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New and rapid access to synthesis of novel polysubstituted imidazoles using antimony trichloride and stannous chloride dihydrate as effective and reusable catalysts

LEYLA POORALI[a], BAHADOR KARAMI[b,*], KHALIL ESKANDARI[b] and MAHBOOBEH AZIZI[a]

[a]Department of Chemistry, Gachsaran Branch, Islamic Azad University, Gachsaran, 75817-75785, Iran
[b]Department of Chemistry, Yasouj University, Yasouj, 75918-74831 P.O. Box 353, Iran
e-mail: karami@mail.yu.ac.ir

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Abstract. In this work, new, efficient and environmentally adapted synthesis of polysubstituted imidazoles in one-pot is repoted. The multicomponent reaction of various aldehydes, benzil, aliphatic and aromatic primary amines and ammonium acetate under solvent-free condition is explained. The highly efficient role of antimony trichloride and stannous chloride dihydrate as catalyst in this synthesis was shown and their effects on the reaction process were studied. By this advantage, several polysubstituted imidazoles as pharmaceutical important molecules can be prepared in high yield and high purity. This method is a very easy and rapid for the synthesis of imidazole derivatives.

Keywords. Benzil; polysubstituted imidazoles; aldehydes; amines; heterogeneous catalyst.

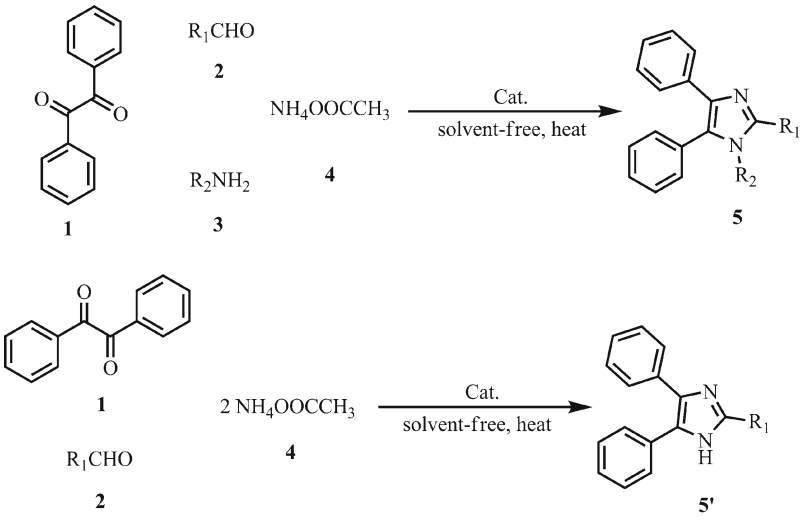
1. Introduction

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, MCR's have attracted much attention.[1,2]

The imidazoles and their derivatives are very important molecules because they have 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] antitumour[9] and pesticides.[10]

Solid and Lewis acid catalysts have been of great interest in organic synthesis.[11] There are many methods for the synthesis of polysubstituted imidazoles by employing of Lewis acids[12] such as condensation of diones, aldehydes, primary amines and ammonia in the presence of various acid catalysts,[13–15] N-alkylation of trisubstituted imidazoles,[16] condensation of benzil or benzoin acetate with aldehydes, primary amines and ammonia in the presence of copper acetate,[17,18] condensation of *o*-diamines with aldehydes and in the presence of tetrabutylammonium fluoride (TBAF),[19] etc. The first 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.[20] In the scope of previous works for synthesis of heterocyclic compounds by inorganic solid acids,[21] in this study, 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 antimony trichloride and stannous chloride dihydrate as effective and reusable catalysts in solvent-free condition (scheme 1). Here, we report a simple, rapid and one-pot procedure for the synthesis of tri and tetrasubstituted imidazoles by the use of antimony trichloride and stannous chloride dihydrate with high yields and short reaction times. Using benzil **1**, aromatic aldehydes **2**, aromatic and aliphatic amine **3**, ammonium acetate **4** and catalytic amount of $SbCl_3$ (or $SnCl_2.2H_2O$) under solvent-free condition lead to tetrasubstituted imidazoles **5**, wherease in the absence of aromatic and aliphatic amine **3**, trisubstituted imidazoles were obtained **5′** (see scheme 1).

