10	89	120–122 (Ref. 23)
6c	2-OHC_6H_4	–	30	90	209–211 (Ref. 24)
6d	2-$OCH_3C_6H_4$	–	25	92	204–206 (Ref. 21)
6e	4-$OCH_3C_6H_4$	–	100	70	227–230 (Ref. 22)
6f	4-Benzyloxyphenyl	–	60	68	235–236 (Ref. 25) [(c)]
6g	2-Fluorenyle	–	35	97	283–286[(b)]
6h	3-Indolyl	–	140	83	311–313[(b)]
6i	4-ClC_6H_4	–	25	90	257–259 (Ref. 26)
6j	3-$NO_2C_6H_4$	–	10	91	308–309 (Ref. 27)

[(a)] Refers to isolated yields.
[(b)] Novel compound.
[(c)] Melting point of this compound was not reported by author.

General Procedure for Synthesis of 1,2,4,5-Tetrasubstituted Imidazoles by $Y(NO_3)_3 \times 6H_2O$

A mixture of aromatic aldehyde (1 mmol), benzil (1 mmol), primary amine (1 mmol), ammonium acetate (1 mmol) and $Y(NO_3)_3 \times 6H_2O$ (mole ratio, r = 15 %) were stirred at 140 °C in solvent-free condition. The progress of reaction was monitored by TLC. After completion of reaction, the mixture was coolled to room temperature and was solved in 50 mL water then was filtered. Obtained products were purified by crystallization from acetone-water mixture (V(acetone) : V(water) = 10 : 1). The products were characterized by IR, NMR, and through comparison of their physical properties with those reported in literature.[13,17–27]

Hence, general procedure for the synthesis of 2,4,5-trisubstituted imidazoles is same to the 1,2,4,5-tetrasubstituted imidazoles, but it needs to 10 % of catalyst, 2 mmol of ammonium acetate instead of 1 mmol in the absence of primary amine.

Representative Spectral Data

*1-Benzyl-2,4,5-triphenyl-1*H-*imidazole* ***(5a)***
M.p. 162–164 °C (Ref. 13) 163–165 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3061, 3026, 2308, 1601, 1521, 1497, 1350, 761, 696. ^{1}H NMR (250 MHz, DMSO-d6) δ / ppm: 5.13 (s, 2H), 7.18–8.41 (m, 20H). ^{13}CNMR (62.69 MHz, DMSO-d_6) δ / ppm: 48.29, 126.00, 126.38, 126.81, 128.11, 129.08, 129.58, 129.90, 130.09, 130.98, 131.09, 135.09, 137.57, 148.09.

*1-Benzyl-2-(4-bromophenyl)-4,5-diphenyl-1*H-*imidazole* ***(5b)***
M.p. 169–170 °C (Ref. 13) 170–172 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3059, 3027, 2938, 1599, 1479, 1358, 1070, 835, 758, 694. ^{1}H NMR (400.13 MHz, DMSO-d6) δ / ppm: 4.86 (s, 2H), 6.61–7.46 (m, 19H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 49.41, 125.86, 126.51, 126.78, 127.53, 128.14, 128.25, 128.74, 128.87, 130.48, 130.79, 131.03, 131.79, 137.33.

*1-Benzyl-4,5-diphenyl-2-p-tolyl-1*H-*imidazole* ***(5c)***
M.p. 156–158 °C (Ref. 17) 156–157 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3060, 3027, 2926, 1600, 1496, 1349, 826, 767, 694. ^{1}HNMR (400.13 MHz, DMSO-d_6) δ / ppm: 2.08 (s, 3H), 4.91 (s, 2H), 6.61–7.40 (m, 19H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 22.52, 49.41, 127.15, 127.47, 127.94, 128.46, 129.22, 129.72, 129.92, 130.10, 130.45, 131.03, 132.23, 138.80, 140.01, 146.34.

*1-Benzyl-2-(4-chlorophenyl)-4,5-diphenyl-1*H-*imidazole* ***(5d)***
M.p. 160–162 °C (Ref. 17) 157–158 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3059, 3029, 2936, 1600, 1480, 1357, 1089, 835, 758, 693. ^{1}HNMR (400.13 MHz, DMSO-d_6) δ / ppm: 4.9 (s, 2H), 6.60–7.50 (m, 19H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 48.31, 125.88, 126.55, 127.54, 129.13, 129.31, 130.28, 130.43, 130.74, 131.04, 134.18, 135.04, 136.81, 137.30, 138.22.

