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ORIGINAL PAPER

A novel one-pot isocyanide-based three-component reaction: synthesis of highly functionalized imidazo-chromen-4-ones

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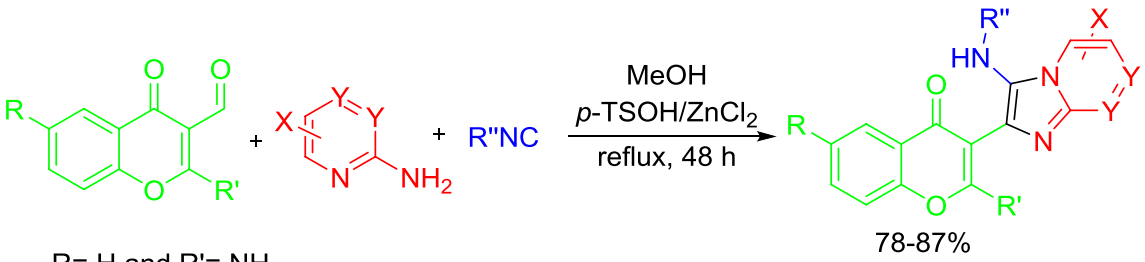
Abstract A novel approach has been developed for the efficient synthesis of structurally diverse imidazo-chromen-4-ones via a three-component condensation reaction of 2-aminoazines and various isocyanides with 4-*oxo*-4*H*-chromene-3-carbaldehyde derivatives in the presence of *p*-TSOH/$ZnCl_2$ as the catalyst in methanol under reflux conditions for 48 h.
Graphical Abstract



R= H and R'= NH_2
R= Br, Cl or Me and R'= H
R''= cyclohexyl, *tert*-butyl, 1,1,3,3-tetramethylbutyl, 2,6-dimethylphenyl or benzyl
X= Me, Br or NH_2
Y= CH or N

Keywords Chromene · Azaindol · Aminoimidazo · Multi-component · Isocyanide

Introduction

Chromenes as one of the privileged structures are a large group of naturally occurring compounds with a wide range of biological activities and are present in large amounts in the diet of humans due to their origin in plants [1–3]. The therapeutic applications of chromenes include tyrosine and protein kinase C inhibitors, antifungal, antiviral, antitubulin, and antihypertensive agents [4]. They have been shown to be active at benzodiazepine receptors [5] and on lipoxygenase and cyclooxygenase [3]. In addition to this, they are anticancer agents, possessing antimutagenic properties as well as the ability to inhibit electron transport through inhibition at NADH: ubiquinone oxidoreductase and phorbol ester-induced ornithinede carboxylase [6, 7].

N-Containing polycyclic structures such as azaindole scaffolds are privileged structures used as important building blocks in natural or synthetic bioactive compounds

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through their isosterism with indole. Various derivatives of this category showed biological activity; for example imidazo[1,2-*a*] pyridine as an antiproliferative and azino-fused benzimidazolium salts as an interchalating agent [8, 9]. Some of the bridgehead nitrogen systems have been shown to be highly potent and selective glycine antagonists, in the treatment of ischemia, Alzheimer's disease [10–12] and neurodegenerative disorders caused by viral infections such as AIDS [13–16]. The promising pharmacological activities of the imidazo[1,2-*a*] annulated nitrogen heterocycles bearing pyridine, pyrimidine, and pyrazine moieties [17] have prompted chemists to develop many synthetic methods.

Recently, the combinations of annulated heterocyclic structures to obtain polycyclic skeletons with diverse biological properties have attracted much attention [18, 19]. While imidazo-chromene, as a hybrid of two important moieties [20–23], can be worthwhile product of this technique, literature surveys have not revealed such interest. Recently, some derivatives with scaffold **A** showed anticancer activity [24]. PF-03716556 (**B**) is an imidazo-chromene introduced as a potent and selective acid pump antagonist for the treatment of gastroesophageal reflux disease [25]. Cassiadinine (**C**) is a natural imidazo-chromene with good antioxidant activity, reduced levels of free radicals in a variety of diseases, including cancer and aging [26] (Fig. 1).

As part of our continuing interest in the development of new synthetic methods in heterocyclic compounds and isocyanide-based multi-component reactions (MCR) [27–30], we report here a novel approach for the synthesis of highly functionalized 3-(3-amino-imidazo[1,2-*a*]pyridin, pyrazin, and pyrimidin-2-yl)-4*H*-chromen-4-one derivatives **4** via a three-component condensation reaction of 4-*oxo*-4*H*-chromene-3-carbaldehydes **1** and 2-aminoazines **2** with various aliphatic and aromatic isocyanides **3** [31, 32] in the presence of *p*-toluenesulfonic acid (*p*-TSOH)/$ZnCl_2$ as the catalyst in methanol under reflux conditions (Scheme 1).

Experimental

Materials

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H NMR Spectra were recorded on a Bruker DRX-300 Avance spectrometer 300.13 MHz and a Bruker WP 200 SY spectrometer 250.13 MHz in DMSO-d_6 solution with TMS as internal standard. The ^{13}C NMR spectra were recorded at 75.47 and 62.47 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL. All the products are new compounds, which were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra, and Mass spectral data.

Typical procedure for the synthesis of 2-amino-3-(6-bromo-3-(cyclohexylamino)imidazo[1,2-*a*]pyridin-2-yl)-4*H*-chromen-4-one (**4a**). 2-Amino-4-oxo-4*H*-chromene-3-carbaldehyde (**1a**) (1 mmol), 5-bromo-2-aminopyridine (**2a**) (1 mmol), and cyclohexyl isocyanide (**3a**) were added to the solution of (1 mmol) *p*-toluenesulfonic acid (*p*-TSOH) (5 % mol)/zinc chloride (5 % mol) in methanol, and the mixture was stirred under reflux conditions for 48 h. The progress of the reaction was monitored by TLC with CH_2Cl_2/*n*-hexan (1:1). After completion of the reaction, the mixture of reaction was cooled to room temperature, the precipitated was separated from the reaction mixture by filtration and recrystalized in DMSO to afford the product (**4a**) in 87 % yield.