*For correspondence



Scheme 1. Synthesis of polysubstituted imidazoles by the use of $SbCl_3$ and $SnCl_2.2H_2O$ as catalyst.

2. Experimental

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).

2.1 *General procedure for synthesis of 1,2,4,5-tetrasubstituted imidazoles by $SbCl_3$ and $SnCl_2.2H_2O$*

A mixture of aromatic aldehyde (1 mmol), benzil (1 mmol), primary amine (1 mmol), ammonium acetate (1 mmol) and $SbCl_3$ (5 mol%) (for $SnCl_2.2H_2O$ 20 mol%) were stirred at 120°C (when $SnCl_2.2H_2O$ handling as catalyst at 140°C) in solvent-free condition. The progress of reaction was monitored by TLC. After completion of reaction, the mixture was cooled to room temperature and was solved in 50 mL water then was filtered. Obtained products were purified by crystallization from acetone–water (10:1). The products were characterized by IR, NMR, and through comparison of their physical properties with those reported in literature.[15,22–32] 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 2 mmol of ammonium acetate instead of 1 mmol in the absence of primary amine.

2.2 *Representative spectral data*

2.2a *Compound* **5a** *(table 1)*: m.p. 170–172°C; Yield 0.360 g, 96%; IR (KBr) (ν_{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): 48.2, 126.0, 126.3, 126.8, 128.1, 129.0, 129.5, 129.9, 130.9, 130.9, 131.0, 135.0, 137.5, 148.0.

2.2b *Compound* **5b** *(table 1)*: m.p. 169–170°C; Yield 0.418 g, 90%; IR (KBr) (ν_{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): 49.4, 125.8, 126.5, 126.7, 127.5, 128.1, 128.2, 128.7, 128.8, 130.4, 130.7, 131.0, 131.7, 137.3.

2.2c *Compound* **5c** *(table 1)*: m.p. 163–166°C; Yield 0.368 g, 92%; IR (KBr) (ν_{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): 22.5, 49.4, 127.1, 127.4, 127.9, 128.4, 129.2, 129.7, 129.9, 130.1, 130.4, 131.0, 132.2, 138.8, 140.0, 146.3.

Table 1. Synthesis of polysubstituted imidazoles catalysed by $SbCl_3$ and $SnCl_2.2H_2O$ under solvent-free condition.

Compound	R^1	R^2NH_2	$SnCl_2.2H_2O$ Time/Yield[a] (min)/(%)	$SbCl_3$ Time/Yield[a] (min)/(%)	M.p. (°C)/(lit.)
5a	C_6H_5	$C_6H_5CH_2NH_2$	50/96	30/96	170–172[15]
5b	4-Br-C_6H_4	$C_6H_5CH_2NH_2$	25/92	20/90	169–170[15]
5c	4-CH_3-C_6H_4	$C_6H_5CH_2NH_2$	80/98	55/92	163–166[22]
5d	4-Cl-C_6H_4	$C_6H_5CH_2NH_2$	60/90	25/92	160–162[22]
5e	2-Cl-C_6H_4	$C_6H_5CH_2NH_2$	20/88	20/90	193–195[23]
5f	3-NO_2-C_6H_4	$C_6H_5CH_2NH_2$	40/85	30/90	150–152[b]
5g	4-CH_3-C_6H_4	CyclohexylNH$_2$	40/75	30/88	160–161[24]
5h	4-OCH_3-C_6H_4	$C_6H_5CH_2NH_2$	60/88	50/90	148–151[25]
5i	2-OH-5-Br-C_6H_3	4-Cl-$C_6H_4NH_2$	30/92	25/98	156–158[b]
5j	4-Benzyloxy-C_6H_4	$C_6H_5CH_2NH_2$	80/85	80/96	138–139[b]
5k	2,4-di-Cl-C_6H_3	$C_6H_5CH_2NH_2$	85/80	70/90	216–219[b]
5l	4-CH_3-C_6H_4	$C_6H_5NH_2$	60/88	30/90	182–184[26]
5′a	C_6H_5	---	50/90	15/95	272–273[27]
5′b	3-Br-C_6H_4	---	30/85	10/88	120–122[28]
5′c	2-OH-C_6H_4	---	60/88	15/90	209–211[29]
5′d	2-OCH_3-C_6H_4	---	60/90	25/92	204–206[25]
5′e	4-OCH_3-C_6H_4	---	45/85	15/88	227–230[27]
5′f	4-Benzyloxy-C_6H_4	---	45/75	20/80	235–236[30]
5′g	2-Fluorenyle	---	50/90	25/97	283–286[b]
5′h	3-Indolyl	---	60/80	30/88	311–313[b]
5′i	4-Cl-C_6H_4	---	40/90	10/94	257–259[31]
5′j	3-NO_2-C_6H_4	---	45/90	10/92	308–309[32]

