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ORIGINAL PAPER

Chromium(III)-salen complex nanoparticles on $AlPO_4$: as an efficient heterogeneous and reusable nanocatalyst for mild synthesis of highly functionalized piperidines, 2-arylbenzimidazoles, and 2-arylbenzothiazoles

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Abstract A simple, convenient, and highly efficient multicomponent one-pot synthesis of highly functionalized piperidines has been developed via tandem reactions of β-keto esters, aromatic aldehydes, and various amines in ethanol at room temperature using catalytic amount (10 mol%) of a chromium(III)-salen complex nanoparticles supported on $AlPO_4$. The heterogeneous catalyst exhibited excellent activity and reusability (up to 8 times) in the synthesis of highly functionalized piperidines. Also, synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles have been efficiently developed under mild condition from *o*-phenylenediamines or 2-aminothiophenol with aryl aldehydes via one-step process using catalytic amount (2.0 mol%) of nanocatalyst in air atmosphere as a green oxidant. The heterogeneous catalyst was characterized by scanning electron microscopy, atomic force microscopy, inductively coupled plasma spectrometry, thermogravimetry for analysis of nitrogen adsorption, and FT-IR spectroscopy.

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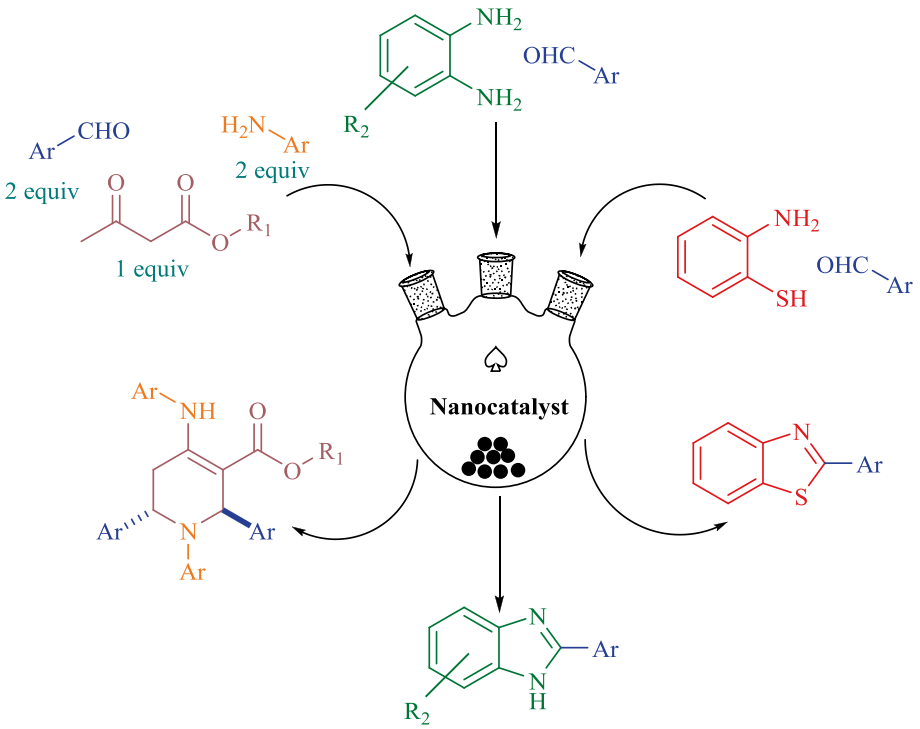
Graphical Abstract



Keywords Chromium(III)-salen complex · Heterogeneous catalyst · Highly functionalized piperidines · 2-Arylbenzimidazoles · 2-Arylbenzothiazoles · Nanoparticles

Introduction

In recent years, one-pot multi-component reactions (MCRs) have emerged as powerful synthetic tools in organic synthesis due to their advantages over the conventional multistep synthesis [1–6]. They provide major advantages including shorter reaction time, lower cost, energy saving, high atom-economy, inexpensive purification, and lack of waste products [7–10]. The MCRs can be good candidates for improving synthesis routes in terms of minimal waste and feasible reactions which satisfy some of the principles of 'Green Chemistry' [2].

Piperidine heterocyclic systems are common in a number of biologically important natural products and as important units in pharmaceuticals [11, 12]. These compounds have been extensively studied due to their wide range of application, e.g., biological activities such as antiparasitic, antiviral, anticancer, antimicrobial, and antimalarial [11, 13]. Owing to their importance in bioorganic and medicinal chemistry, there are several reports about synthesis of these compounds [14–17].

The synthesis of highly substituted piperidines have been developed using several approaches such as intramolecular Michael reactions [14], tandem cyclopropane ring-opening/Conia-ene cyclization [15], aza-Prins-cyclizations [16, 17], intramolecular Mannich reaction onto iminium ions [18], imino Diels–Alder reactions [19, 20], cyclohydrocarboxylation [21], aziridine ring expansion [22], and radical cyclization [23]. An alternative strategy for the preparation of these compounds is using MCRs. The highly substituted piperidines have been reported using MCRs strategy by employing calix[*n*]arenes [11], L-proline/TFA [13], tetrabutylammonium tribromide (TBATB) [24], CAN [25], picric acid [26], Fe@Si-Gu-Prs [27], L-proline nitrate [28], ZnO NPs [29], and ZrP_2O_7 nanoparticles [30]. However, many of these methods have some drawbacks such as low yield, expensive and excess amount of catalysts, long reaction time and non-recyclability of the catalyst. Therefore, there is a need for highly efficient, versatile, and eco-friendly synthetic protocol to obtain functionalized piperidines in excellent yields.

The benzimidazole and benzothiazole derivatives are found in various bioactive compounds having antiulcer [31, 32], antihistaminic [33], antiviral [34], antihypertensive [35], and anticancer [36, 37] properties. In addition, benzimidazoles are very important intermediates in organic reactions [38, 39]. Therefore, the facile synthesis of benzimidazoles and benzothiazole has gained considerable attention in recent years [40–43].

One of the classical methods for the synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles is the reaction of *o*-phenylenediamines or 2-aminophenol with various aldehydes [44]. Various oxidative reagents, such nitrobenzene (high-boiling oxidant/solvent) [45, 46], 1,4- benzoquinone [47], DDQ [48], air [44], benzofuroxan [49], MnO_2 [50], $In(OTf)_3$ [43], H_2O_2/HCl [51], $NaHSO_3$ [52, 53], and $Na_2S_2O_5$ [54], cobalt(III)-salen complex supported on activated carbon [55], Cu(II) complex [56], copper nanoparticles on activated carbon [57], vanadium(IV)-salen complex nanoparticles immobilized onto silica [58], sodium perborate [59] and surfactant (DBSA) as catalyst and I_2 as co-catalyst [60] have been employed in procedures.

The most important topics in modern synthetic organic chemistry is development of efficient reagents and reusable catalytic systems [61]. Although homogeneous catalysts have some limitations such as instability, difficulty in application capabilities, corrosion problems and non-recyclability, their immobilization can facilitate recovery which is of considerable attention in both research and industrial activities [62].

Both supported and unsupported chromium salen complex catalysts show wide applicability such as oxidation of benzaldehyde [63], selective oxidation of benzyl alcohol [64], asymmetric ring opening of epoxides [65], enantioselective intramolecular addition of tertiary enamides to ketones [66], asymmetric hetero Diels–Alder reaction [67], and enantioselective alkylation of acyclic α,α-disubstituted tributyltin enolates [68].

In continuation to our previous study on preparation and applications of efficient heterogeneous catalysts [69–74], this paper reports a simple, mild, and highly efficient one-pot methodology for synthesis of highly substituted piperidines, 2-arylbenzimidazoles and 2-arylbenzothiazoles.

Experimental section

Instrumentation, analysis and starting material

Chemical materials and solvents were purchased from either Fluka, Aldrich or Merck Companies. The NMR spectra were recorded on a Bruker Avance DPX-250 (^{1}H-NMR 250 MHz and ^{13}C NMR 62.9 MHz) spectrometer in pure deuterated solvents with tetramethylsilane as an internal standard. The IR spectra were obtained using a Shimadzu FT-IR 8300 spectrophotometer. Scanning electron micrographs were obtained by SEM instrumentation (SEM, XL-30 FEG SEM, Philips, at 20 kV). An atomic forced microscope model DME-SPM, version 2.0.0.9 was used for taken AFM images. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instruments at 70 or 20 eV. Melting points were determined in open capillary tubes in a Büchi-535 circulating oil melting point apparatus. The thermogravimetry (TG) of the samples was analyzed using a laboratory-made TGA instrument. The ICP analysis data were obtained using a Varian Vista-pro analyzer. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates. Column chromatography was carried out on short glass columns packed with silica gel 60 (70–230 mesh). The Schiff base *N*,*N*′-salicylaldehyde)ethylenediamine (Salen) was prepared according to a reported procedures [58, 75]. The Cr(III)-salen complex was synthesized based on a previously reported procedure [76, 77]. A mixture of Salen and $CrCl_3$-$6H_2O$ was refluxed, while stirring, in ethanol. The solid product was filtered, washed with cold ethanol, dried under vacuum, and finally was recrystallized in chloroform. The $AlPO_4$ and $AlPO_4$-ethylenediamine were synthesized by following a reported procedure [78–80].

Immobilization of Cr(III)-salen complexes onto silica

Chromium(III)-salen complex (0.1 g) was added to $AlPO_4$-ethylenediamine (1.0 g) and then was vigorously stirred followed by ultrasonic treatment for 10 min to ensure uniform dispersion of Cr(III)-salen complex on $AlPO_4$-ethylenediamine surface. Aliquot of 75 mL of dry toluene was added to the mixture while was stirred vigorously and refluxed for 6 h. The resulting solid was filtered, soxhlet-extracted with ethanol/acetonitrile (v/v = 1) as solvent for 12 h to remove the homogeneous complexes adsorbed on the support before being dried at 80 °C for overnight.