2-Amino-3-(6-bromo-3-(cyclohexylamino)imidazo[1,2-*a*]pyridin-2-yl)-4*H*-chromen-4-one **(4a):** Scarlet powder (0.39 g, 87 %); M.p. 290–292 °C. IR (KBr) (ν_{max}/cm^{-1}): 3250, 3073, 2928, 2852, 1641, 1603, 1513, 1490, 1447. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.02 (5H, br s, CH_2 of cyclohexyl), 1.40 (1H, br s, CH_2 of cyclohexyl), 1.52 (2H, br s, CH_2 of cyclohexyl), 1.70 (2H, br s, CH_2 of cyclohexyl), 2.68 (1H, br s, *CH*–NH), 5.15 (1H, br s, NH), 7.38–7.44 (1H, m, H–Ar), 7.40 (2H, t, $^3J_{HH}$ = 8.6 Hz,

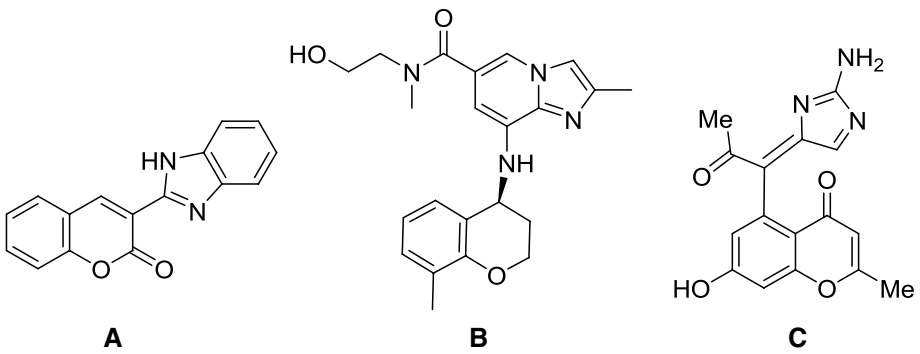
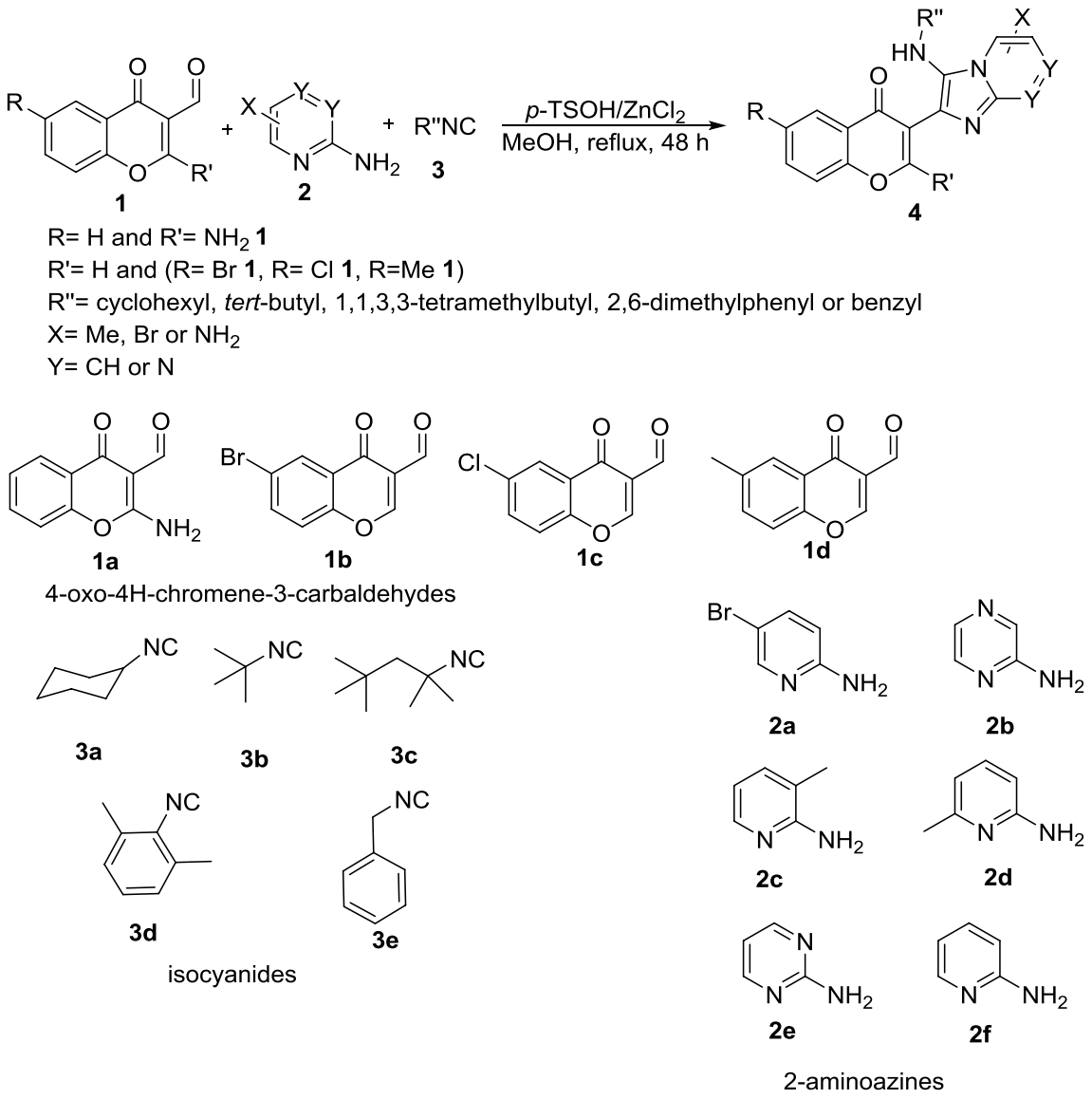