[a]Refers to isolated yields
[b]Novel compound

2.2d *Compound* **5d** *(table 1)*: m.p. 160–162°C; Yield 0.386 g, 92%; IR (KBr) (ν_{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): 48.3, 125.8, 126.5, 127.5, 129.1, 129.3, 130.2, 130.4, 130.7, 131.0, 134.1, 135.0, 136.8, 137.3, 138.2.

2.2e *Compound* **5e** *(table 1)*: m.p. 193–195°C; Yield 0.378 g, 90%; IR (KBr) (ν_{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): 43.1, 126.0, 126.5, 126.6, 127.4, 128.4, 128.6, 128.9, 129.1, 129.3, 129.7, 129.8, 130.3, 130.6, 130.8, 131.0, 131.1, 132.9, 133.8, 134.2, 134.9, 136.8, 137.6, 145.1.

2.2f *Compound* **5f** *(table 1)*: m.p. 150–152°C; Yield 0.388 g, 90%; IR (KBr) (ν_{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): 47.4, 122.3, 122.5, 124.7, 125.6, 125.7, 126.7, 127.1, 127.8, 127.9, 128.5, 129.3, 129.9, 130.2, 131.5, 132.9, 133.5, 135.7, 144.2, 147.2. m/z: 431 M^+, 386, 340, 295, 190, 165, 134, 91, 57. Anal. Calcd for $C_{28}H_{21}N_3O_2$: C, 77.94; H, 4.91; N, 9.74. Found: C, 77.87; H, 4.83; N, 9.62.

2.2g *Compound* **5g** *(table 1)*: m.p. 160–161°C; Yield 0.345 g, 88%; IR (KBr) (ν_{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): 21.4, 25.1, 26.2, 33.5, 58.3, 125.9, 126.0, 126.6, 127.6, 127.8, 127.9, 128.1, 128.6, 128.7, 128.8, 129.0, 129.0, 129.1, 129.5, 129.8, 132.2, 132.8, 134.7, 137.6, 138.7, 147.8.

2.2h *Compound* **5h** *(table 1)*: m.p. 148–151°C; Yield 0.374 g, 90%; IR (KBr) (ν_{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): 47.1, 54.2, 112.9, 122.4, 124.9, 125.2, 125.7, 126.2, 127.0, 127.4, 127.5, 127.7, 128.0, 128.7, 129.3, 130.0, 130.1, 133.5, 136.6, 136.7, 146.9, 159.0.

2.2i *Compound* **5i** *(table 1)*: m.p. 156–158°C; Yield 0.490 g, 98%; IR (KBr) (ν_{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): 115.1, 123.9, 125.5, 127.6, 134.3, 137.3, 139.2, 140.5, 151.3, 164.7, 166.9. m/z: 502 M^+, 267, 214, 193, 165, 75, 57. Anal. Calcd for $C_{27}H_{18}BrClN_2O$: C, 64.62; H, 3.62; N, 5.58. Found: C, 64.51; H, 3.53; N, 5.49.