*1-Benzyl-2-(2-chlorophenyl)-4,5-diphenyl-1*H-*imidazole* ***(5e)***
M.p. 139–140 °C (Ref. 18) 140–142 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3062, 3026, 2930, 1602, 1485, 1349, 1079, 758, 690. ^{1}HNMR (400.13 MHz, DMSO-d_6) δ / ppm: 4.74 (s, 2H), 6.42–7.42 (m, 19H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 43.17, 126.00, 126.50, 126.68, 127.48, 128.44, 128.69, 128.99, 129.15, 129.36, 129.74, 129.81, 130.33, 130.61, 130.89, 131.08, 131.15, 132.92, 133.80, 134.24, 134.95, 136.80, 137.65, 145.13.

*1-Benzyl-2-(3-nitrophenyl)-4,5-diphenyl-1*H-*imidazole* ***(5f)***
M.p. 150–152 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3061, 3026, 2308, 1601, 1521, 1497, 1350, 810, 730, 696. ^{1}H NMR (400.13 MHz, DMSO-d6) δ / ppm: 5.19(s, 2H), 6.89 (d, J = 6.15 Hz, 2H), 7.21–7.63 (m, 14H), 8.04 (d, J = 7.8 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.57 (s, 1H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ/ppm: 47.42, 122.30, 122.59, 124.71, 125.67, 125.73, 126.71, 127.15, 127.84, 127.97, 128.56, 129.36, 129.93, 130.24, 131.57, 132.98, 133.51, 135.78, 144.23, 147.20. *Anal. Calcd.* mass fractions of elements, w / %, for $C_{28}H_{21}N_3O_2$ (M_r = 431.49): C 77.94, H 4.91, N 9.74. Found: C 77.87, H 4.83, N 9.62.

*1-Cyclohexyl-4,5-diphenyl-2-p-tolyl-1*H-*imidazole* ***(5g)***
M.p. 160–161 °C (Ref. 20) 162–164 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3058, 3020, 2930, 1600, 1495, 1349, 825, 766, 695. ^{1}HNMR (400.13 MHz, $CDCl_3$) δ / ppm: 0.95 (m, 2H), 1.35–1.55 (m, 6H), 1.75 (m, 2H), 2.35 (s, 3H), 3.80–3.97 (m, 1H), 6.70–7.45 (m, 14H). ^{13}CNMR (100.62 MHz, $CDCl_3$) δ / ppm: 21.45, 25.12, 26.21, 33.59, 58.31, 125.94, 126.01, 126.68, 127.60, 127.89, 127.97, 128.18, 128.65, 128.76, 128.89, 129.01, 129.04, 129.15, 129.50, 129.87, 132.25, 132.81, 134.77, 137.68, 138.74, 147.84.

*1-Benzyl-2-(4-methoxyphenyl)-4,5-diphenyl-1*H-*imidazole* ***(5h)***
M.p. 163–166 °C (Ref. 21) 164–165 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3063, 3019, 2295, 1609, 1519, 1493, 1354, 696. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ / ppm: 3.81 (s, 3H), 5.08 (s, 2H), 6.82–7.56 (m, 15H), 7.58 (d, J = 2.3 Hz, 4H). ^{13}CNMR (100.62 MHz, $CDCl_3$) δ / ppm: 47.16, 54.26, 112.95, 122.40, 124.94, 125.21, 125.71, 126.26, 127.00, 127.49, 127.52, 127.71, 128.02, 128.70, 129.37, 130.03, 130.12, 133.53, 136.64, 136.78, 146.94, 159.04.

*1-(4-Chlorophenyl)-2-(2-hydroxy-5-bromophenyl)-4,5-diphenyl-1*H-*imidazole* ***(5i)***
M.p. 156–158 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3458, 3063, 1659, 1593, 1578, 1211, 1174, 1096. ^{1}HNMR (400.13 MHz, DMSO-d_6) δ/ppm: 6.92–8.53 (m, 17H), 13.06 (s, 1H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 115.17,

123.92, 125.53, 127.64, 134.31, 137.31, 139.26, 140.54, 151.31, 164.74, 166.94. *Anal. Calcd*. mass fractions of elements, w / %, for $C_{27}H_{18}BrClN_2O$ (M_r = 501.80): C 64.62, H 3.62, N 5.58. Found: C 64.51, H 3.53, N 5.49.