Fig. 1 Examples of some biologically active imidazo-chromenes



Scheme 1 Synthesis of 3-(3-(alkylamino)-imidazo[1,2-*a*]pyridin, pyrazin, and pyrimidin-2-yl)-4*H*-chromen-4-one derivatives **4**

H–Ar), 7.57 (1H, d, $^3J_{HH}$ = 10.3 Hz, H–Ar), 7.68 (1H, t, $^3J_{HH}$ = 8.0 Hz, H–Ar), 8.00 (1H, br s, H–Ar), 8.40 (1H, s, H–Ar), 8.70 (2H, br s, NH_2). ^{13}CNMR (62.5 MHz, DMSO-d_6/TFA): δ = 24.8, 25.4, 33.5, 54.5, 86.2, 110.2, 113.3, 117.2, 121.7, 124.8, 125.5, 125.8, 129.9, 133.9, 134.1, 134.9, 153.2, 164.1, 174.0. Anal. Calcd for $C_{22}H_{21}BrN_4O_2$: C, 58.29; H, 4.67; N, 12.36; Found: C, 58.29; H, 4.65; N, 12.37.

2-Amino-3-(6-bromo-3-(tert-butylamino)imidazo[1,2-*a*]pyridin-2-yl)-4*H*-chromen-4-one **(4b):** Yellow powder (0.34 g, 80 %); M.p. > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3343, 3191, 2963, 2921, 2853, 1608, 1511, 1477. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.97 (9H, s, $C(CH_3)_3$), 5.22 (1H, s, NH), 6.73 (1H, d, $^3J_{HH}$ = 5.6 Hz, H–Ar), 7.1 (1H, s, H–Ar), 7.27–7.37 (3H, m, H–Ar), 7.59 (1H, t, $^3J_{HH}$ = 8.3 Hz, H–Ar), 8.10 (1H, d, $^3J_{HH}$ = 8.6 Hz, H–Ar), 8.65 (2H, s, NH_2). ^{13}CNMR (62.5 MHz, DMSO-d_6/TFA): δ = 28.5, 55.3, 87.4, 110.5, 117.2, 121.8, 123.8, 125.7, 128.1, 133.9, 135.3, 136.5, 153.2, 163.7, 173.5. Anal. Calcd for $C_{20}H_{19}BrN_4O_2$: C, 56.22; H, 4.48; N, 13.11; Found: C, 56.23; H, 4.47; N, 13.09.

2-Amino-3-(6-bromo-3-((2,4,4-trimethylpentan-2-yl) amino)imidazo[1,2-*a*]pyridin-2-yl)-4*H*-chromen-4-one **(4c):** Yellow powder (0.39 g, 81 %); M.p. 298–300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3363, 2953, 2899, 2866, 1608, 1513, 1447. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.89 (6H, s, $2CH_3$), 1.00 (9H, s, $3CH_3$), 1.55 (2H, s, CH_2), 5.18 (1H, s, NH), 6.66 (1H, s, H–Ar), 7.05 (1H, s, H–Ar), 7.29–7.31 (3H, m, H–Ar), 7.56 (1H, s, H–Ar), 8.07 (1H, d, $^3J_{HH}$ = 8.6 Hz, H–Ar), 8.60 (2H, s, NH_2). Anal. Calcd

for $C_{24}H_{27}BrN_4O_2$: C, 59.63; H, 5.63; N, 11.59; Found: C, 59.63; H, 5.62; N, 11.58.

2-Amino-3-(3-(benzylamino)-6-bromoimidazo[1,2-*a*] pyridin-2-yl)-4*H*-chromen-4-one **(4d):** Brown powder (0.39 g, 85 %); M.p. 253–255 °C. IR (KBr) (ν_{max}/cm^{-1}): 3414, 3250, 3091, 2912, 1726, 1605, 1560, 1461, 1215, 758. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.91 (2H, br, CH_2), 4.81 (1H, br s, NH), 6.66 (1H, s, H–Ar), 6.96–8.37 (4H, m, H–Ar and NH_2). Anal. Calcd for $C_{23}H_{17}BrN_4O_2$: C, 59.88; H, 3.71; N, 12.15; Found: C, 59.76; H, 3.72; N, 12.21.

2-Amino-3-(3-(cyclohexylamino)imidazo[1,2-*a*] pyrazin-2-yl)-4*H*-chromen-4-one **(4e):** Yellow powder (0.29 g, 78 %); M.p. 241–243 °C. IR (KBr) (ν_{max}/cm^{-1}): 3270, 2921, 2839, 1605, 1515, 1467. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.81(5H, br s, CH_2 of cyclohexyl), 1.06 (1H, br s, CH_2 of cyclohexyl), 1.21 (2H, br s, CH_2 of cyclohexyl), 1.68–1.71 (2H, m, CH_2 of cyclohexyl), 2.74 (1H, br s, *CH*–NH), 5.39 (1H, br s, *NH*–CH), 7.13–8.20 (7H, m, H–Ar), 8.94 (2H, s, NH_2). ^{13}CNMR (62.5 MHz, DMSO-d_6): δ = 24.5, 25.4, 33.7, 55.2, 92.5, 115.8, 116.5, 122.5, 125.1, 125.6, 129.0, 129.7, 132.5, 132.8, 141.7, 152.3, 164.5, 172.5. Anal. Calcd for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.65; Found: C, 67.15; H, 5.60; N, 18.69.

2-Amino-3-(3-(tert-butylamino)-5-methylimidazo[1,2-*a*]pyridin-2-yl)-4*H*-chromen-4-one **(4f):** Gray powder (0.28 g, 79 %); M.p. 197–200 °C. IR (KBr) (ν_{max}/cm^{-1}): 3418, 3262, 2968, 2853, 1645, 1607, 1521, 1491, 1367. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.98 (9H, s, $3CH_3$), 2.52 (3H, s, CH_3), 4.68 (1H, s, NH), 7.06–7.70 (5H, m, H–Ar), 8.07 (1H, br, H–Ar), 8.55 (1H, br, H–Ar), 8.68 (2H, s, NH_2). Anal. Calcd for $C_{21}H_{24}N_4O_2$: C, 69.59; H, 6.12; N, 15.46; Found: C, 69.53; H, 6.11; N, 15.48.