2.2j *Compound* **5j** *(table 1)*: m.p. 138–139°C; Yield 0.472 g, 96%; IR (KBr) (ν_{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): 48.2, 70.0, 115.0, 123.7, 126.0, 126.3, 126.8, 127.4, 127.5, 128.1, 128.1, 128.6, 128.8, 129.8, 130.5, 131.1, 131.2, 134.7, 136.7, 137.7, 137.9, 148.0, 159.3. m/z: 492 M^+, 402, 311, 283, 165, 91, 65. Anal. Calcd for $C_{35}H_{28}N_2O$: C, 85.34; H, 5.73; N, 5.69. Found: C, 85.18; H, 5.61; N, 5.54.

2.2k *Compound* **5k** *(table 1)*: m.p. 216–219°C; Yield 0.407 g, 90%; IR (KBr) (ν_{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): 120.8, 121.1, 122.9, 123.4, 123.7, 125.0, 126.0, 126.8, 127.2, 127.3, 127.4, 127.5, 129.0, 129.5, 131.2, 132.3, 133.7, 135.2, 136.9, 145.2. m/z: 452 M^+, 363, 295, 190, 164, 91. Anal. Calcd for $C_{28}H_{20}Cl_2N_2$: C, 73.85; H, 4.43; N, 6.15. Found: C, 73.71; H, 4.36; N, 6.09.

2.2l *Compound* **5l** *(table 1)*: m.p. 182–184°C; Yield 0.347 g, 90%; IR (KBr) (ν_{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): 20.2, 124.2, 125.4, 126.3, 126.6, 126.8, 127.0, 127.1, 127.2, 127.4, 127.7, 127.7, 127.9, 128.4, 129.7, 130.1, 136.2, 137.1, 146.0.

2.2m *Compound* **5′b** *(table 1)*: m.p. 120–122°C; Yield 0.330 g, 88%; IR (KBr) (ν_{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): 121.8, 125.6, 126.0, 126.7, 127.4, 127.7, 127.7, 128.1, 131.0.

2.2n *Compound* **5′c** *(table 1)*: m.p. 209–211°C; Yield 0.281 g, 90%; IR (KBr) (ν_{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): 111.3, 116.8, 117.9, 122.0, 126.3, 127.1, 127.3, 128.0, 129.5, 144.6, 156.4.

2.2o *Compound* **5′d** *(table 1)*: m.p. 204–206°C; Yield 0.300 g, 92%; IR (KBr) (ν_{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): 126.4, 126.8, 127.3, 128.2, 128.5, 129.0, 129.6, 129.9, 130.2, 131.0, 132.9, 133.9.

2.2p *Compound* **5′e** *(table 1)*: m.p. 227–230°C; Yield 0.286 g, 88%; IR (KBr) (ν_{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): 55.3, 114.2, 122.7, 126.7, 127.3, 127.8, 128.5, 146.1, 160.1.

2.2q *Compound* **5′f** *(table 1)*: m.p. 235–236°C; Yield 0.321 g, 80%; IR (KBr) (ν_{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): 69.7, 115.4, 123.8, 126.0, 127.1, 127.5, 128.2, 128.3, 128.6, 128.8, 128.9, 129.1, 135.7, 137.4, 146.0, 158.9.

2.2r *Compound* **5′g** *(table 1)*: m.p. 283–286°C; Yield 0.372 g, 97%; IR (KBr) (ν_{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): 39.9, 120.3, 120.6, 122.3, 124.5, 125.6, 126.7, 127.4, 128.2, 128.9, 129.3, 141.2, 141.6, 143.8, 143.9, 146.4. m/z: 384 M^+, 340, 190, 165, 134, 91, 65. Anal. Calcd for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29. Found: C, 87.41; H, 5.29; N, 7.22.

2.2s *Compound* **5′h** *(table 1)*: m.p. 311–313°C; Yield 0.294 g, 88%; IR (KBr) (ν_{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): 106.9, 112.1, 120.2, 121.9, 122.4, 124.5, 125.5, 127.3, 128.0, 128.9, 136.7, 144.1. m/z: 335 M^+, 165, 142, 115, 77, 55. Anal. Calcd for $C_{23}H_{17}N_3$: C, 82.36; H, 5.11; N, 12.53. Found: C, 82.29; H, 5.21; N, 12.40.