*1-Benzyl-2-(4-benzyloxyphenyl)-4,5-diphenyl-1*H-*imidazole* ***(5j)***
M.p. 138–139 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 2857, 1601, 1575, 1526, 1289, 1247, 1177. ^{1}HNMR (400.13 MHz, DMSO-d_6) δ / ppm: 2.18 (s, 2H), 5.06 (s, 2H), 6.83–7.82 (m, 24H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 48.29, 70.03, 115.05, 123.79, 126.06, 126.38, 126.85, 127.41, 127.53, 128.11, 128.16, 128.68, 128.86, 129.89, 130.50, 131.14, 131.23, 134.70, 136.76, 137.75, 137.94, 148.02, 159.33. *Anal. Calcd*. mass fractions of elements, w / %, for $C_{35}H_{28}N_2O$ (M_r = 492.61): C 85.34, H 5.73, N 5.69. Found: C 85.18, H 5.61, N 5.54.

*1-Benzyl-2-(2,4-dichlorophenyl)-4,5-diphenyl-1*H-*imidazole* ***(5k)***
M.p. 216–219 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3069, 2924, 1557, 1523, 1459, 1092. ^{1}HNMR (400.13 MHz, DMSO-d_6) δ / ppm: 2.18 (s, 2H), 7.45–8.41 (m, 13H), 8.64 (d, J = 7.6 Hz, 1H), 8.77 (t, J = 8.4 Hz, 2H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 120.88, 121.13, 122.98, 123.47, 123.76, 125.00, 126.03, 126.82, 127.20, 127.39, 127.43, 127.56, 129.00, 129.58, 131.28, 132.31, 133.77, 135.20, 136.93, 145.22. *Anal. Calcd*. mass fractions of elements, w / %, for $C_{28}H_{20}Cl_2N_2$ (M_r = 455.38): C 73.85, H 4.43, N 6.15. Found: C 73.71, H 4.36, N 6.09.

*1,4,5-Triphenyl-2-p-tolyl-1*H-*imidazole* ***(5l)***
M.p. 182–184 °C (Ref. 20) 185–188 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3055, 3022, 2930, 1600, 1495, 1349, 826, 767, 694. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ / ppm: 2.34 (s, 3H), 7.07–7.36 (m, 17H), 7.64 (d, J = 7.1 Hz, 2H). ^{13}CNMR (100.62 MHz, $CDCl_3$) δ / ppm: 20.23, 124.24, 125.49, 126.39, 126.67, 126.85, 127.09, 127.12, 127.27, 127.45, 127.77, 127.79, 127.98, 128.46, 129.74, 130.11, 136.23, 137.10, 146.06.

*2-(3-Bromophenyl)-4,5-diphenyl-1*H-*imidazole* ***(6b)***
M.p. 120–122 °C (Ref. 23) 118–122 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3387, 3062, 1584, 1529, 1480, 1241, 1100. ^{1}HNMR (400.13 MHz, $CDCl_3$) δ / ppm: 7.26–7.78 (m, 14H), 9.40 (s, 1H). ^{13}CNMR (100.62 MHz, $CDCl_3$) δ / ppm: 121.86, 125.62, 126.02, 126.75, 127.41, 127.70, 127.76, 128.11, 131.05.

*2-(2-Hydroxyphenyl)-4,5-diphenyl-1*H-*imidazole* ***(6c)***
M.p. 209–211 °C (Ref. 24) 209–210 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3450, 3385, 1584, 1529, 1480, 1240, 1098. ^{1}HNMR (400.13 MHz, $CDCl_3$) δ / ppm: 6.92 (d, J = 7.28 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.26–7.62 (m, 12H), 9.36 (s, 1H), 12.83 (s, 1H). ^{13}CNMR (100.62 MHz, $CDCl_3$) δ / ppm: 111.39, 116.80, 117.92, 122.00, 126.32, 127.14, 127.38, 128.07, 129.54, 144.67, 156.45.

*2-(2-Methoxyphenyl)-4,5-diphenyl-1*H-*imidazole* ***(6d)***
M.p. 204–206 °C (Ref. 24) 210–211 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3388, 3062, 2933, 1584, 1530, 1481, 1240, 1099. ^{1}HNMR (400.13 MHz, DMSO-d_6) δ / ppm: 4.05 (s, 3H), 7.03–7.69 (m, 13H), 8.50 (d, J = 8 Hz, 1H), 10.51 (s, 1H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 126.45, 126.83, 127.33, 128.22, 128.59, 129.07, 129.67, 129.91, 130.26, 131.02, 132.98, 133.97.