2-Amino-3-(3-(cyclohexylamino)-5-methylimidazo[1,2-*a*]pyridin-2-yl)-4*H*-chromen-4-one **(4g)**: Yellow powder (0.32 g, 82 %); M.p. 179–182 °C. IR (KBr) (ν_{max}/cm^{-1}): 3361, 2926, 2852, 1609, 1518, 1455, 1364. ^{1}H NMR (300 MHz, DMSO): δ = 1.01–1.70 (10H, m, $5CH_2$), 2.50 (3H, s, CH_3), 2.62 (1H, br s, *CH*–NH), 5.44 (1H, d, $^3J_{HH}$ = 7.6 Hz, NH), 6.57–8.26 (7H, m, H–Ar), 8.70 (2H, s, NH_2). Anal. Calcd for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23; N, 14.42; Found: C, 71.03; H, 6.31; N, 14.47.

2-Amino-3-(3-(cyclohexylamino)-8-methylimidazo[1,2-*a*]pyridin-2-yl)-4*H*-chromen-4-one **(4h):** Yellow powder (0.32 g, 82 %); M.p. 203–205 °C. IR (KBr) (ν_{max}/cm^{-1}): 3425, 2928, 2854, 1640, 1606, 1518, 1489, 1456. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.00–1.70 (10H, m, $5CH_2$), 2.28 (3H, s, CH_3), 2.63 (1H, br s, *CH*–NH), 5.20 (1H, br, NH), 6.92–8.15 (7H, m, H–Ar), 8.86 (2H, s, NH_2). Anal. Calcd for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23; N, 14.42; Found: C, 71.19; H, 6.29; N, 14.33.

2-Amino-3-(3-(benzylamino)imidazo[1,2-*a*]pyridin-2-yl)-4*H*-chromen-4-one **(4i):** Gray powder (0.32 g, 84 %); M.p. > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3424, 3350, 3251, 3085, 2919, 1609, 1517, 1462, 1223. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.06 (2H, d, $^2J_{HH}$ = 7.9 Hz, CH_2), 4.91 (1H, br s, NH), 7.15–8.49 (15H, m, H–Ar and NH_2). Anal. Calcd for $C_{23}H_{18}N_4O_2$: C, 72.24; H, 4.74; N, 14.65; Found: C, 72.21; H, 4.70; N, 14.71.

2-Amino-3-(3-((2,4,4-trimethylpentan-2-yl)amino) imidazo[1,2-*a*]pyrimidin-2-yl)-4*H*-chromen-4-one **(4j):** Green powder (0.33 g, 83 %); M.p. 226–229 °C. IR (KBr) (ν_{max}/cm^{-1}): 3444, 2963, 1747, 1683, 1627, 1538, 1466. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.91 (6H, s, $2CH_3$), 0.99 (9H, s, $3CH_3$), 1.51 (2H, s, CH_2), 4.76 (1H, s, NH), 7.1 (1H, d, $^3J_{HH}$ = 6.6 Hz, H–Ar), 7.46–7.51 (2H, m, H–Ar), 7.71 (1H, t, $^3J_{HH}$ = 10.0 Hz, H–Ar), 8.12 (1H, d, $^3J_{HH}$ = 10.0 Hz, H–Ar), 8.51 (1H, s, H–Ar), 8.77 (2H, br s, NH_2), 8.83 (1H, d, $^3J_{HH}$ = 6.6 Hz, H–Ar). Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.13; H, 6.71; N, 17.27; Found: C, 68.14; H, 6.71; N, 17.29.

2-Amino-3-(3-(cyclohexylamino)imidazo[1,2-*a*] pyrimidin-2-yl)-4*H*-chromen-4-one **(4k):** Yellow powder (0.29 g, 78 %); M.p. 176–179 °C. IR (KBr) (ν_{max}/cm^{-1}): 3267, 3089, 2926, 2854, 1609, 1560, 1515, 1459. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.00–1.65 (10H, m, $5CH_2$), 2.78 (1H, br s, *CH*–NH), 5.30 (1H, br s, NH), 6.78–8.87 (7H, m, H–Ar), 8.96 (2H, s, NH_2). Anal. Calcd for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.65; Found: C, 67.16; H, 5.63; N, 18.66.

6-Bromo-3-(3-(cyclohexylamino)-8-methylimidazo[1,2-*a*]pyridin-2-yl)-4*H*-chromen-4-one **(4l):** Yellow powder (0.39 g, 86 %); M.p. 192–195 °C. IR (KBr) (ν_{max}/cm^{-1}): 3256, 2923, 2840, 1623, 1533, 1461, 1306. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96–1.82 (10H, m, $5CH_2$), 2.50 (1H, br s, *CH*–NH), 2.67 (3H, s, CH_3), 4.99 (1H, br s, *NH*–CH), 6.78–8.50 (6H, m, H–Ar), 8.99 (1H, s, *CH*–O). Anal. Calcd for $C_{23}H_{22}BrN_3O_2$: C, 61.07; H, 4.90; N, 9.29; Found: C, 61.08; H, 4.87; N, 9.31.