2.2t *Compound* **5′i** *(table 1)*: m.p. 257–259°C; Yield 0.310 g, 94%; IR (KBr) (ν_{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 (100.62 MHz, $CDCl_3$) δ (ppm): 125.9, 126.7, 127.3, 127.6, 128.2, 132.7, 144.3.

2.2u *Compound* **5′j** *(table 1)*: m.p. 308–309°C; Yield 0.313 g, 92%; IR (KBr) (ν_{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): 119.4, 122.6, 127.1, 128.4, 128.6, 130.4, 131.1, 131.8, 143.3, 148.3.

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

Entry	Solvent	Time (min)	Yield (%)
1	Water	90	46
2	Ethanol	35	75
3	Methanol	40	78
4	Chloroform	120	49
5	Acetonitrile	80	73
6	Solvent-free	30	96

3. Results and discussion

Firstly, the 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 these synthesises. In model reaction, in the presence of $SbCl_3$ (5 mol%) as catalyst, the mixture of benzil (1 mmol), benzaldehyde (1 mmol), ammonium acetate (1 mmol), bnzylamine (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 condition is the best condition to accomplish this synthesis (table 2). The same results were obtained when $SnCl_2.2H_2O$ was handled as catalyst.

We carried out the model reaction in the absence of catalyst at solvent-free condition and room-temperature for 24 h, which lead to very poor yield (12%) of product. In the absence of catalyst to 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 antimony trichloride (or stannous chloride dihydrate) and solvent-free condition are the best conditions for this synthesis.

We also evaluated quantity of required catalyst in synthesis of imidazole derivatives for model reaction (compound **5a**). It was found that maximum yield (96%) obtained, when the reaction was loaded with 5 mol% of $SbCl_3$ or 20 mol% of $SnCl_2.2H_2O$. Same result was obtained from trisubstituted imidazoles when compound **5′a** was chosen as model reaction (table 3).

Table 3. Optimization of molar ratio of the catalysts in synthesis of tri and tetrasubstituted imidazoles.

$SbCl_3$	Trisubstituted imidazole	Tetrasubstituted imidazole	$SnCl_2.2H_2O$	Trisubstituted imidazole	Tetrasubstituted imidazole
(mol%)	Time (min)/Yield (%)	Time (min)/Yield (%)	(mol%)	Time (min)/Yield (%)	Time (min)/Yield (%)
1	60/65	110/60	2	90/65	90/60
2	50/75	40/70	5	90/75	60/65
5	15/95	30/96	10	65/80	60/75
10	45/82	35/78	15	60/82	50/80
15	65/80	70/83	20	50/90	50/96
20	75/78	75/85	25	75/78	75/85

In the following study on the model reactions, we have examined the reactions at various temperatures to find out the effect of temperature on the progress of reaction in the presence of optimized amount of catalysts (table 4). The maximum rate of reaction was obtained at 120°C in the presence of $SbCl_3$ and at 140°C in the presence of $SnCl_2.2H_2O$ as the optimum temperature for tri and tetrasubstituted imidazoles.

As can be seen from table 4, at 80°C, reaction was completed slowly. Increasing temperature to 120°C (to

Table 4. Optimization of temperature for model reaction.

Temp. (°C)[a]	Trisubstituted imidazole[a] Time (min)/Yield (%)	Tetrasubstituted imidazole[a] Time (min)/Yield (%)	Temp. (°C)[b]	Trisubstituted imidazole[b] Time (min)/Yield (%)	Tetrasubstituted imidazole[b] Time (min)/Yield (%)
80	90/80	110/75	80	100/70	110/68
100	75/82	90/85	100	75/80	90/75
120	50/90	30/96	120	60/82	60/80
140	60/85	40/90	140	50/90	50/96
160	100/65	45/70	160	80/70	60/70

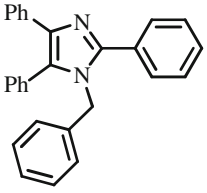
[a]$SbCl_3$ as catalyst
[b]$SnCl_2.2H_2O$ as catalyst

Table 5. Comparison of the results for the synthesis of 1-benzyl 2,4,5-triphenyl imidazole (compound **5a**) as a model reaction with other catalysts.