*2-(4-Methoxyphenyl)-4,5-diphenyl-1*H-*imidazole* ***(6e)***
M.p. 227–230 °C (Ref. 22) 228–230 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3433, 3027, 1613, 1578, 1542, 1248, 1176. ^{1}HNMR (400.13 MHz, DMSO-d_6) δ / ppm: 3.87 (s, 3H), 6.98–7.86 (m, 10H), 7.55 (s, 2H), 7.85 (d, J = 8.4 Hz, 2H), 9.23 (s, 1H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 55.36, 114.27, 122.78, 126.78, 127.30, 127.80, 128.55, 146.14, 160.16.

*2-(4-Benzyloxyphenyl)-4,5-diphenyl-1*H-*imidazole* ***(6f)***
M.p. 235–236 °C (Ref. 25); IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3054, 3018, 2930, 1608, 1578, 1541, 1230, 1181. ^{1}HNMR (400.13 MHZ, DMSO-d_6) δ / ppm: 5.16 (s, 2H), 7.11–7.54 (m, 17H), 8.01 (d, J = 8.8 Hz, 2H), 12.51 (s, 1H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 69.78, 115.42, 123.82, 126.09, 127.18, 127.52, 128.26, 128.36, 128.63, 128.82, 128.93, 129.10, 135.79, 137.41, 146.06, 158.99.

*2-Fluorenyl-4,5-diphenyl-1*H-*imidazole* ***(6g)***
M.p. 283–286 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3350, 3054, 2950, 1601, 1532, 1500. ^{1}HNMR (400.13 MHz, DMSO-d_6) δ / ppm: 4.01 (s, 2H), 7.33–8.00 (m, 15H), 8.130 (d, J = 7.6 Hz, 1H), 8.32 (s, 1H), 12.733 (s, 1H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 39.92, 120.36, 120.68, 122.37, 124.57, 125.64, 126.73, 127.42, 128.28, 128.90, 129.36, 141.23, 141.63, 143.88, 143.95, 146.42. *Anal. Calcd*. mass fractions of elements, w / %, for $C_{28}H_{20}N_2$ (M_r = 384.47): C 87.47, H 5.24, N 7.29. Found: C 87.41, H 5.29, N 7.22.

*3-Indolyl-4,5-diphenyl-1*H-*imidazole* ***(6h)***
M.p. 311–313 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3413, 3055, 1598, 1490, 1451. ^{1}HNMR (400.13 MHZ, DMSO-d_6) δ / ppm: 7.128–7.587 (m, 13H), 8.006 (d, J = 2.4 Hz, 1H), 8.462 (d, J = 7.2 Hz, 1H), 11.404 (s, 1H), 12.4 (s, 1H). ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 106.95, 112.13, 120.24, 121.92, 122.40, 124.53, 125.51, 127.36, 128.05, 128.92, 136.75, 144.11. *Anal. Calcd*. mass fractions of elements, w / %, for $C_{23}H_{17}N_3$ (M_r = 335.40): C 82.36, H 5.11, N 12.53. Found: C 82.29, H 5.21, N 12.40.

*2-(4-Chlorophenyl)-4,5-diphenyl-1*H-*imidazole* ***(6i)***
M.p. 257–259 °C (Ref. 26) 257–260 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3386, 3062, 1584, 1529, 1481, 1240, 1099. ^{1}HNMR (400.13 MHZ, $CDCl_3$) δ / ppm: 6.99–7.36 (m, 12H), 7.86 (d, J = 7 Hz, 2H), 12.09 (s, 1H). ^{13}CNMR

Table 2. The effect of solvents in synthesis of polysubstituted imidazoles for model reaction

Solvent	*t* / min	Yield / %
Water	90	46
Ethanol	35	75
Methanol	40	78
Chloroform	120	49
Acetonitrile	80	73
Solvent-free	30	96

(100.62 MHz, $CDCl_3$) δ / ppm: 125.94, 126.72, 127.39, 127.68, 128.24, 132.70, 144.31.