6-Bromo-3-(3-(cyclohexylamino) imidazo[1,2-*a*] pyridin-2-yl)-4*H*-chromen-4-one **(4m):** Green powder (0.35 g, 81 %); M.p. 282–285 °C. IR (KBr) (ν_{max}/cm^{-1}): 3263, 2917, 2853, 1605, 1555, 1504, 1461, 1447. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.03–1.05 (5H, m, CH_2 of cyclohexyl), 1.41 (1H, br s, CH_2 of cyclohexyl), 1.54 (2H, br s, CH_2 of cyclohexyl), 1.75 (2H, br s, CH_2 of cyclohexyl), 2.74 (1H, br s, *CH*–NH), 4.80 (1H, d, $^3J_{HH}$ = 7.6 Hz, *NH*–CH), 7.03–8.30 (7H, m, H–Ar), 8.58 (1H, s, *CH*–O). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.9, 25.6, 33.7, 55.6, 114.0, 115.9, 117.5, 118.8, 121.7, 124.0, 124.2, 125.2, 127.2, 127.7, 130.0, 137.5, 141.2, 154.8, 158.2, 174.6. Anal. Calcd for $C_{22}H_{20}BrN_3O_2$: C, 60.28; H, 4.60; N, 9.59; Found: C, 60.28; H, 4.58; N, 9.59.

6-Bromo-3-(3-(cyclohexylamino)imidazo[1,2-*a*]pyrazin-2-yl)-4*H*-chromen-4-one **(4n):** Gray powder (0.34 g, 78 %); M.p. 239–242 °C. IR (KBr) (ν_{max}/cm^{-1}): 3419,

2929, 2854, 1743, 1611, 1543, 1461. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.81–1.47 (10H, m, 5CH_2), 2.26 (1H, s, *CH*–NH), 7.08–8.18 (7H, m, H–Ar), 8.94 (1H, s, *CH*–O), 10.08 (1H, s, *NH*–CH). Anal. Calcd for $C_{21}H_{19}BrN_4O_2$: C, 57.41; H, 4.36; N, 12.75; Found: C, 57.31; H, 4.32; N, 12.87.

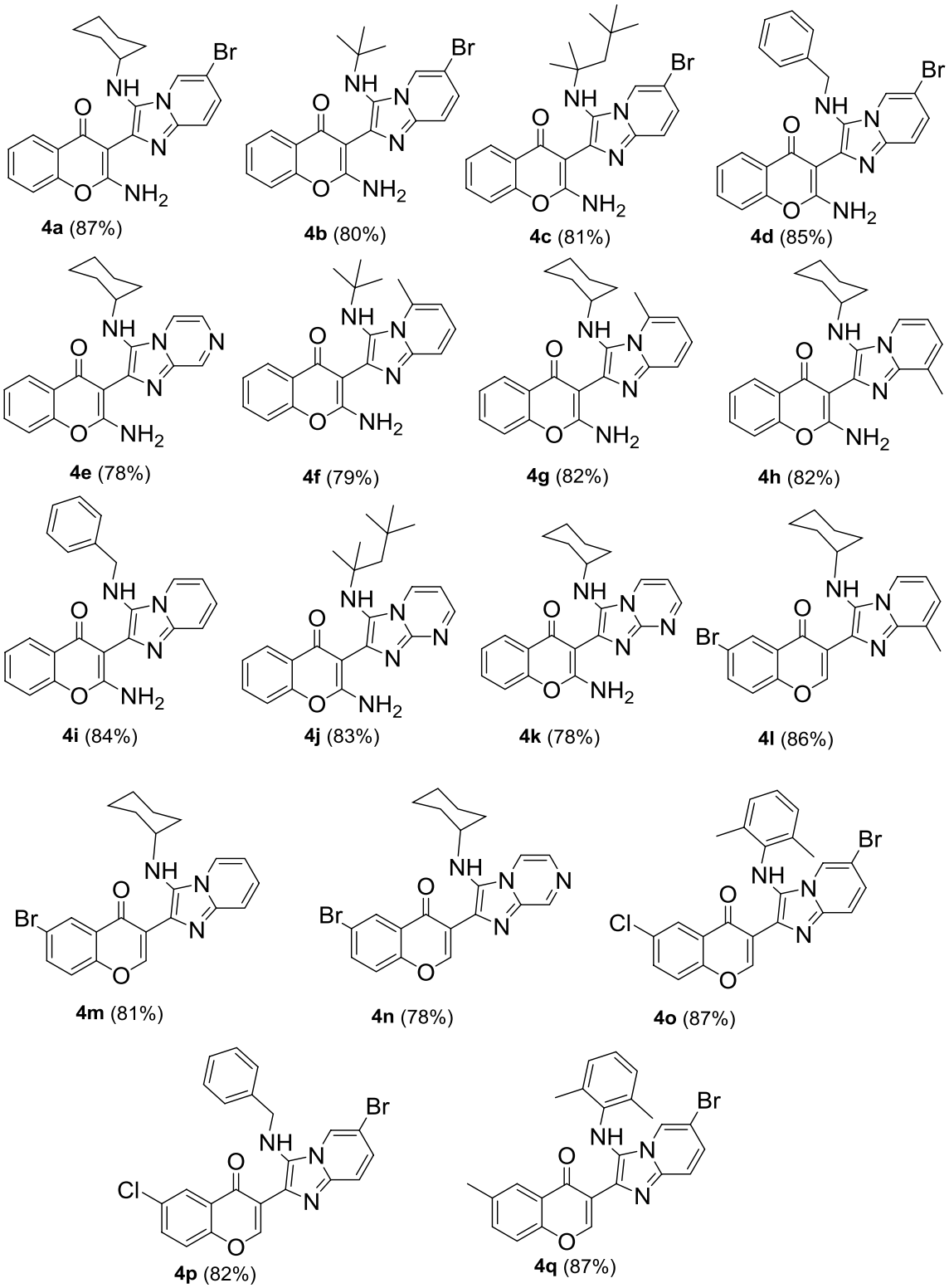


Fig. 2 Structures and isolated yields of the products **4**

3-(6-Bromo-3-((2,6-dimethylphenyl)amino) imidazo[1,2-*a*]pyridin-2-yl)-6-chloro-4*H*-chromen-4-one **(4o):** Gray powder (0.33 g, 87 %); M.p. 220–223 °C. IR (KBr) (ν_{max}/cm^{-1}): 3317, 2924, 2853, 1726, 1632, 1545, 1464, 1094, 815. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.85$ (6H, s, $2CH_3$), 3.34 (1H, s, NH), 6.17–8.86 (11H, m, H–Ar, CHO and NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.5, 118.0, 120.0, 122.4, 122.6, 125.6, 126.7, 128.6, 129.4, 134.2, 154.5, 155.9. Anal. Calcd for $C_{24}H_{17}BrClN_3O_2$: C, 58.26; H, 3.46; N, 8.49; Found: C, 58.27; H, 3.46; N, 8.49.