General procedure for the synthesis of highly functionalized piperidines in the presence of chromium(III) salen complex as a homogeneous catalyst

To a solution mixture containing *β*-keto ester (1.0 mmol), aromatic aldehyde (2.0 mmol) and amine (2.0 mmol) in 5 mL of ethanol, chromium(III) salen complex (10 mol%) was added followed by stirring at room temperature. After completion of the reaction, the solvent was evaporated to give the crude product, which was purified by silica gel

column chromatography (short column) employing *n*-hexane/ethyl acetate (10:1) as eluent.

General procedure for the synthesis of highly functionalized piperidines in the presence of chromium(III) salen complex nanoparticles supported on $AlPO_4$ as a heterogeneous catalyst

To a mixture of *β*-keto ester (1.0 mmol), aromatic aldehyde (2.0 mmol) and amine (2.0 mmol) in ethanol (5 mL), chromium(III) salen complex supported on $AlPO_4$ (10 mol%) as a heterogeneous catalyst was added. The mixture was stirred at room temperature. The progress of the reaction was monitored by TLC using *n*-hexane/ethyl acetate (10:1) as eluent. After completion of the reaction, the mixture was centrifuged and rinsed with CH_2Cl_2 (3 × 15 mL). The recovered solid (heterogeneous) catalyst was dried and stored for another consecutive runs. The product was concentrated by evaporating the solvent which was subsequently purified through filtering and washing with aqueous ethanol. To ensure purification, silica gel column chromatography (short column) was employed using *n*-hexane/ethyl acetate (10:1) as eluent.

General procedure for the synthesis of 2-arylbenzimidazoles in the presence of chromium(III) salen complex nanoparticles supported on $AlPO_4$

A mixture of *o*-phenylenediamine (1.0 mmol), aryl aldehyde (1.0 mmol) and chromium(III) salen complex nanoparticles supported on $AlPO_4$ (2.0 mol%) in ethanol (5 mL) was stirred at room temperature. After completion of the reaction (TLC), the mixture was centrifuged and rinsed with ethanol (3 × 15 mL). The recovered nanocatalyst was dried and stored for another consecutive runs. The solvent was evaporated to give the crude product, which was purified by silica gel column chromatography employing *n*-hexane/ethyl acetate (8:1) as eluent.

General procedure for the synthesis of 2-arylbenzothiazoles in the presence of chromium(III) salen complex nanoparticles supported on $AlPO_4$

A mixture of 2-aminothiophenol (1.0 mmol) and arylaldehyde (1.0 mmol) was stirred in 5.0 mL of ethanol in the presence of nanocatalyst (2.0 mol%) at 50 °C. After the reaction was completed, the mixture was centrifuged and rinsed with ethanol (3 × 15 mL). The solvent was evaporated to give the crude product, which was purified by silica gel column chromatography with *n*-hexane/ethyl acetate (10:1) to afford pure 2-arylbenzothiazole.

Spectroscopic data

Methyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (1)

White solid; mp 194–196 °C; (Lit. [25] mp 194–195 °C). IR (KBr): 694, 748, 925, 979, 1033, 1072, 1257, 1373, 1450, 1496, 1589, 1658, 2862, 2954, 3016, 3240, 3440 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz):*δ* 2.84 (dd, $J_1 = 15.0$ Hz, $J_2 = 2.5$ Hz, 1 H), 2.96 (dd, $J_1 = 15.0$ Hz, $J_2 = 5.5$ Hz, 1 H), 4.01 (s, 3 H), 5.23–5.24 (m, 1 H), 6.34–6.37 (m, 2H), 6.56 (s, 1 H), 6.62 (d, $J = 8.0$ Hz, 2 H), 6.68 (t, $J = 7.25$ Hz, 1 H), 7.10–7.17 (m, 5 H), 7.23–7.43 (m, 10 H), 10.36 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): *δ* 33.8, 51.2, 55.3, 58.3, 98.1, 113.1, 116.4, 126.0, 126.5, 126.8, 127.3, 128.4, 128.6, 128.8, 129.0, 129.1, 138.0, 142.9, 144.1, 147.1, 156.4, 167.7. Mass *m/z* (%): 462 ($M^+ + 2$, 5.3), 461 ($M^+ + 1$, 12.4), 460 (M^+, 12.6), 384 (100.0), 351 (23.6), 278 (34.1), 246 (25.2), 220 (21.0), 180 (21.4), 104 (15.6), 77 (29.7). Anal. Calcd for $C_{31}H_{28}N_2O_2$ (460.574): C, 80.84; H, 6.13; N, 6.08; found: C, 80.69; H, 6.22; N, 6.19.

Methyl 4-(p-toluidino)-2,6-diphenyl-1-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (2)

White solid; mp 222–224 °C; (Lit. [11] mp 220–222 °C). IR (KBr): 702, 1072, 1257, 1319, 1380, 1450, 1512, 1596, 1658, 3425 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): *δ* 2.17 (s, 3 H), 2.27 (s, 3 H), 2.74 (dd, $J_1 = 15.0$ Hz, $J_2 = 2.5$ Hz, 1 H), 2.89 (dd, $J_1 = 15.0$ Hz, $J_2 = 5.5$ Hz, 1 H), 3.94 (s, 3 H), 5.12–5.14 (m, 1 H), 6.17 (d, $J = 8.2$ Hz, 2 H), 6.43–6.46 (m, 3 H), 6.87–6.92 (m, 4 H), 7.17–7.35 (m, 10 H), 10.19 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): *δ* 20.2, 20.9, 33.6, 51.0, 55.2, 58.3, 56.6, 97.5, 112.9, 125.1, 126.0, 126.3, 126.5, 126.7, 127.1, 128.3, 128.7, 129.5, 135.2, 135.7, 143.1, 144.3, 144.9, 156.7, 168.7. Mass *m/z* (%):490 ($M^+ + 2$, 0.5), 489 ($M^+ + 1$, 2.9), 488 (M^+, 4.6), 414 (3.2), 397 (33.6), 290 (14.0), 261 (11.8), 235 (12.7), 196 (48.1), 145 (21.4), 118 (13.7), 99 (18.1), 83 (100.0), 57 (74.9). Anal. Calcd for $C_{33}H_{32}N_2O_2$ (488.627): C, 81.12; H, 6.60; N, 5.73; found: C, 81.23; H, 6.71; N, 5.82.

Methyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (3)

White solid; mp 225–227 °C; (Lit. [25] mp 224–225 °C). IR (KBr): 702, 840, 1033, 1072, 1180, 1242, 1450, 1512,

1604, 1651, 2839, 3255, 3417 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 2.65 (dd, $J_1 = 15.2$ Hz, $J_2 = 2.5$ Hz, 1 H), 2.81 (dd, $J_1 = 15.7$ Hz, $J_2 = 5.7$ Hz, 1 H), 3.67 (s, 3 H), 3.75 (s, 3 H), 3.93 (s, 3 H), 5.07–5.08 (m, 1 H), 6.21 (d, $J = 8.7$ Hz, 2 H), 6.36 (s, 1 H), 6.46 (d, $J = 9.0$ Hz, 2 H), 6.61–6.69 (m, 4 H), 7.18–7.31 (m, 10 H), 10.12 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 33.6, 50.9, 55.4, 55.6, 55.7, 58.3, 97.0, 114.0, 114.5, 126.2, 126.5, 126.8, 127.1, 127.9, 128.2, 128.6, 130.6, 141.5, 143.3, 144.3, 150.9, 157.0, 157.8, 168.6. Mass *m/z* (%): 522 ($M^+ + 2$, 0.2), 521 ($M^+ + 1$, 1.3), 520 (M^+, 1.6), 427 (1.9), 308 (13.2), 210 (16.1), 83 (100.0). Anal. Calcd for $C_{33}H_{32}N_2O_4$ (520.625): C, 76.13; H, 6.20; N, 5.38; found: C, 76.05; H, 6.31; N, 5.46.

Methyl 1-phenyl-4-(phenylamino)-2,6-dip-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4)

White solid; mp 219–220 °C; (Lit. [25] mp 215–216 °C). IR (KBr): 694, 748, 1072, 1188, 1257, 1319, 1373, 1442, 1504, 1589, 1658, 2862, 2947, 3016, 3232 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 2.35 (s, 3 H), 2.37 (s, 3 H), 2.79 (dd, $J_1 = 15.0$ Hz, $J_2 = 2.5$ Hz, 1 H), 2.91 (dd, $J_1 = 15.0$ Hz, $J_2 = 5.5$ Hz, 1 H), 3.95 (s, 3 H), 5.14–5.15 (m, 1 H), 6.31–6.35 (m, 2 H), 6.44 (s, 1 H), 6.56 (d, $J = 8.0$ Hz, 2 H), 6.62 (t, $J = 7.2$ Hz, 1 H), 7.06–7.13 (m, 11 H), 7.24 (d, $J = 8.0$ Hz, 2 H), 1029 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 21.1, 21.2, 33.8, 51.1, 55.0, 58.0, 98.2, 113.0, 116.1, 125.7, 125.9, 126.4, 126.7, 128.9, 129.0, 129.1, 129.4, 135.9, 136.7, 138.0, 139.8, 141.1, 147.2, 156.4, 168.7. Mass *m/z* (%): 490 ($M^+ + 2$, 0.1), 489 ($M^+ + 1$, 1.3), 488 (M^+, 2.1), 413 (3.9), 196 (28.7), 145 (13.8), 99 (13.7), 83 (100.0), 57 (61.2). Anal. Calcd for $C_{33}H_{32}N_2O_2$ (488.627): C, 81.12; H, 6.60; N, 5.73; found: C, 81.24; H, 6.71; N, 5.65.

Methyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5)

White solid; mp 225–227 °C; (Lit. [25] mp 225–226 °C). IR (KBr): 694, 748, 856, 979, 1072, 1188, 1265, 1326, 1372, 1404, 1504, 1596, 1651, 2869, 3039, 3240 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 2.78 (dd, $J_1 = 15.0$ Hz, $J_2 = 2.5$ Hz, 1 H), 2.88 (dd, $J_1 = 15.2$ Hz, $J_2 = 5.2$ Hz, 1 H), 3.96 (s, 3 H), 3.14–3.15 (m, 1 H), 6.42–6.46 (m, 3 H), 6.50 (d, $J = 8.2$ Hz, 2 H), 6.68 (t, $J = 7.2$ Hz, 1 H), 7.08–7.28 (m, 13 H), 10.31 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 33.8, 51.3, 54.8, 57.4, 97.6, 113.0, 116.8, 125.8, 126.1, 127.9, 128.2, 128.5, 128.9, 129.1, 129.2, 132.2, 132.9, 137.7, 141.0, 142.5, 146.5, 156.1, 168.3. Mass *m/z* (%): 531 ($M^+ + 2$, 1.4), 530 ($M^+ + 1$, 3.8), 529 (M^+, 1.9), 417 (32.6), 385 (11.9), 312 (23.9), 254 (27.9), 216 (16.6), 120 (13.1), 83 (100.0). Anal. Calcd for $C_{31}H_{26}Cl_2N_2O_2$ (529.464): C, 70.32; H, 4.95; N, 5.29; found: C, 70.41; H, 5.08; N, 5.35.

Methyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (6)

White solid; mp 184–186 °C; (Lit. [25] mp 182–183 °C). IR (KBr): 694, 756, 1033, 1072, 1180, 1249, 1373, 1450, 1504, 1596, 1651, 2839, 2954, 3232, 3448 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 2.78 (dd, $J_1 = 15.0$ Hz, $J_2 = 2.7$ Hz, 1 H), 2.89 (dd, $J_1 = 15.0$ Hz, $J_2 = 5.2$ Hz, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 3.95 (s, 3 H), 5.11–5.12 (m, 1 H), 6.37–6.40 (m, 3 H), 6.56 (d, $J = 8.0$ Hz, 2 H), 6.63 (t, $J = 7.2$ Hz, 1 H), 6.86 (d, $J = 8.5$ Hz, 4 H), 7.06–7.15 (m, 7 H), 7.23–7.27 (m, 2 H), 10.31 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 33.8, 51.1, 54.6, 55.2, 55.3, 57.6, 98.2, 113.0, 113.7, 114.1, 116.2, 125.8, 127.5, 127.8, 129.0, 134.7, 135.9, 138.0, 147.1, 156.4, 158.2, 158.8, 168.7. Mass *m/z* (%): 522 ($M^+ + 2$, 0.6), 521 ($M^+ + 1$, 1.8), 520 (M^+, 2.1), 414 (6.3), 308 (15.4), 210 (17.9), 83 (100.0). Anal. Calcd for $C_{33}H_{32}N_2O_4$ (520.625): C, 76.13; H, 6.20; N, 5.38; found: C, 76.01; H, 6.04; N, 5.46.

Methyl 1-(4-chlorophenyl)-4-(4-chlorophenylamino)-2,6-dip-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (7)

White solid; mp 219–221 °C; (Lit. [7] mp 218–220 °C). IR (KBr): 756, 810, 1072, 1188, 1265, 1334, 1373, 1458, 1496, 1604, 1651, 2869, 2947, 3240, 3448 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 2.35 (s, 3 H), 2.38 (s, 3 H), 2.73(dd, $J_1 = 15.2$ Hz, $J_2 = 2.2$ Hz, 1 H), 2.90 (dd, $J_1 = 15.0$ Hz, $J_2 = 5.7$ Hz, 1 H), 3.97 (s, 3 H), 5.10–5.12 (m, 1 H), 6.23 (d, $J = 8.5$ Hz, 2 H), 6.38 (s, 1 H), 6.48 (d, $J = 9.0$ Hz, 2 H), 7.00–7.22 (m, 12 H), 10.25 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 21.1, 21.2, 33.6, 51.2, 55.2, 58.1, 98.7, 114.1, 121.1, 126.3, 126.5, 127.0, 128.7, 128.9, 129.0, 129.1, 129.5, 131.3, 136.2, 136.5, 137.1, 139.2, 140.2, 145.6, 155.6, 168.5. Mass *m/z* (%): 559 ($M^+ + 2$, 5.9), 558 ($M^+ + 1$, 14.6), 557 (M^+, 11.5), 445 (73.3), 413 (27.0), 326 (71.6), 268 (57.9), 230 (49.4), 165 (10.3), 125 (19.0), 91 (100.0). Anal. Calcd for $C_{33}H_{30}Cl_2N_2O_2$ (557.517): C, 71.09; H, 5.42; N, 5.02; found: C, 71.18; H, 5.54; N, 5.13.

Methyl 4-(p-toluidino)-2,6-bis(4-methoxyphenyl)-1-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (8)

White solid; mp 191–193 °C; (Lit. [11] mp 181 °C).IR (KBr): 802, 1033, 1072, 1172, 1249, 1458, 1512, 1604, 1658, 2839, 3008, 3232, 3440 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 2.18 (s, 3 H), 2.29 (s, 3 H), 2.70–2.76 (m, 1

H), 2.83 (dd, $J_1 = 15.0$ Hz, $J_2 = 4.7$ Hz, 1 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 3.93 (s, 3 H), 5.06–5.08 (m, 1 H), 6.26 (d, $J = 7.2$ Hz, 2 H), 6.34 (s, 1 H), 6.46 (d, $J = 7.5$ Hz, 2 H), 6.83 (d, $J = 8.7$ Hz, 4 H), 6.91 (t, $J = 9.0$ Hz, 4 H), 7.09 (d, $J = 7.5$ Hz, 2 H), 7.24 (d, $J = 9.2$ Hz, 2 H), 10.22 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 20.2, 20.9, 33.7, 50.9, 54.7, 55.2, 55.3, 57.5, 97.6, 113.0, 113.6, 114.0, 125.0, 125.9, 127.5, 127.8, 129.4, 129.5, 135.0, 135.3, 135.6, 136.2, 144.9, 156.8, 158.1, 158.7, 168.7. Mass *m/z* (%): 550 ($M^+ + 2$, 7.4), 549 ($M^+ + 1$, 14.1), 548 (M^+, 15.3), 458 (22.2), 425 (34.6), 323 (66.5), 264 (41.4), 210 (100.0), 123 (34.1), 83 (51.0). Anal. Calcd for $C_{35}H_{36}N_2O_4$ (548.679): C, 76.62; H, 6.61; N, 5.11; found: C, 76.51; H, 6.79; N, 5.24.

Methyl 4-(p-toluidino)-2,6-bis(4-chlorophenyl)-1-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (9)

White solid; mp 214–215 °C; (Lit. [11] mp 213–215 °C). IR (KBr): 794, 979, 1010, 1072, 1180, 1257, 1512, 1581, 1650, 2862, 3016, 3255, 3442 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.19 (s, 3 H), 2.30 (s, 3 H), 2.72 (dd, $J_1 = 15.0$ Hz, $J_2 = 3.0$ Hz, 1 H), 2.81 (dd, $J_1 = 15.0$ Hz, $J_2 = 5.0$ Hz, 1 H), 3.93 (s, 3 H), 5.06–5.08 (m, 1 H), 6.30 (d, $J = 8.2$ Hz, 2 H), 6.34 (s, 1 H), 6.38 (d, $J = 8.7$ Hz, 2 H), 6.90 (d, $J = 8.7$ Hz, 2 H), 6.97 (d, $J = 7.5$ Hz, 2 H), 7.08 (d, $J = 8.5$ Hz, 2 H), 7.24–7.28 (m, 6 H), 10.20 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 20.2, 21.0, 33.6, 51.1, 54.9, 57.4, 97.0, 113.0, 125.8, 125.9, 127.9, 128.1, 128.4, 128.8, 129.6, 132.1, 132.8, 135.0, 136.0, 141.2, 142.7, 144.4, 156.4, 168.4. Mass *m/z* (%): 559 ($M^+ + 2$, 1.2), 558 ($M^+ + 1$, 5.6), 557 (M^+, 4.6), 445 (36.0), 413 (10.7), 326 (41.4), 268 (24.8), 229 (27.4), 125 (12.7), 83 (100.0). Anal. Calcd for $C_{33}H_{30}Cl_2N_2O_2$ (557.517): C, 71.09; H, 5.42; N, 5.02; found: C, 71.23; H, 5.31; N, 5.14.

Methyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-dip-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10)

White solid; mp 223–225 °C; (Lit. [25] mp 226–227 °C). IR (KBr): 810, 1033, 1072, 1180, 1249, 1458, 1520, 1604, 1658, 2839, 2939, 3255, 3441 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.33 (s, 3 H), 2.36 (s, 3 H), 2.64 (dd, $J_1 = 15.2$ Hz, $J_2 = 2.7$ Hz, 1 H), 2.80 (dd, $J_1 = 15.0$ Hz, $J_2 = 5.7$ Hz, 1 H), 3.67 (s, 3 H), 3.76 (s, 3 H), 3.91 (s, 3 H), 5.02–5.03 (m, 1 H), 6.23 (d, $J = 8.7$ Hz, 2 H), 6.29 (s, 1 H), 6.46 (d, $J = 9.0$ Hz, 2 H), 6.61–6.69 (m, 4 H), 7.04–7.12 (m, 6 H), 7.20 (d, $J = 8.0$ Hz, 2 H), 1012 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 21.1, 21.2, 33.6, 50.9, 55.4, 55.6, 57.9, 97.1, 113.9, 114.0, 114.5, 126.4, 126.7, 127.9, 128.8, 129.2, 130.8, 135.7, 136.5, 140.2, 141.3, 141.7, 150.8, 157.0, 157.7, 168.7. Mass *m/z* (%): 550 ($M^+ + 2$, 3.4), 549 ($M^+ + 1$, 8.0), 548 (M^+, 12.7), 458 (14.8), 425 (24.4), 322 (56.1), 264 (38.3), 225 (100.0), 123 (32.1), 83 (74.8). Anal. Calcd for $C_{35}H_{36}N_2O_4$ (548.679): C, 76.62; H, 6.61; N, 5.11; found: C, 76.51; H, 6.69; N, 5.22.