*2-(3-Nitrophenyl)-4,5-diphenyl-1*H-*imidazole* ***(6j)***
M.p. 308–309 °C (Ref. 27) >295 °C; IR (KBr) $\tilde{\nu}_{max}$ / cm^{-1}: 3380, 3065, 1580, 1527, 1479, 1239, 1099, 810, 758. ^{1}HNMR (400.13 MHZ, DMSO-d_6) δ / ppm: 7.30–7.53 (m, 10H), 7.78 (t, J = 8 Hz, 1H), 8.51 (d, J = 8 Hz, 1H), 8.95 (t, J = 1.8 Hz, 1H), 9.41 (d, J = 8 Hz, 1H), 13.10 (s, 1H), ^{13}CNMR (100.62 MHz, DMSO-d_6) δ / ppm: 119.40, 122.61, 127.13, 128.44, 128.68, 130.44, 131.17, 131.82, 143.38, 148.37.

RESULTS AND DISCUSSION

Firstly, synthesis of 1-benzyl-2,4,5-triphenyl imidazoles was chosen as a model reaction (compound **5a**) in the synthesis of polysubstituted imidazoles to determine the optimum condition for this synthesis. In model reaction, in the presence of $Y(NO_3)_3 \times 6H_2O$ (15 %) as catalyst, the mixture of benzil (1 mmol), benzaldehyde (1 mmol), ammonium acetate (1 mmol), benzylamine (1 mmol) carried out in different solvents such as water, ethanol, methanol, chloroform, acetonitrile and solvent-free conditions. From these experiments, it was clearly demonstrated that the solvent-free conditions offer the best conditions to accomplish this synthesis (Table 2).

Carrying out the model reaction in the absence of catalyst at solvent-free conditions and room temperature for 24 h lead to a very poor yield (12 %) of the product. In the absence of catalyst for enhance the yield of the desired product, temperature of the reaction was increased to 200 °C, but no appreciable increment in the product yield was observed. Therefore, we found that the presence of the catalytic amount of $Y(NO_3)_3 \times 6H_2O$ and solvent-free condition are the best conditions for this synthesis.

We also evaluated quantity of required catalyst in synthesis of tetrasubstituted imidazoles for model reaction (compound **5a**). It was found that maximum yield (96 %) obtained, when the reaction was carried out with 15 % of $Y(NO_3)_3 \times 6H_2O$, but for the synthesis of 2,4,5-trisubtitutedimidazoles, the best amount of the catalyst was found 10 % of catalyst, when the reaction between benzil **1** (1 mmol), aromatic aldehydes **2** (1 mmol) and ammonium acetate **4** (2 mmol) was chosen as a model reaction (Table 3).

We also examined the model reactions at various temperatures to find out its effect on the progress of the

Table 3. Optimization of mole ratio of the catalyst in synthesis of tri and tetrasubstituted imidazoles

Mole ratio of $Y(NO_3)_3 \times 6H_2O$ / %	Trisubstituted imidazole		Tetrasubstituted imidazole	
	t / min	Yield / %	*t* / min	Yield / %
0.5	110	75	120	50
1	90	80	110	60
5	60	88	60	80
10	50	90	40	90
15	50	90	30	96
20	40	90	25	80

Table 4. Optimization of temperature for model reaction

ϑ / °C	Trisubstituted imidazole		Tetrasubstituted imidazole	
	t / min	Yield / %	*t* / min	Yield / %
80	225	70	180	65
100	160	85	110	80
120	100	85	80	85
140	50	90	30	96
160	60	88	40	90

Table 5. Reusability results of $Y(NO_3)_3 \times 6H_2O$ on the reaction process for the model reaction

Total reusability	*t* / min	Yield / %
1	30	96
2	30	95
3	35	95
4	45	97
5	55	97

reaction in the presence of optimized amount of catalyst (Table 4). The maximum rate of reaction was obtained at 140 °C as the optimum temperature for tri and tetrasubstituted imidazoles.

As can be concluded from Table 4, the reaction proceeded slowly at 80 °C. With increasing temperature to 140 °C, reaction yield was increased and time of reaction was decreased, when the reaction was heated above 140 °C, so high temperatures did not further improved yield and decrease time of reaction.

According to the archived optimal condition, we conducted the synthesis of polysubstituted imidazoles in the presence of $Y(NO_3)_3 \times 6H_2O$ as catalyst in solvent-free condition at 140 °C.