3-(3-(Benzylamino)-6-bromoimidazo[1,2-*a*]pyridin-2-yl)-6-chloro-4*H*-chromen-4-one **(4p):** Brown powder (0.39 g, 82 %); M.p. 273–275 °C. IR (KBr) (ν_{max}/cm^{-1}): 3425, 3049, 2975, 2918, 1706, 1664, 1592, 1437, 1251. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.60$ (1H, br s, NH), 4.22 (2H, br, CH_2), 6.82–8.65 (12H, m, H–Ar and CHO). Anal. Calcd for $C_{23}H_{15}BrClN_3O_2$: C, 57.46; H, 3.15; N, 8.74; Found: C, 57.45; H, 3.15; N, 8.73.

3-(6-Bromo-3-((2,6-dimethylphenyl)amino) imidazo[1,2-*a*]pyridin-2-yl)-6-methyl-4*H*-chromen-4-one **(4q):** Yellow powder (0.41 g, 87 %); dec >251 °C. IR (KBr) (ν_{max}/cm^{-1}): 3310, 3065, 2912, 2839, 1645, 1614, 1484, 1319, 1088, 814. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.87$ (6H, s, $2CH_3$), 2.39 (3H, s, CH_3), 6.44–8.36 (11H, m, H–Ar, CHO and NH). Anal. Calcd for $C_{25}H_{20}BrN_3O_2$: C, C, 63.30; H, 4.25; N, 8.86; Found: C, 63.30; H, 4.26; N, 8.86.

2-Amino-3-(((4-methylbenzyl)imino)methyl)-4*H*-chromen-4-one **(8):** White powder (0.24 g, 82 %); M.p. 232–235 °C. IR (KBr) (ν_{max}/cm^{-1}): 3264, 2919, 2846, 1719, 1640, 1601, 1527, 1432. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.01$ (3H, s, CH_3), 4.26 (2H, s, CH_2), 6.93–7.97 (9H, m, H–Ar, and 1H of CHN), 8.76 (2H, s, NH_2). ^{13}CNMR (62.5 MHz, DMSO-d_6/TFA): $\delta = 21.0$, 94.8, 116.5, 121.5, 124.4, 125.9, 129.3, 129.5, 133.8, 134.9, 137.3, 154.0, 163.7, 175.6. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58; Found: C, 73.95; H, 5.51; N, 9.58.

Result and discussion

In a pilot experiment, 2-amino-4-oxo-4*H*-chromene-3-carbaldehyde (**1a**) (1 mmol), 5-bromo-2-aminopyridine (**2a**) (1 mmol), and cyclohexyl isocyanide (**3a**) (1 mmol) in the presence of *p*-TSOH (5 mol %)/$ZnCl_2$ (5 mol %) as the catalyst were stirred in methanol under reflux conditions. Upon completion (48 h) the reaction mixture was cooled to room temperature, the precipitated was separated by filtration and recrystallized in DMSO to afford the product (**4a**) in 87 % yield.

To explore the scope and limitations of this reaction, we extended the procedure to various 2-aminoazines **2** and isocyanides **3** with 4-*oxo*-4*H*-chromene-3-carbaldehyde derivatives **1**. As indicated in Fig. 2, the reactions proceed very efficiently and led to the formation a new class of the highly functionalized 3-(3-(alkylamino)-imidazo[1,2-*a*] pyridin, pyrazin, and pyrimidin-2-yl)-4*H*-chromen-4-one derivatives **4** in fairly good yields (Fig. 2).

The structures of the new products were deduced from their IR, ^{1}H NMR, ^{13}C NMR spectra, and CHN analysis data. The ^{1}H NMR spectrum of (**4a**) consisted of a multiplet as four broad singlets for the methylene protons of cyclohexyl ring ($\delta = 1.02$ (5H), 1.40 (1H), 1.52 (2H), and 1.70 (2H) ppm), two broad singlets for the NH–*CH* cyclohexyl ($\delta = 2.68$ ppm) and NH protons ($\delta = 5.15$ ppm), a multiplet for aromatic porotons (7.27–8.40 ppm, 7H), a broad singlet for NH_2 ($\delta = 8.70$ ppm). Also, the ^{1}H decoupled ^{13}C NMR spectrum of (**4a**) is completely consistent with the product structure.

Due to low solubility, we could not provide ^{13}C NMR spectra for most of the products.

Finally, the structure of the product (**4a**) was confirmed unambiguously by single-crystal X-ray analysis (Fig. 3).

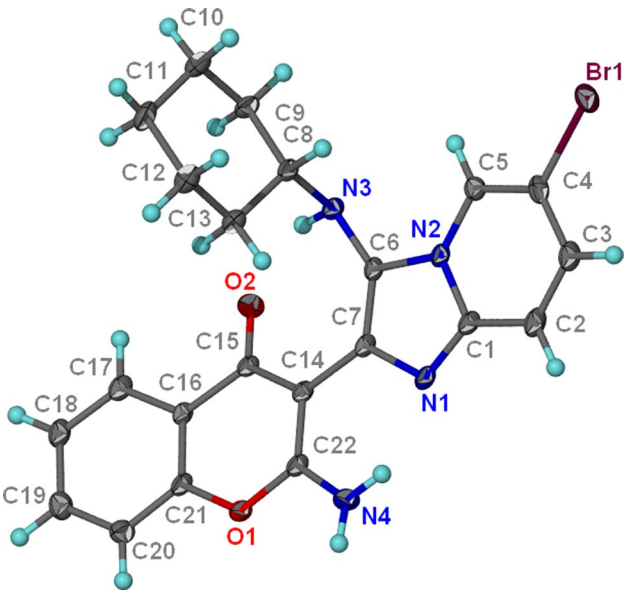


Fig. 3 ORTEP diagram for **4a**

Table 1 Effect of catalyst on the reaction yield

Entry	Catalyst	Yield (%)[a]
1	*p*-TSOH	Trace
2	$ZnCl_2$	0
3	*p*-TSOH/$ZnCl_2$ (1:1)[b]	87