Methyl 1-(4-chlorophenyl)-4-(4-chlorophenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (11)

White solid; mp 218–219 °C. IR (KBr): 694, 732, 802, 1080, 1188, 1260, 1319, 1333, 1450, 1496, 1596, 1651, 3255, 3448 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.68–2.74 (m, 1 H), 2.88 (dd, $J_1 = 15.0$ Hz, $J_2 = 5.0$ Hz, 1 H), 3.96 (s, 3 H), 5.12–5.13 (m, 1 H), 6.18 (d, $J = 8.2$ Hz, 2 H), 6.41–6.47 (m, 3 H), 7.00–7.30 (m, 15 H), 10.22 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 33.5, 51.3, 55.3, 58.3, 98.5, 114.1, 121.2, 126.3, 126.5, 126.7, 127.1, 127.5, 128.5, 128.8, 128.9, 129.1, 131.5, 136.4, 142.3, 143.2, 145.5, 155.6, 168.5. Mass *m/z* (%): 531 ($M^+ + 2$, 0.6), 530 ($M^+ + 1$, 2.0), 529 (M^+, 1.1), 417 (20.8), 312 (13.5), 254 (14.7), 216 (10.3), 120 (19.6), 83 (100.0). Anal. Calcd for $C_{31}H_{26}Cl_2N_2O_2$ (529.464): C, 70.32; H, 4.95; N, 5.29; found: C, 70.41; H, 5.08; N, 5.19.

Ethyl 1-phenyl-4-(phenylamino)-2,6-dip-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (12)

White solid mp 233–235 °C; (Lit. [25] mp 230–231 °C). IR (KBr): 694, 748, 948, 1026, 1072, 1172, 1257, 1325, 1373, 1504, 1596, 1651, 2869, 2923, 2977, 3240 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.50 (t, $J = 7.0$ Hz, 3 H), 2.36 (s, 3H), 2.37 (s, 3H), 2.80 (dd, $J_1 = 15.0$ Hz, $J_2 = 2.5$ Hz, 1 H), 2.92 (dd, $J_1 = 15.0$ Hz, $J_2 = 5.5$ Hz, 1 H), 4.33–4.53 (m, 2 H), 5.15–5.16 (m, 1 H), 6.32–6.36 (m, 2 H), 6.46 (s, 1 H), 6.56–6.66 (m, 3 H), 7.07–7.14 (m, 11 H), 7.27 (d, $J = 8.0$ Hz, 2 H), 10.34 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 14.9, 21.1, 21.2, 33.8, 55.0, 58.0, 59.7, 98.5, 113.0, 116.1, 125.6, 125.8, 126.4, 126.7, 128.9, 128.9, 129.0, 129.4, 135.8, 136.7, 138.1, 139.8, 141.2, 147.2, 156.2, 168.4. Mass *m/z* (%): 504 ($M^+ + 2$, 0.5), 503 ($M^+ + 1$, 3.5), 502 (M^+, 3.7), 411 (21.7), 306 (19.2), 234(11.6), 194 (28.1), 97 (42.7), 57 (100.0). Anal. Calcd for $C_{34}H_{34}N_2O_2$ (502.654): C, 81.24; H, 6.82; N, 5.57; found: C, 81.33; H, 6.94; N, 5.68.

Methyl 1-(4-chlorophenyl)-4-(4-chlorophenylamino)-2,6-di(pyridin-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (13)

White solid; mp 201–203 °C. IR (KBr): 748, 802, 1080, 1188, 1257, 1319, 1434, 1496, 1596, 1651, 2947, 3078, 3263, 3442 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.14 (dd, $J_1 = 15.2$ Hz, $J_2 = 2.2$ Hz, 1 H), 3.58 (dd, $J_1 = 15.5$ Hz,

J_2 = 6.2 Hz, 1 H), 3.91 (s, 3 H), 5.25–5.27 (m, 1 H), 6.31–6.43 (m, 5 H), 6.98 (d, J = 9.0 Hz, 2 H), 7.09–7.19 (m, 5 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.53–7.66 (m 2 H), 10.27 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 32.5, 51.2, 57.4, 59.9, 96.5, 113.7, 121.1, 121.4, 121.6, 121.7, 122.2, 126.4, 128.7, 129.1, 131.2, 136.3, 136.4, 136.8, 145.5, 149.5, 156.3, 162.0, 162.9, 168.3. Mass *m/z* (%): 533 (M^+ + 2, 4.0), 532 (M^+ + 1, 5.6), 531 (M^+, 5.3), 452 (12.4), 405 (5.3), 373 (8.8), 300 (11.1), 241 (8.0), 127 (10.7), 83 (100.0). Anal. Calcd for $C_{29}H_{24}Cl_2N_4O_2$ (531.439): C, 65.54; H, 4.55; N, 10.54; found: C, 65.43; H, 4.59; N, 11.06.

Methyl 2,6-di(thiophen-2-yl)-1-p-tolyl-4-(p-tolylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (14)

White solid; mp 205–207 °C. IR (KBr): 694, 794, 1072, 1257, 1458, 1512, 1604, 1658, 3255, 3432 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.21 (s, 3 H), 2.32 (s, 3 H), 2.89 (dd, J_1 = 15.2 Hz, J_2 = 3.0 Hz, 1 H), 3.09 (dd, J_1 = 15.2 Hz, J_2 = 5.2 Hz, 1 H), 3.91 (s, 3 H), 5.36–5.40 (m, 1 H), 6.41 (s, 1 H), 6.50 (d, J = 8.0 Hz, 2 H), 6.69 (d, J = 8.7 Hz, 2 H), 6.81–7.04 (m, 8 H), 7.12–7.15 (m, 2 H), 10.38 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 20.3, 21.0, 34.2, 51.0, 52.8, 53.6, 96.8, 113.6, 116.7, 123.5, 124.0, 124.2, 124.3, 124.4, 125.8, 126.3, 126.5, 126.6, 129.4, 129.5, 129.7, 130.0, 135.4, 135.7, 144.0, 147.6, 149.7, 156.6, 168.2. Mass *m/z* (%): 502 (M^+ + 2, 2.4), 501 (M^+ + 1, 6.6), 500 (M^+, 11.0), 299 (24.5), 266 (22.5), 200 (11.2), 97 (42.0), 57 (100.0). Anal. Calcd for $C_{29}H_{28}N_2O_2S_2$ (500.672): C, 69.57; H, 5.64; N, 5.60; found: C, 69.70; H, 5.56; N, 5.71.

Ethyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (15)

White solid; mp 229–231 °C; (Lit. [26] mp 228–230 °C). IR (KBr): 694, 748, 1010, 1064, 1172, 1257, 1326, 1365, 1496, 1596, 1651, 2869, 3047, 3232 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.47 (t, J = 7.0 Hz, 3 H), 2.76 (dd, J_1 = 15.0 Hz, J_2 = 2.7 Hz, 1 H), 2.86 (dd, J_1 = 15.2 Hz, J_2 = 5.0 Hz, 1 H), 4.31–4.51 (m, 2 H), 5.09–5.11 (m, 1 H), 6.39–6.50 (m, 5 H), 6.67 (t, J = 6.8 Hz, 1 H), 7.06–7.27 (m, 13 H), 10.32 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 14.8, 33.7, 54.7, 57.4, 59.9, 97.8, 113.0, 116.8, 125.7, 126.0, 127.8, 128.1, 128.4, 128.8, 129.0, 129.1, 129.3, 129.6, 132.1, 132.9, 137.7, 141.0, 142.5, 146.5, 155.8, 168.0. Mass *m/z* (%): 544 (M^+ + 1, 2.3), 543 (M^+, 2.6), 431 (58.7), 385 (18.2), 326 (23.7), 254 (26.0), 216 (25.4), 137 (20.1), 83 (100.0). Anal. Calcd for $C_{32}H_{28}Cl_2N_2O_2$ (543.491): C, 70.72; H, 5.19; N, 5.15; found: C, 70.64; H, 5.25; N, 5.28.

Methyl 2,6-bis(3-nitrophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (16)

Pale yellow solid; mp 182–183 °C; (Lit. [25] mp 181–182 °C). IR (KBr): 694, 748, 1072, 1188, 1257, 1350, 1496, 1535, 1596, 1658, 2862, 3417 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.89 (d, J = 3.7 Hz, 2 H), 3.99 (s, 3 H), 5.33–5.35 (m, 1 H), 6.39–6.50 (m, 5 H), 6.70 (t, J = 7.2 Hz, 1 H), 7.07–7.17 (m, 5 H), 7.45–7.51 (m, 3 H), 7.67 (d, J = 7.5 Hz, 1 H), 7.95 (s, 1 H), 8.09–8.15 (m, 2 H), 8.23 (s, 1 H), 10.31 (s, 1 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 33.7, 51.5, 55.1, 57.0, 96.7, 113.1, 117.7, 121.4, 121.5, 121.9, 122.5, 125.6, 126.6, 129.1, 129.3, 129.7, 132.5, 137.1, 144.4, 145.7, 146.3, 148.5, 148.6, 155.5, 168.0. Mass *m/z* (%): 551 (M^+ + 1, 0.2), 550 (M^+, 1.0), 428 (8.1), 396 (3.1), 307 (2.0), 265 (1.2), 196 (1.5), 118 (2.3), 83 (100.0). Anal. Calcd for $C_{31}H_{26}N_4O_6$ (550.567): C, 67.63; H, 4.76; N, 10.18; found: C, 67.55; H, 4.84; N, 10.30.