Catalyst	Mol (%)	Solvent/Temp. (°C)	Time (min)/Yield (%)	[Refs]
$SbCl_3$	5	Solvent free/120	30/96	This work
$SnCl_2.2H_2O$	20	Solvent free/140	50/96	This work
I_2	10	Solvent free/100	60/85	33
$[(CH_2)_4SO_3HMIM][HSO_4]$[a]	15	Solvent free/140	120/90	34
TFA[b]	20	Solvent free, MW (150 W)	4/92	35
$K_5CoW_{12}O_{40}\cdot 3H_2O$[c]	10	Solvent free/140	120/90	36
SiO_2[d]	2 g	Solvent free, MW	8/87	37
SiO_2[d]	0.1	CH_2Cl_2,Solar heat	120/80	38
$AlPO_4$	1	Solvent free/140	120/85	15
$BF_3.SiO_2$[e]	21	Solvent free/140	120/80	39
L-Proline	15	MeOH/60	510/86	25
$InCl_3.3H_2O$	10	MeOH/r.t.	444/79	40
$ZrCl_4$	20	CH_3CN/r.t.	60/86	41

[a]3-Methyl-1-(4-sulphonic acid)-butylimidazolium hydrogen sulphate
[b]Trifluoroacetic acid
[c]Potassium dodecatugstocobaltate trihydrate
[d]Silica gel as acidic support
[e]Silica-supported boron trifluoride

Table 6. Reusability results of catalysts on the reaction process for the model reaction.

Product	Total reusability	$SbCl_3$ Yield (%)/ Time (min)	$SnCl_2.2H_2O$ Yield (%)/ Time (min)
	1	96/30	96/50
	2	95/30	95/50
	3	95/35	95/50
	4	97/45	94/60
	5	97/55	92/60

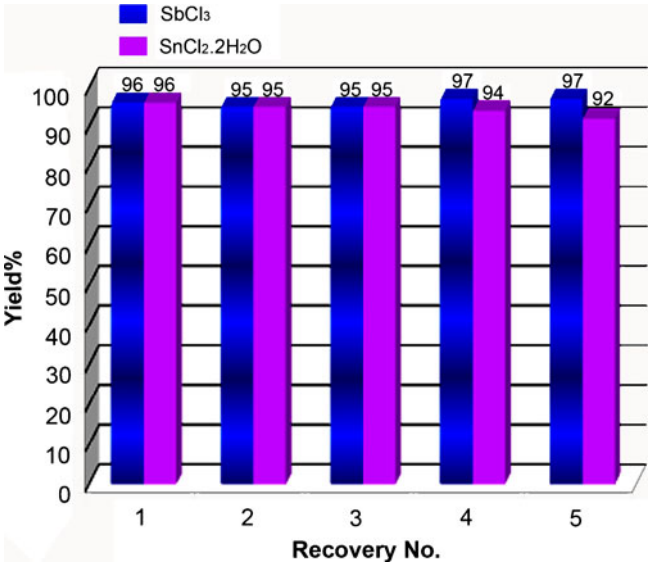


Figure 1. The reusability of the catalysts for model reaction.

140°C for $SnCl_2.2H_2O$), increased the yield of reaction and decreased the time of reaction. When the reaction was heated above 120°C (above 140°C for $SnCl_2.2H_2O$), it was observed that high temperatures did not further improve the yield and did not decrease the reaction time.

According to the archived optimal condition, we conducted the synthesis of polysubstituted imidazoles in solvent-free condition at 120°C in the presence of $SbCl_3$ and at 140°C in the presence of $SnCl_2.2H_2O$ as catalysts.