Reaction conditions: 2-amino-4-*oxo*-4*H*-chromene-3-carbaldehyde (**1a**) (1 mmol), 2-aminopyridine (**2a**) (1 mmol), cyclohexylisocyanide (**3a**) (1 mmol), MeOH (10 mL), 48 h

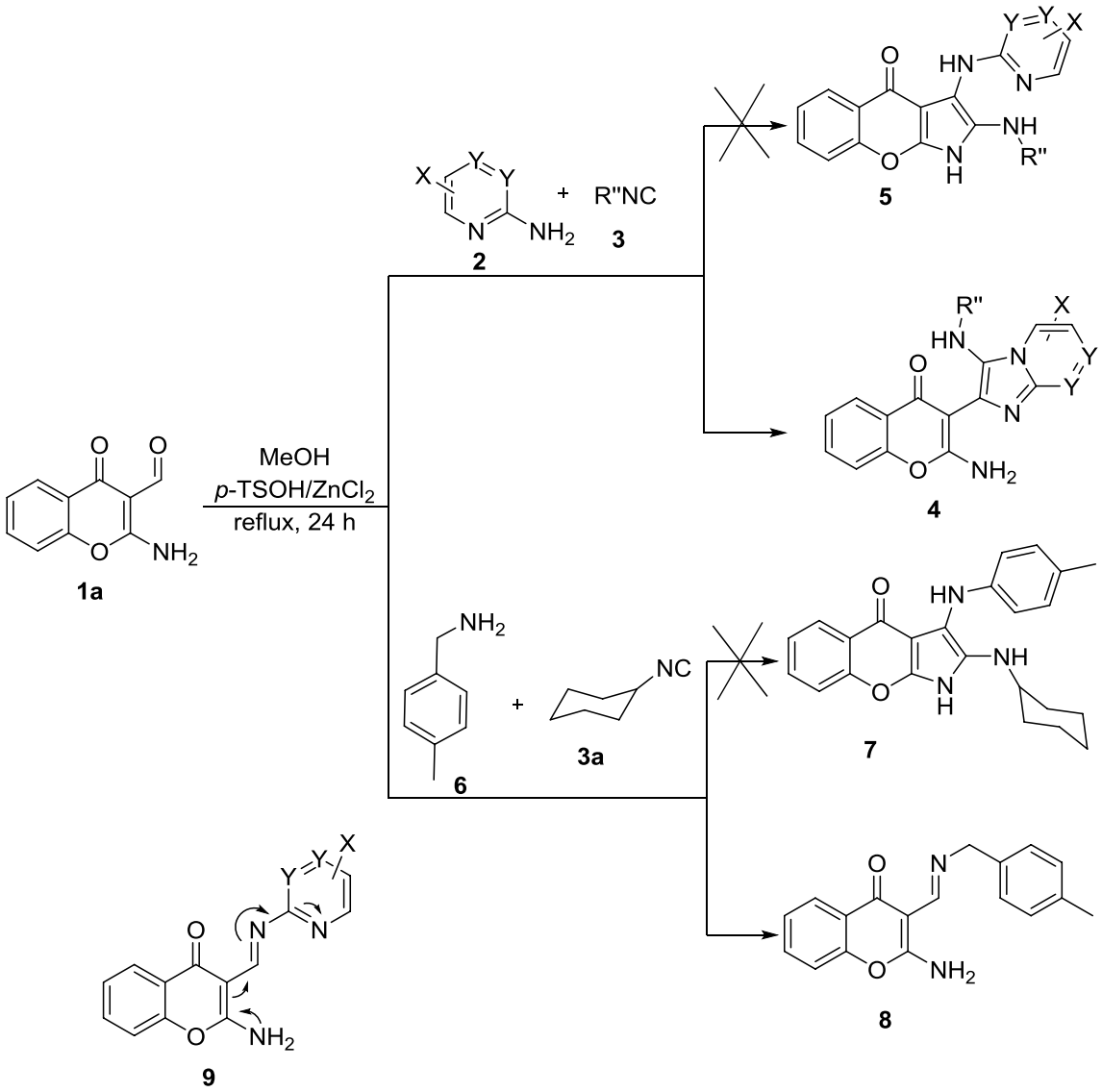
[a] Isolated yield

[b] Mol ratio

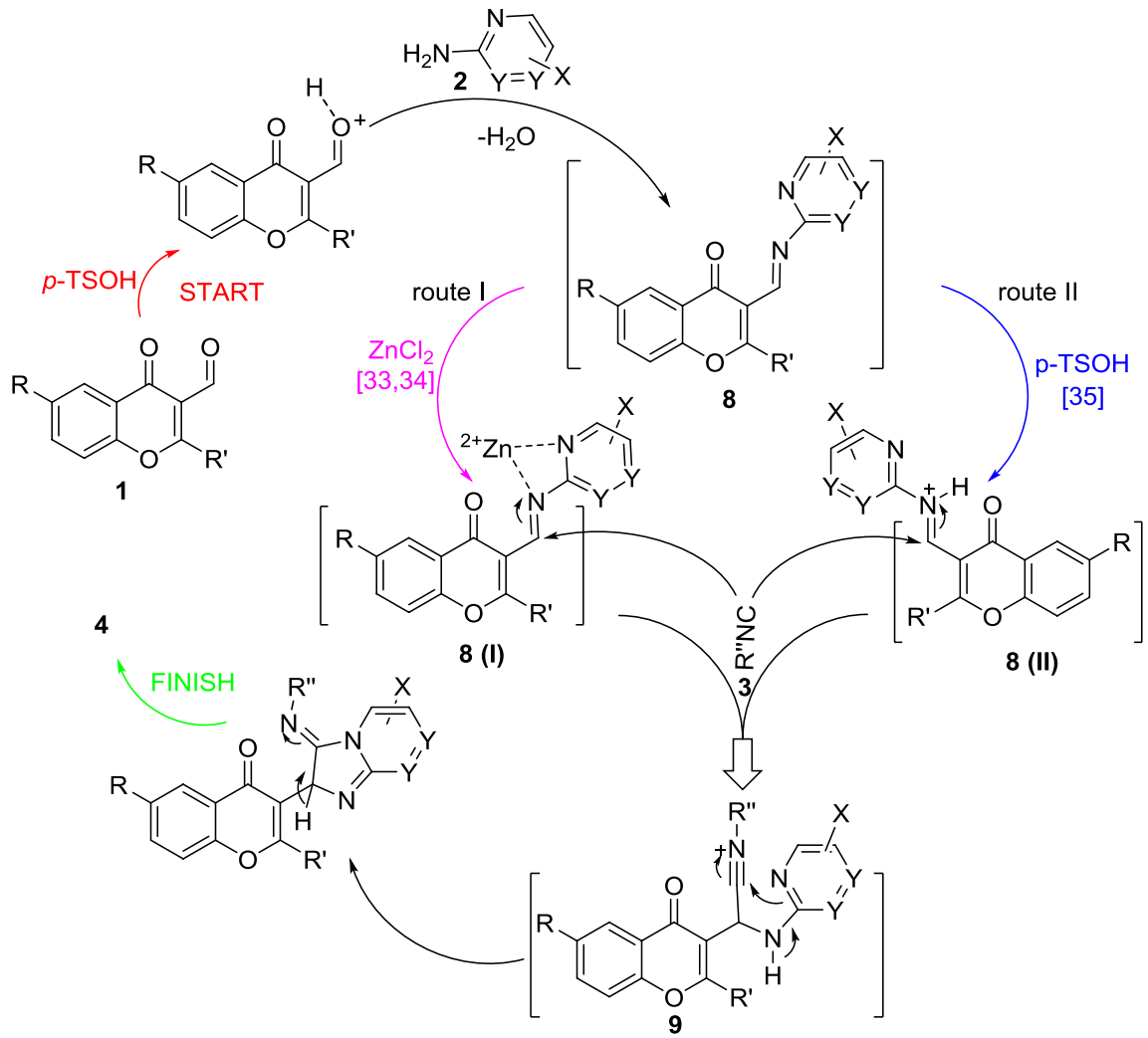
To illustrate the need of catalyst, the reaction of 2-amino-4-*oxo*-4*H*-chromene-3-carbaldehyde (**1a**) (1 mmol), 2-aminopyridine (**2a**) (1 mmol), and cyclohexyl isocyanide (**3a**) (1 mmol) was studied in the presence of *p*-TSOH, $ZnCl_2$, and either of them in MeOH under reflux conditions. As indicated in Table 1, only a trace amount of product (**4a**) was obtained after 48 h in the presence of *p*-TSOH (entry 1), the reaction was not proceeded in the presence of $ZnCl_2$ (entry 2), and both of them are necessary for obtaining desired yield (entry 3).

It is important to note, in the case of compound (**1a**), we expected to obtain the product **5** via an intramolecular nucleophilic reaction of NH_2 group of (**1a**). However, due to participation in resonance (Scheme 2, **9**), it is not able to act as a nucleophile (Scheme 2). The versatility of this MCR with respect to the 4-methylbenzylamine (**6**) instead of 2-aminoazine **2**, under the same reaction conditions, was also studied for the synthesis of compound **7** (Scheme 2). In the event, the expected MCR product **6** was not observed; instead the reaction afforded the corresponding 2-amino-3-((4-methylbenzylimino)methyl)-4*H*-chromen-4-one **8** via a condensation reaction of (**1a**) and **5**, without participation of isocyanide **3**, with 73 % yield.