2-(4-Methylphenyl)-1*H*-benzimidazole (17) [55]

^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.35 (s, 3H), 7.15–7.20 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.46–7.56 (m, 2H), 8.07 (d, J = 8.1 Hz, 2H), 12.84 (s, 1H). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 20.9, 121.9, 126.3, 127.4, 128.9, 129.4, 139.5, 151.3.

2-(4-Chlorophenyl)-1*H*-benzimidazole (22) [55]

^{1}H NMR (DMSO-d_6, 250 MHz): δ 7.18–7.21 (m, 2 H), 7.60 (m, 4 H), 8.17 (d, J = 8.6 Hz, 2H), 12.99 (s, 1 H). ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 111.4, 118.9, 121.9, 122.7, 128.1, 129.0, 134.5, 150.1.

4-(1*H*-Benzimidazol-2-yl)phenol (28) [55]

^{1}H NMR (DMSO-d_6, 250 MHz): δ 6.93 (dd, J_1 = 8.5 Hz, J_2 = 1.2 Hz, 2H), 7.10–7.22 (m, 2H), 7.52–7.53 (m, 2H), 8.02 (d, J = 8.6 Hz, 2H), 10.07 (s, 1H), 12.65 (s, 1H). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 115.7, 121.0, 121.6, 128.1, 151.8, 159.1.

2-(2,5-Dimethoxyphenyl)-1*H*-benzimidazole (31) [55]

^{1}H NMR (DMSO-d_6, 250 MHz): δ 3.78 (s, 3H), 3.95 (s, 3H), 6.99–7.20 (m, 4H), 7.65 (m, 2H), 8.0.01 (d, J = 3.1 Hz, 1H), 12.14 (s, 1H). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 55.4, 56.0, 112.0, 113.3, 113.6, 117.0, 118.4, 121.5, 122.1, 134.7, 142.6, 148.7, 151.0, 153.1.

2-(Pyridin-4-yl)-1*H*-benzo[*d*]imidazole (34)

White solid; mp 217–219 °C; IR (KBr): 686 (s), 748 (s), 825 (s), 995 (s), 1319 (s), 1434 (s), 1604 (s), 3047 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.25–7.37 (m, 2 H), 7.67–7.71 (m, 2 H), 7.99 ((dd, $J = 4.5$, $J = 1.6$ Hz, 2 H), 8.75 ((dd, $J = 4.5$, $J = 1.6$ Hz, 2 H). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 120.3, 122.8, 137.1, 148.7, 150.4. Mass *m/z* (%): 195 (M^+, 69.1), 168 (18.1), 149 (31.9), 94 (41.5), 73 (50.0), 57 (100.0). Anal. Calcd for C_{12} H_9 N_3 (195.223): C, 73.83; H, 4.65; N, 21.52. Found: C, 73.81; H, 4.68; N, 21.49.

2-(1*H*-Benzo[*d*]imidazol-2-yl)-6-(morpholinomethyl) phenol (33)

White solid; mp 185–187 °C; IR (KBr): 748 (s), 864 (s), 1002 (s), 1111 (s), 11,257 (m), 1458 (s), 1519 (s), 1612 (s), 3202 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 2.65 (s, 4 H), 3.81 (s, 6 H), 7.91 (t, $J = 7.8$, 1 H), 7.12 (d, $J = 7.4$, 1 H), 7.24 (m, 2 H), 7.64 (m, 2 H), 8.36 (d, $J = 7.9$, 1 H), 10.94 (br, 2 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 52.8, 61.0, 66.6, 119.9, 121.5, 122.5, 128.3, 130.7, 156.0. Mass *m/z* (%): 309 (M^+, 25.8), 280 (10.6), 251 (25.5), 224 (100.0), 195 (32.8), 135 (19.6), 111 (12.6), 86 (23.6), 57 (75.4). Anal. Calcd for C_{18} H_{19} N_3 O_2 (309.366): C, 69.88; H, 6.19; N, 13.58. Found: C, 69.83; H, 6.24; N, 13.55.

2-*p*-Tolylbenzo[*d*]thiazole (34) [58]

^1H NMR ($CDCl_3$, 250 MHz): δ 2.29 (s, 3H), 7.15 (d, $J = 7.9$ Hz, 2H), 7.23–7.36 (m, 2H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.86 (d, $J = 8.2$ Hz, 2H), 7.94 (d, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 21.5, 121.6, 123.1, 125.0, 126.2, 127.8, 129.7, 131.0, 135.0, 141.3, 154.3, 168.2.

2-(2,5-Dimethoxyphenyl)benzo[*d*]thiazole (35) [58]

^1H NMR ($CDCl_3$, 250 MHz): δ 3.90 (s, 3H), 3.98 (s, 3H), 7.00–7.02 (m, 2H), 7.37–7.41(m, 1H), 7.47–7.50 (m, 1H), 7.93 (d, $J = 8.6$ Hz, 1H), 8.09–8.12 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 55.9, 56.3, 112.7, 113.4, 118.7, 121.3, 122.7, 122.8, 124.7, 125.9, 136.3, 151.8, 152.1, 153.9, 162.9.

4-(Benzo[*d*]thiazol-2-yl)phenol (40)

^1H NMR (DMSO, 250 MHz): δ 6.90 (d, $J = 8.6$ Hz, 2H), 7.32–7.49 (m, 2H), 7.87–8.02 (m, 4H), 10.34 (s, 1H). ^{13}C NMR (DMSO, 62.9 MHz) δ 115.5, 116.0, 121.8, 122.2, 124.1, 124.7, 126.2, 128.5, 129.0, 134.1, 153.6, 160.4, 167.5.

3-(Benzo[*d*]thiazol-2-yl)phenol (41)

^1H NMR (DMSO, 250 MHz): δ 6.93–6.97 (m, 1H), 7.34–7.49 (m, 5H), 8.00–8.10 (m, 2H), 10.00 (s, 1H). ^{13}C NMR (DMSO, 62.9 MHz) δ 113.4, 118.2, 118.5, 122.0, 122.7, 125.3, 126.5, 130.4, 134.0, 134.3, 153.4, 157.9, 167.4.

2-(2-Chlorophenyl)benzo[*d*]thiazole (42)

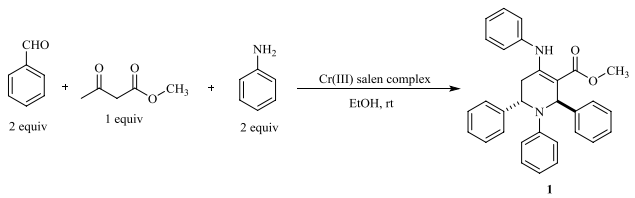
^1H NMR ($CDCl_3$, 250 MHz): δ 7.27–7.41 (m, 5H), 7.83 (d, $J = 7.8$ Hz, 1H), 8.02–8.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 121.4, 123.5, 125.4, 126.3, 127.1, 130.8, 131.1, 131.7, 132.2, 132.7, 136.1, 152.5, 164.0.

Results and discussion

In continuation of our study on the synthesis and formation of metal-salen complexes with different molecules [57, 58, 69, 70, 75, 81–84], this paper reports the possibility of synthesizing highly substituted piperidines using chromium(III)-salen complex as catalyst. Following a previously reported procedures [78–80, 85], chromium(III)-salen complex as a homogeneous catalyst was prepared. $CrCl_3$-$6H_2O$ and salen was mixed in ethanol. The mixture was then refluxed for 6 h. After the reaction was completed, the solid product was filtered, washed with cold ethanol, dried under vacuum and recrystallized in chloroform.

First of all, the effects of catalyst, solvent, and the molar ratio of the reagents were investigated by using a reaction mixture of benzaldehyde, aniline, and methylacetoacetate as the model reaction (Scheme 1).

The catalytic efficiency of chromium(III)-salen for synthesis of product **1** by using methyl acetoacetate (1.0 mmol), benzaldehyde (2.0 mmol) and aniline (2.0 mmol) in various mol% of chromium(III)-salen



Scheme 1 The model reaction of synthesis of highly functionalized piperidines

Table 1 Effect of different solvents on the synthesis of compound **1** from the reaction of benzaldehyde, aniline, and methylacetoacetate at room temperature using chromium(III)-salen complex (10 mol%)

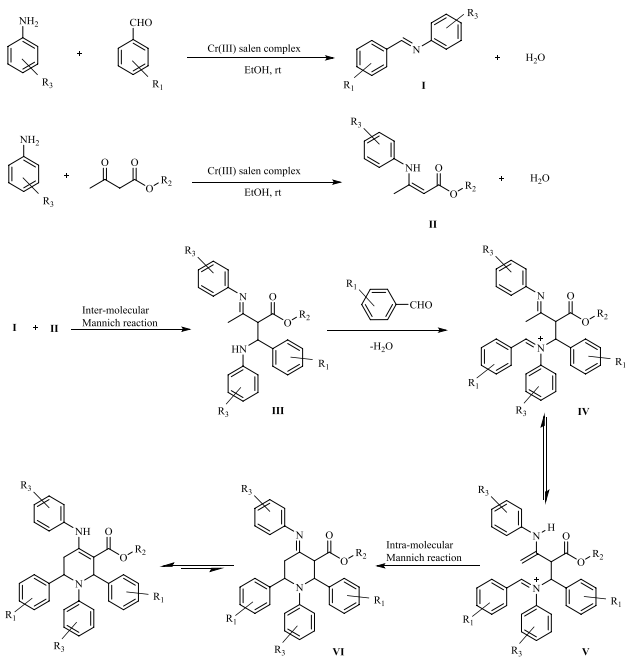
Entry[]	Solvent	Time (h)	Yield (%)[a]
1	$CHCl_3$	24	<10
2	Dioxane	24	<10
3	THF	24	<10
4	DMSO	24	25
5	H_2O	24	–
6	CH_3CN	24	45
7	EtOH	16	81
8	Neat	24	31

[a] Isolated yield

was investigated. The results indicated that 10 mol% chromium(III)-salen complex was sufficient to obtain a high yield of the desired product in a short time. At chromium(III)-salen complex amounts higher than 10 mol%, there was no significant change in the reaction yield. The chemical structure of product **1** was characterized by the spectroscopic techniques and was confirmed based on available literature data. In the absence of chromium(III)-salen complex, no product resulted which indicated that the presence of the catalyst was clearly required for the reaction to proceed.