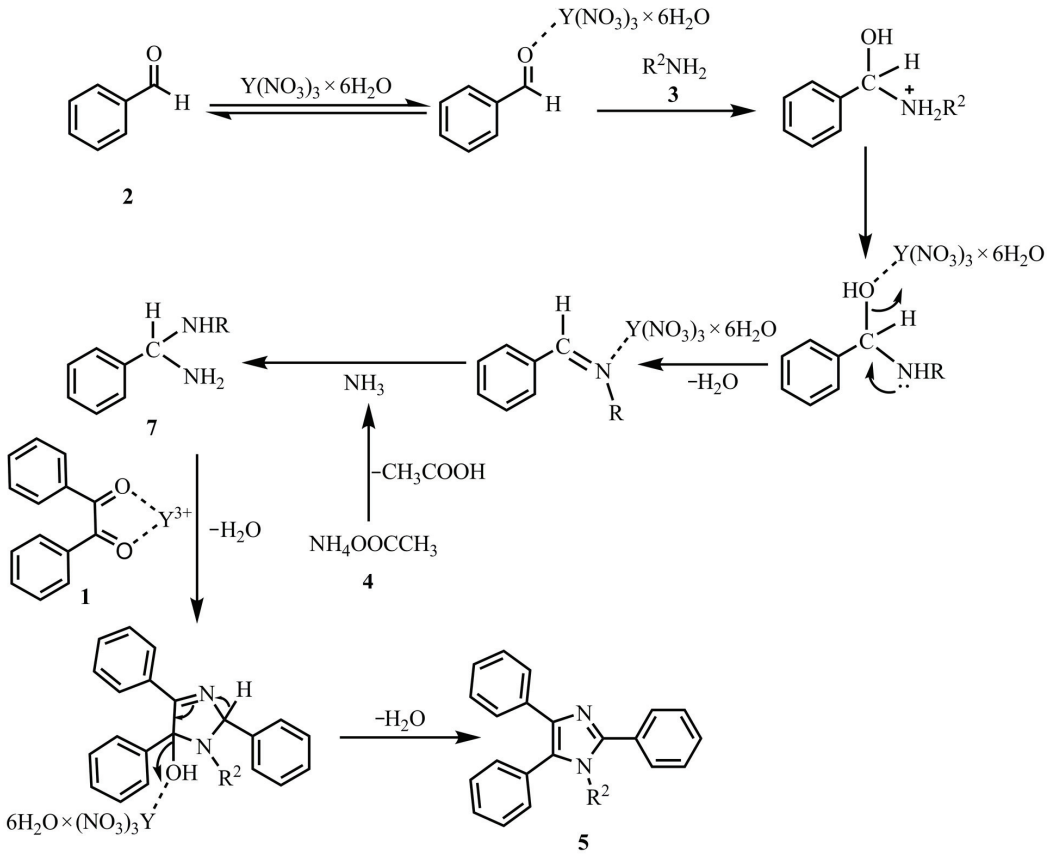
Reusability of the Catalyst

At the end of the reaction, the catalyst was filtered, washed with diethyl ether, dried at 130 °C for 1 h, and reused in another reaction. We found that $Y(NO_3)_3 \times 6H_2O$ showed high catalytic activity. Moreover, it can be recovered and reused several times without significant loss of activity. The results of these observations for the model reaction are shown in Table 5.

A probable mechanism for the synthesis of tetrasubstituted imidazoles may be postulated as shown below (Scheme 2).

As can be seen in Scheme 2, $Y(NO_3)_3 \times 6H_2O$ is a Lewis acid so that it can activated the carbonyl group of aldehydes **2** to decrease the energy of transition state. Then nucleophilic attack of amine **3** on the activated carbonyl of aldehydes, resulted to the formation of imine, and it followed by nucleophilic attack of the insitu generated ammonia from **4** to the imine, giving the intermediate **7**. From condensation of intermediate **7** with benzil **1** and dehydration of it, corresponding imidazoles **5** are produced.

The probable mechanism for synthesis of trisubstituted imidazoles is the same (amine was substituted with ammonium acetate).



Scheme 2. The suggested mechanism for synthesis of tetrasubstituted imidazoles.

CONCLUSION

In this work, we found a thermal exposure synthetic method of polysubstituted imidazoles, that it is a simple, efficient and green chemistry via multicomponent one-pot reaction in the presence of $Y(NO_3)_3 \times 6H_2O$ as an inexpensive and eco-friendly catalyst in solvent-free condition. Products were isolated in excellent yields, and the catalyst efficiently recovered and reused. That is considered as economic advantages of this synthesis. It is believed that this procedure will find important applications in the synthesis of wide range of polysubstituted imidazoles.

Supplementary Materials. – Supporting informations to the paper are enclosed to the electronic version of the article. These data can be found on the website of *Croatica Chemica Acta* (http://public.carnet.hr/ccacaa).

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