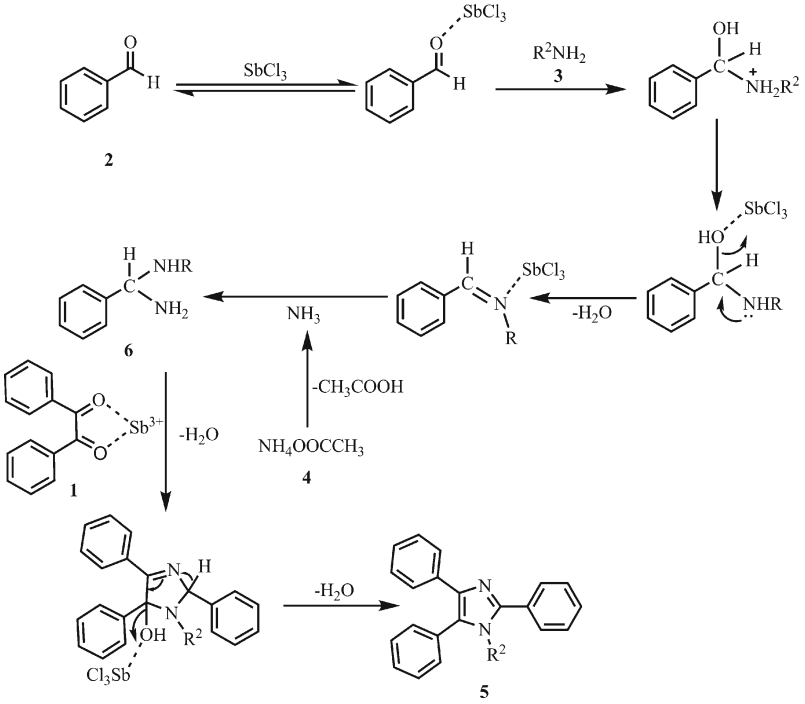
Comparison of this method with others for the synthesis of 1-benzyl 2,4,5-triphenyl imidazole (compound **5a**) as a model reaction is shown in table 5.[15,25,33–41] These results show that these catalysts are in good conditions for the synthesis of imidazole derivatives than other catalysts and methods that were reported. This method not only affords the products in excellent yields, but also avoids the problems associated with catalyst cost, handling, safety, and pollution.

3.1 *Reusability of the catalyst*

At the end of the reactions, the catalysts were filtered, washed with diethyl ether, dried at 130°C for 1 h, and reused in another reaction. We found that antimony trichloride and stannous chloride dihydrate showed high catalytic activity with very short reaction times. Moreover, can be recovered and reused five times without significant loss of activity. The results of these observations for the model reaction are shown in table 6 and figure 1.

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

As can be seen from scheme 2, in the presence of catalyst as Lewis acid ($SbCl_3$ for example), the carbonyl group of aldehyde **2** is activated and the energy of transition state for nucleophilic attack is decreased. Then nucleophilic attack of amine **3** on the activated carbonyl



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

of aldehydes, resulted to the formation of imine, and it followed by nucleophilic attack of the *in situ* generated ammonia from **4** to the imine, giving the intermediate **6**. From condensation of intermediate **6** with benzil **1** and dehydration of it, corresponding imidazoles **5** are produced.

Moreover, the probable mechanism for the synthesis of trisubstituted imidazoles is same with tetrasubstituted imidazoles but in this case, ammonium acetate was handled instead of primary amine. As well as, the reaction with aliphatic diketones and aliphatic aldehydes was tested, but the reaction progress was unsuccessful and no products were obtained. We believe that it is due to enolization of aliphatic diketones and aliphatic aldehydes which may cause reducing activity of aldehydes and 1, 2- diketones mechanistically and no desired products were obtained.

4. Conclusions

In this work, we reported a thermal exposure synthetic method for the preparation of polysubstituted imidazoles. It is a simple, efficient and rapid via multicomponent one-pot reaction in the presence of $SbCl_3$ and $SnCl_2.2H_2O$ as inexpensive and effective catalysts in solvent-free condition. Furthermore, products were isolated in excellent yields. Also, catalyst was efficiently recovered and reused, that is considered as economic advantages for the synthesis. It is believed that this procedure would find important applications in the synthesis of wide range of polysubstituted imidazoles.

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