The effect of solvents on the synthesis of highly substituted piperidines from the reaction of aromatic aldehydes, β-keto esters, and amines at room temperature using chromium(III)-salen complex was also investigated as shown in Table 1. It was found that the progress of these reactions largely depended on the nature of the solvent; however, ethanol has been more effective than the other solvents. When the reaction was carried out under solvent-free conditions, the product was obtained in low yield (31%). As a result, the stoichiometric ratio of 2:2:1 (aldehyde: amine: β-keto ester) in the presence of 10 mol% chromium(III)-salen complex in ethanol was found to be the optimum conditions for obtaining the maximum yield.

Using the optimized experimental conditions, highly substituted piperidines was synthesized by performing a one pot multi-component reaction between β-keto esters, aromatic aldehydes, and various amines in the presence of Cr(III) salen complex as the catalyst. A mechanism for this synthesis is proposed (Scheme 2) similar to that established in the literature [2, 7, 24, 25]; however, the exact explanation for this mechanism is not clear yet. A possible explanation could be based on the reaction of aniline with aromatic aldehyde or β-ketoester yielding the corresponding imine (**I**) or enamine (**II**), respectively.



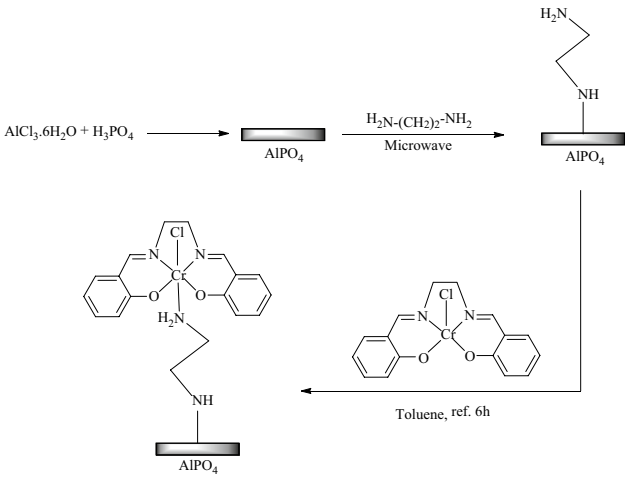
Scheme 2 Proposed mechanism for the Cr(III)-salen complex-catalyzed synthesis of highly substituted piperidines

The catalyst probably facilitates formation of imine (**I**) or enamine (**II**) by increasing the electrophilicity of the carbonyl group. The imine (**I**) reacts with enamine (**II**) to give intermediate (**III**) through inter-molecular Mannich-type reaction. The intermediate (**III**) reacts with aromatic aldehyde to give intermediate (**IV**) through eliminating a water molecule. The intermediate (**IV**) tautomerizes to give the intermediate (**V**); the intramolecular hydrogen bond is a spontaneous tendency for tautomerization. The tautomer (**V**) undergoes intramolecular Mannich-type reaction to form intermediate (**VI**) and this tautomerizes to give the product due to conjugation with the ester group.

Preparation of Cr(III)-salen complex supported on $AlPO_4$ nanoparticles as a heterogeneous nanocatalyst

Immobilization of a homogeneous catalyst can in principle facilitate its reuse and recovery which is of considerable interest in modern synthetic organic chemistry [62].

Since chromium(III) salen catalyzes the synthesis of highly substituted piperidines under mild condition from β-keto esters, aromatic aldehydes and various amines, a heterogeneous catalyst was set out simply by impregnating Cr(III)-salen complex on $AlPO_4$ nanoparticles as the support.



Scheme 3 Preparation of immobilized Cr(III)-salen catalyst on ethylenediamine functionalized $AlPO_4$

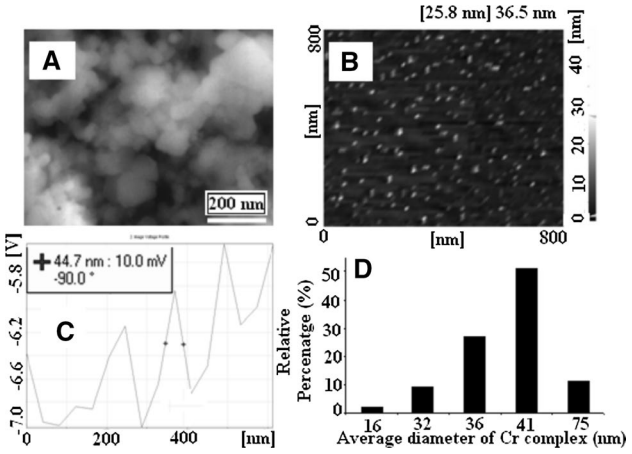


Fig. 1 Characterization of Cr(III)-salen complex with **a** SEM, **b** AFM images, **c** voltage profile, and **d** histogram

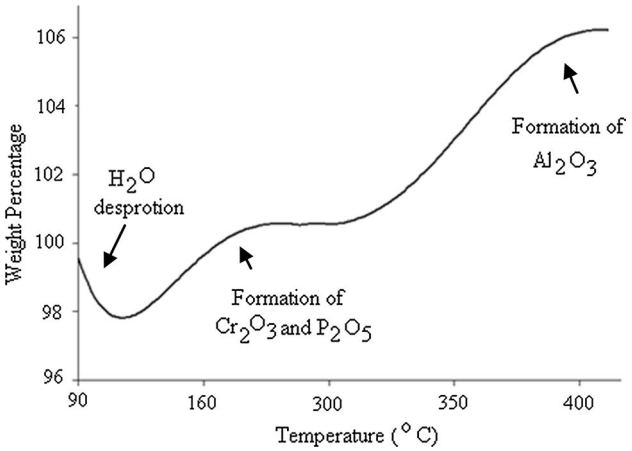


Fig. 2 Thermogram of Cr(III)-salen complex immobilized on AlPO4 support

The amorphous $AlPO_4$ (Al/P = 1) nanoparticles, as support, were synthesized following a reported procedure [78–80]. The $AlPO_4$-ethylenediamine was synthesized according to the literature [78, 79] and used as a support for the immobilization of Cr(III)-salen complex. In a typical experiment, 15.0 g $AlPO_4$, 40 mL diethyl ether and 2 mL ethylenediamine, were stirred at room temperature for 1 h. Then, diethyl ether was removed and the product was subsequently heated for 1.5 h at 100 °C. The mixture was placed in the center of a domestic microwave oven and was heated up for 10 min (190 W, 5 min and 380 W, 5 min) to ensure reaction completion. After irradiation, the mixture was cooled and washed with ethanol to remove the unreacted ethylenediamine; the product was then vacuum-dried and separated.

The reaction pathway for the preparation of the immobilized catalyst is shown in Scheme 3. Chromium(III)-salen complex (0.1 g) was added to $AlPO_4$-ethylenediamine (1.0 g) at room temperature and agitated with vigorous stirring followed by ultrasonic treatment for 10 min to ensure uniform dispersion of Cr(III)-salen complex on $AlPO_4$-ethylenediamine surface. Then, 75 mL of dry toluene was added to the mixture. The resulting suspension was refluxed while vigorously stirred for 6 h. The solid product was filtered, soxhlet-extracted with ethanol and acetonitrile (v/v = 1) as solvent for 12 h to remove the residue of the homogeneous complex that had been adsorbed on the surface of the support. It was dried at 80 °C for overnight. The Cr(III)-salen catalyst was successfully immobilized on $AlPO_4$ and was subsequently used for the catalytic synthesis of highly substituted piperidines under mild conditions.

Characterization of Cr(III)-salen complex supported on $AlPO_4$

In this experiment, different techniques were adopted to characterize the immobilized Cr(III)-salen complex. The scanning electron microscopic (SEM) and atomic forced microscopic (AFM) images (Fig. 1a, b) revealed that $AlPO_4$ was an appropriate support for deposition of Cr(III)-salen complex. The voltage profile image of Cr(III)-salen complex, corresponding to the AFM image (Fig. 1b), has also been shown in Fig. 1c. Based on the voltage profile image, large quantity with narrow size distribution (<100 nm) was observed as shown in Fig. 1d. In accordance with the histogram, the average size of Cr(III)-salen complex was estimated to be ~40 nm.