Two suggested pathways for the formation of compound **4** are presented in Scheme 3. It is conceivable that the initial event is the formation of intermediate **8** by the condensation of **1** and **2**. In the next step, it is reasonable to assume that the intermediates **8 (I)** and **8 (II)** were obtained by the coordination of Zn(II) to the intermediate **8** (route I) [33, 34] or protonation of the iminium moiety **8** with *p*-TSOH



Scheme 2 Use of 4-methyl benzyl amine (**6**) instead of 2-aminoazine **2** in the reaction



Scheme 3 Proposed mechanism

(route II) [35], followed by the nucleophilic addition of isocyanides **3** afforded intermediate **9**. Then, compounds **4** produced by an intramolecular condensation reaction and tatumerization of intermediate **9** (Scheme 3).

It is important to note, due to instability of intermediate **8**, we did not able to separate and examine its reaction with isocyanides **3** in the presence of each of catalysts for more revelation of the second step of proposed mechanism.

Conclusions

In summary, we have developed a novel three-component reaction of 4-*oxo*-4*H*-chromene-3-carbaldehyde derivatives and 2-aminoazines with various aliphatic and aromatic isocyanides providing of the highly functionalized 3-(3-aminoimidazo[1,2-*a*]pyridin, pyrazin, and pyrimidin-2-yl)-4*H*-chromen-4-one derivatives in the presence of *p*-TSOH/$ZnCl_2$ as the catalyst in methanol under reflux conditions in fairly good yields. Broader substrate scope of this reaction makes it a useful and attractive process for the synthesis of a great library of these important compounds. The potential uses of this route in synthetic and medicinal chemistry may be significant, since the products share structural and functional group properties of the biologically active molecules.

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