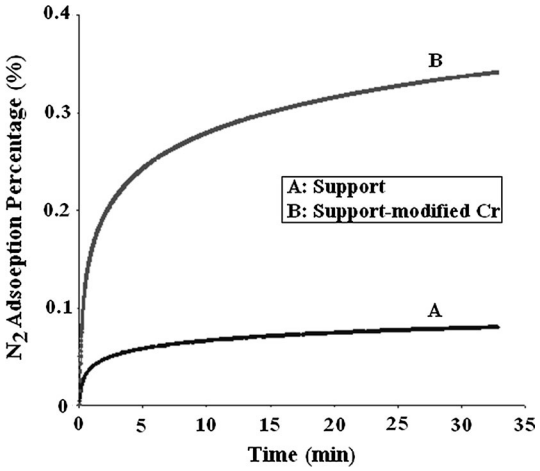


Fig. 3 Nitrogen adsorption percentage of *a* pure $AlPO_4$, and *b* $AlPO_4$ when was used as support for Cr(III)-salen complex

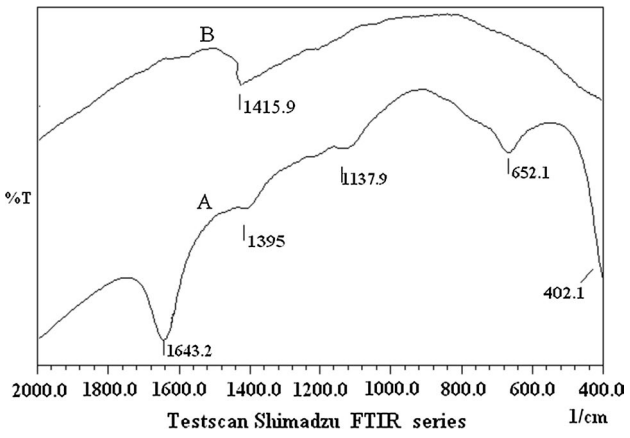


Fig. 4 The FT-IR spectra of *a* immobilized Cr(III)-salen complex and *b* –NH2-functionalized $AlPO_4$ support

The thermal behavior of Cr(III)-salen complex was also investigated using a home-made thermogravimetric (TG) analyzer as shown in Fig. 2. According to this figure, the significant quench in the weight percentage of the complex at ~110 °C is related to the desorption of water and organic species from the surface of the immobilized Cr(III)-salen complex. The increase in the weight percentage at ~160 °C is related to the oxidation phosphorous and formation of Cr_2O_3 and P_2O_5 proving that Cr(III)-salen complex is decomposed at this temperature. The oxidation of the phosphorous compounds is so exothermic that the temperature ramp of the TG instrumentation system could not be controlled. This causes oxidation of aluminum and formation of Al_2O_3 at a temperature of ~380 °C.

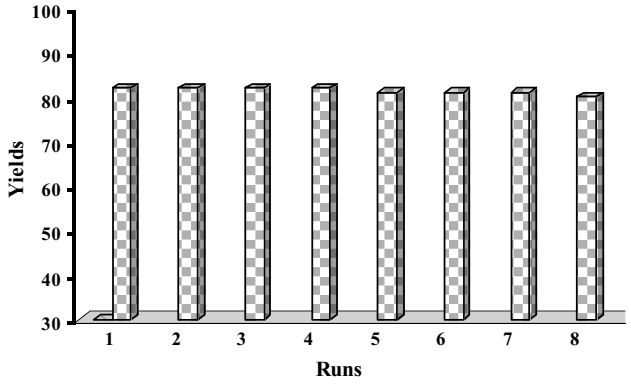


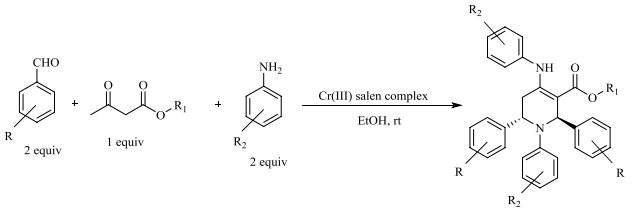
Fig. 5 Recyclability of chromium(III)-salen complex nanoparticles supported on $AlPO_4$ in the synthesis of highly substituted piperidine

The active surface area of the immobilized Cr(III)-salen complex was compared with pure $AlPO_4$ via following the nitrogen adsorption capacity of each solid sample as shown in Fig. 3. The result (Fig. 3) revealed that an increase of about 350 $m^2\ kg^{-1}$ was observed for the active surface area of $AlPO_4$ when was used as the support of Cr(III)-salen complex.

For further characterization of Cr(III)-salen complex, spectroscopic techniques such as FT-IR spectrometry and inductively coupled plasma (ICP) were also adopted. Figure 4 exhibits the FT-IR spectra of Cr(III)-salen complex (Fig. 4a) supported on the $AlPO_4$ functionalized with -NH_2 (Fig. 4b). According to the FT-IR spectra (Fig. 4a), the strong peak at ~650 cm^{-1} is related to the Cr–O bond. Formation of Cr–N and Cr–O bonds is evidenced according to the stretching bonds based on the weak absorption shoulder observed at ~402 cm^{-1} (Fig. 4a), which is in good agreement with results previously reported [85–87]. In accordance with the FT-IR spectra (Fig. 4a, b), a significant shift of ~21 cm^{-1} (from 1415.9 to ~1395 cm^{-1}) clearly reveals the formation of new Cr–N bond during the chemically immobilization of Cr(III)-salen complex on the $AlPO_4$ functionalized with –NH_2– support.

As shown in Fig. 5, the recyclability of the immobilized catalyst was tested. The catalytic activity of the catalyst was largely unchanged even after eight consecutive runs. The heterogenized catalyst exhibited good activities and excellent reusabilities (up to eight runs) in the synthesis of highly substituted piperidines.

To check the leaching, the immobilized catalyst suspension in ethanol was stirred at room temperature for 10 h. The catalyst was removed, and the filtrate was used for the synthesis of highly substituted piperidine under the optimized conditions. No reaction was observed to be



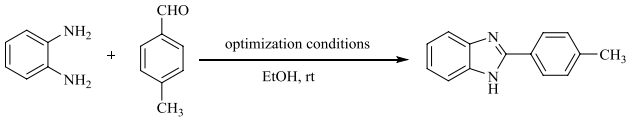
Scheme 4 Synthesis of highly substituted piperidines from different aryl aldehydes, anilines, and β-keto esters

proceeded after 16 h. The results demonstrated that the heterogeneous catalyst was stable after its practical utility.

Homogeneous and heterogeneous catalytic system for synthesis of highly substituted piperidine

Under the optimized experimental conditions, the reaction between β-keto esters, aromatic aldehydes, and various amines was carried out in the presence of both homogeneous and heterogeneous catalysts in ethanol at room temperature. Both catalysts offered high selectivity and good reactivity toward synthesis of highly substituted piperidines under mild condition.

To explore the generality and scope of this method, a variety of β-keto esters, aromatic aldehydes, heterocyclic aldehydes, and various amines (Scheme 4) were used for synthesis of the corresponding highly substituted piperidines. Various anilines and aromatic aldehydes with substituents such as Me, OMe, Cl, and NO_2 were treated with



Scheme 5 Model reaction for synthesis of 4-methylbenzaldehyde

methyl acetoacetate under identical reaction conditions. Also, heteroaryl aldehydes, such as thiophene-2-carboxaldehyde and pyridine-2-carboxaldehyde, were well tolerated under these conditions (Table 2, entries 13 and 14). The percentage yield and reaction time for each highly substituted piperidines are shown in Table 2. It should be mentioned that the developed procedure was not applicable to aliphatic aldehydes and aliphatic amines for synthesis of highly substituted piperidines. However, various 1,3-dicarbonyl compounds such as ethyl acetoacetate and methyl acetoacetate as well as different aromatic aldehydes and anilines produced desired piperidine derivatives in good yields. The products were characterized by melting point, IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis which showed similar results to those reported in the literature for anti-compounds.

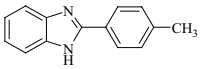
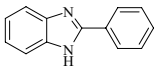
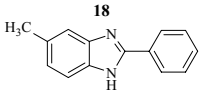
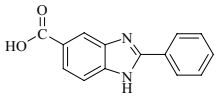
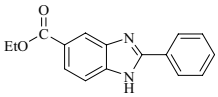
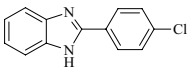
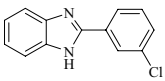
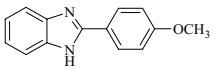
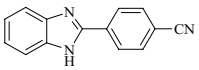
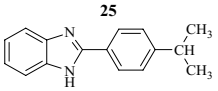
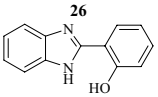
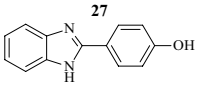
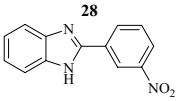
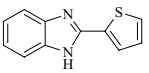
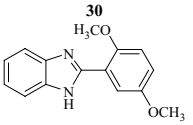
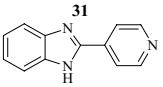
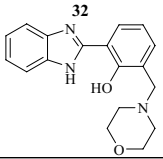
In the next step, we expanded the catalytic system to the synthesis of benzimidazoles and benzothiazoles. To exploit simple and suitable conditions for synthesis of 2-arylbenzimidazoles, the reaction of *o*-phenylenediamine with 4-methylbenzaldehyde was chosen as a model (Scheme 5).

Table 2 Homogeneous and heterogeneous Cr(III)–salen complex-catalyzed multicomponent reactions for the synthesis of highly substituted piperidines

Entry	Aldehyde	R_1	R_2	Product	Homogeneous catalyst		Heterogeneous catalyst	
					Time (h)	Yield (%)[a]	Time (h)	Yield (%)[a]
1	C_6H_5CHO	Me	H	**1**	16	81	15	82
2	C_6H_5CHO	Me	4-Me	**2**	17	85	15	85
3	C_6H_5CHO	Me	4-OMe	**3**	17	82	16	84
4	4-MeC_6H_4CHO	Me	H	**4**	17	83	16	84
5	4-ClC_6H_4CHO	Me	H	**5**	15	85	14	85
6	4-$MeOC_6H_4CHO$	Me	H	**6**	16	82	15	84
7	4-MeC_6H_4CHO	Me	4-Cl	**7**	17	82	16	84
8	4-$MeOC_6H_4CHO$	Me	4-Me	**8**	18	81	17	83
9	4-ClC_6H_4CHO	Me	4-Me	**9**	16	81	15	81
10	4-MeC_6H_4CHO	Me	4-OMe	**10**	15	79	14	81
11	C_6H_5CHO	Me	4-Cl	**11**	18	78	17	78
12	4-MeC_6H_4CHO	Et	H	**12**	21	79	19	80
13	2-Pyridinylcarboxaldehyde	Me	4-Cl	**13**	22	65	22	67
14	2-Thiophenyl	Me	4-Me	**14**	21	70	20	73
15	4-ClC_6H_4CHO	Et	H	**15**	18	77	18	78
16	3-$NO_2C_6H_4CHO$	Me	H	**16**	24	73	21	74

[a] Isolated yields

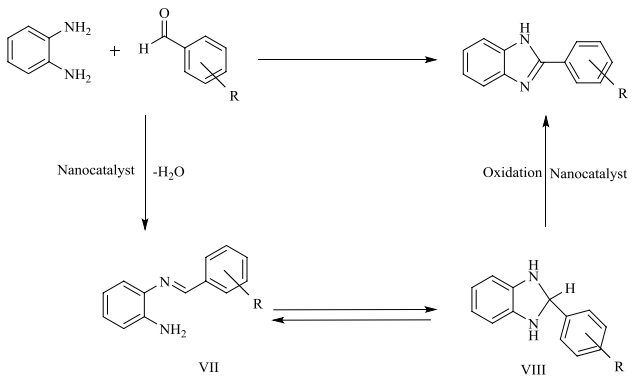
Table 3 Condensation reaction of *o*-phenylenediamine (1.0 mmol) with different aromatic aldehydes (1.0 mmol) in the presence of chromium(III)-salen complex nanoparticles supported on $AlPO_4$ (2 mol%) in ethanol at room temperature

Entry	Product	Time (h)	Yield[a]	References
1	 **17**	55 min	95	[25]
2	 **18**	1	96	[25]
3	 **19**	40 min	96	[25]
4	 **20**	3	93	[25]
5	 **21**	50 min	92	[30]
6	 **22**	2	90	[25]
7	 **23**	2.5	91	[25]
8	 **24**	1.5	93	[25]
9	 **25**	5	87	[25]
10	 **26**	1	93	[25]
11	 **27**	3	90	[25]
12	 **28**	2	91	[25]
13	 **29**	4	89	[25]
14	 **30**	5	87	[25]
15	 **31**	2	92	[30]
16	 **32**	5	92	–
17		6	86	–

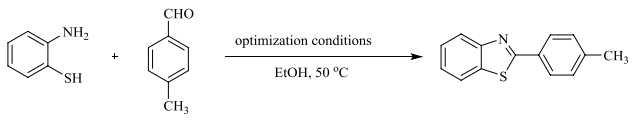
[a] Isolated yield

In order to ascertain the optimum conditions of the reaction, we optimized various parameters including solvent and the amount of catalyst for the synthesis of 4-methylbenzaldehyde. The best results were obtained with the use of 2 mol% of chromium(III)-salen complex nanoparticles supported on $AlPO_4$. The effect of solvents on the condensation reaction was also investigated. Among different solvents examined, ethanol clearly stands out as the solvent of choice with its fast reaction rate, shorter reaction time, environmental acceptability and excellent yield of product. The use of other solvent gave low yield of product. Under optimized reaction conditions, we studied the generality and selectivity of nanocatalyst for the condensation of electronically divergent aromatic aldehydes with *o*-phenylenediamines (Table 3). Furthermore, aliphatic aldehydes are not applicable for the synthesis of 2-arylbenzimidazoles in the presented procedure. Therefore, chromium(III)-salen complex nanoparticles supported on $AlPO_4$ possess good catalytic activity for the synthesis of 2-arylbenzimidazoles using various *o*-phenylenediamines and aromatic aldehydes.

In order to assess the feasibility of applying this procedure on a preparative scale, we performed the coupling of *o*-phenylenediamine with 4-methylbenzaldehyde under the optimized conditions in a 50 mmol scale using chromium(III)-salen complex nanoparticles supported on $AlPO_4$. As expected, the reaction proceeded smoothly,



Scheme 6 A possible pathway for the synthesis of 2-arylbenzimidazoles



Scheme 7 Model reaction of synthesis 2-*p*-tolylbenzo[*d*]thiazole

similar to the case in a smaller scale (Table 3, entry 1), and the desired product was obtained in 95% isolated yield. Therefore, we believe that it will find wide range of applications in organic synthesis as well as in industry.

Herein, we proposed a mechanism for the chromium(III)-salen complex nanoparticles supported on $AlPO_4$ catalyzed preparation of 2-arylbenzimidazoles (Scheme 6), which is in analogy to the established mechanism as reported in the literature [51, 55, 57]. We believe that the synthesis of 2-arylbenzimidazoles under these conditions follows through the known imine **VII** by the reaction of an aromatic aldehyde and *o*-phenylenediamine in the presence of nanocatalyst by the elimination of a water molecule, which exists in equilibrium with the cyclic hydrobenzimidazoles **VIII**. The chromium(III)-salen complex nanoparticles supported on $AlPO_4$ probably facilitates the formation of imine **VII** by increasing the electrophilicity of the carbonyl group. Subsequently, in the presence of nanocatalyst and air, the cyclic hydrobenzimidazoles **VIII** oxidized by O_2 to give 2-arylbenzimidazoles.

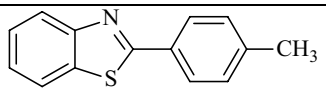
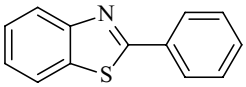
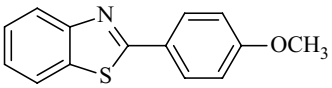
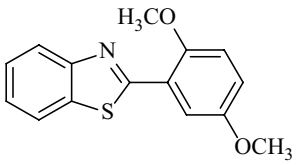
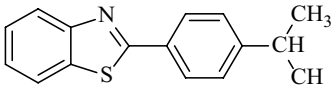
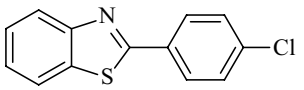
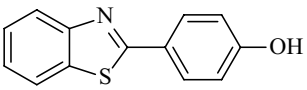
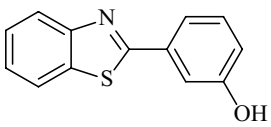
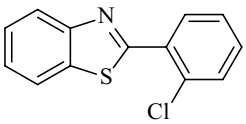
We then applied these reaction conditions to the synthesis of 2-*p*-tolylbenzo[*d*]thiazole (Scheme 7). We studied the effect of reaction temperature. The reaction of benzaldehyde (1.0 mmol) and 2-aminothiophenol (1.0 mmol) using catalytic amount (2.0 mol%) of a chromium(III)-salen complex nanoparticles supported on $AlPO_4$ was carried at different temperature. At room temperature, the reaction rate and yield was found to be very slow, and it increased with temperature. At 50 °C, the reaction rate was found to be a maximum, and further increases in temperature did not show any enhancement. Thus, stirring the reaction mixture at 50 °C in the presence of chromium(III)-salen complex nanoparticles supported on $AlPO_4$ was optimal for the synthesis of benzothiazole derivatives.

The scope and generality of this procedure using chromium(III)-salen complex nanoparticles supported on $AlPO_4$ was explored with a variety of aryl aldehydes and 2-aminothiophenol. In all cases, condensation reactions afforded the desired benzothiazole derivatives in good yields. (Table 4).

Conclusions

A novel, highly selective, and efficient methodology for synthesis of highly substituted piperidines via multi-component one-pot process under mild conditions has been developed. To do this, β-keto esters, aromatic aldehydes and various amines were used, while 10 mol% homogeneous chromium(III)-salen complex and heterogeneous

Table 4 Condensation reaction of 2-aminobenzenethiol (1.0 mmol) with different aromatic aldehydes (1.0 mmol) in the presence of chromium(III)-salen complex nanoparticles supported on $AlPO_4$ (2 mol%) in ethanol at room temperature

Entry	Product	Time (h)	Yield[a]	References
1	 **34**	2	96	[25]
2	 **35**	3	95	[25]
3	 **36**	2.5	92	[25]
4	 **37**	4	87	[25]
5	 **38**	3	93	[25]
6	 **39**	4.5	91	[30]
7	 **40**	3	94	[25]
8	 **41**	2.5	95	[25]
9	 **42**	2	95	[25]

[a] Isolated yield

chromium(III)-salen complex (supported on $AlPO_4$ nanoparticles) were used as catalysts. The advantages of the present procedure are relatively mild reaction conditions, high diastereoselectivity productions, recyclability of the catalyst, high atom-economy, and excellent yields which make it a useful alternative to the existing procedures reported for synthesis of highly substituted piperidines. Also, we have developed a general, simple and efficient one-pot synthetic rout to 2-arylbenzimidazoles and 2-arylbenzothiazoles from *o*-phenylenediamines and 2-aminothiophenol with aryl aldehydes, respectively, using chromium(III)-salen complex nanoparticles supported on $AlPO_4$ (2 mol%) as the reusable nano catalyst under mild reaction conditions. The mild reaction conditions, the fast reaction times, large scale synthesis, easy and quick isolation of products and excellent yields are main advantages of this procedure which makes it an attractive and useful contribution to the present

methodologies. Moreover, the heterogeneous catalyst could be recovered and recycled by a simple centrifugation and subsequently being used for at least eight consecutive runs without significant loss of its catalytic activity.

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