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ORIGINAL PAPER

A revisit to the multi-component reaction of indole, aldehyde, and *N*-substituted aniline catalyzed by PMA–SiO_2

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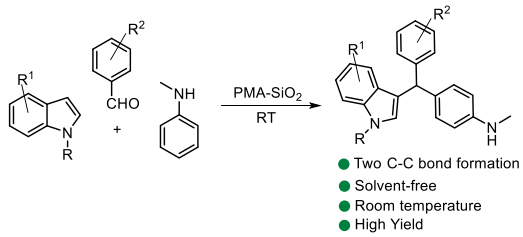
Abstract

PMA–SiO_2-catalyzed multi-component reaction of indole, aromatic aldehyde, and *N*-substituted aniline at room temperature under solvent-free condition is reported here. The reaction was previously reported, where a C–C and C–N bond were formed. However, we established a different structure for the product with the help of NMR as well as single-crystal X-ray studies, where the C-4 atom of *N*-substituted aniline is linked to the aldehydic carbon, and consequently, two new C–C bonds are formed. The mechanism of the reaction is established through trapping of the intermediate which is also different from the previous report. To the best of our knowledge, only one report is available in the literature for the synthesis of this class of important compounds.

Graphical abstract



Keywords Multi-component · PMA–SiO_2 · *N*-Substituted aniline · Solvent-free · Alkylideneindoleninium ion

Introduction

Multi-component reactions (MCRs) are one of the most interesting tools for the synthesis of complex molecular structures due to their advantages over conventional multi-step synthesis. Due to the broad range of applications, pharmaceutical companies have showed their interest in MCRs [1, 2]. MCRs are used for assembling libraries of complex structures in drug discovery and developments [3, 4]. The limitations of conventional multi-step synthesis like higher cost, longer reaction time, less atom economy, and expensive purification process are overcome by the MCRs [5–9]. MCR minimizes the waste product formation and consumes lower energy [10, 11].

Naturally obtained 3-substituted indoles have interesting pharmacological activities [12–15]. They are considered as the key units of many promising therapeutic agents [16], such as antibacterial [17], hypoglycaemic [18], analgesic [18], antiviral [19], and protein kinase inhibitors [20]. The essential α-amino acid tryptophan found in human contains 3-substituted indole moiety which is responsible for the feeling of well-being and happiness [21]. Some of the important bioactive 3-substituted indole compounds are

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shown in Fig. 1. One of the most interesting 3-substituted indole is indole-3-carbinol (**A**). This compound is reported to have anticancer [22] and anti-obesity activity [23]. Mushroom *Phellinus linteus* is used as a traditional medicine in many countries for the treatment of inflammation, arthritis, stomach ache, gastrointestinal disorder, lymphatic disease, etc. This pharmaceutical activity of mushroom is due to 7-methoxyindole-3-carboxylic acid methylester (**B**) and 1-methylindole-3-carboxaldehyde (**C**) [24]. Compound **D** has anti-diabetic activity [25] and **E** functions as an aromatase inhibitor against breast cancer [26]. In many cases, 3-substituted indoles are used as an intermediate for the synthesis of wide range of bioactive compounds. Due to their tremendous applications in various fields, the synthetic procedures of 3-substituted indole compounds are in demand.

Recently, the use of phosphomolybdic acid (PMA), a heteropolyacid, has been observed as a useful reagent/catalyst in various organic transformations. The demand for it is due to its strong acidic nature in comparison with the common acids such as H_2SO_4, TsOH, $BF_3{\cdot}Et_2O$, $ZnCl_2$, etc. which facilitate the reactions in relatively lower concentration and temperature [27]. It gained interest as a key catalyst in the development and commercialization of several synthetic methods. The MCR of aldehyde, *N*-methylaniline, and indole in the presence of PMA in combination with SiO_2 has been reported earlier by Yadav et al. [28]. According to their report, the reaction gave 3-substituted indole derivatives **5** at room temperature, wherein one C–C and C–N bond were formed (Scheme 1). On the other hand, Pal et al. reported that when *N*-methylaniline was replaced by *N*,*N*-disubstituted aniline, it reacts through its C-4 atom in the presence of the same catalyst under heating [29].

Results and discussion

We attempted to synthesize compound **5** by the reported method [28] to use it as a starting material for another reaction. Based on the similar observed NMR spectral data of **5** as reported, we tried to proceed with compound **5** to the next step. However, repeated failure of the reaction forced us to analyze the structure of **5** more closely. The single-crystal X-ray analysis of the synthesized compound clarified that the actual structure of the compound was **4** in which two new C–C bonds were formed and not **5** (Scheme 1).

Very recently, compound **4** was also synthesized by Bosica et al. using a heterogeneous catalyst WSi/A15 [30]. However, the current method is more advantageous over the previous one due to operational simplicity. As these types of molecules are very important in synthetic laboratory and pharmaceutical industries, we decide to publish the correct structure of the product formed from the reaction of the trio in the presence of PMA–SiO_2 (Scheme 1).

In Yadav et al. report, they used 2 eq. of *N*-methylaniline to reduce the formation of side product bis(indolyl)methanes (BIMs) [31–36]. To minimize the loading of *N*-methylaniline to establish the optimal condition, we screened the reaction using various equivalents of the aniline. We observed that 1.2 eq. of *N*-methylaniline was sufficient to get the maximum yield (**4a**, 90%), in which no BIM was formed. Moreover, mixing of these three substrates all together afforded excellent yield of the product **4** which is the same as the product obtained using the earlier procedure, with no formation of BIM. We next synthesized a series of compounds to establish the structure assigned by us. To our delight, compound **4** containing a broad range of substituents was formed in good yields, as summarized in

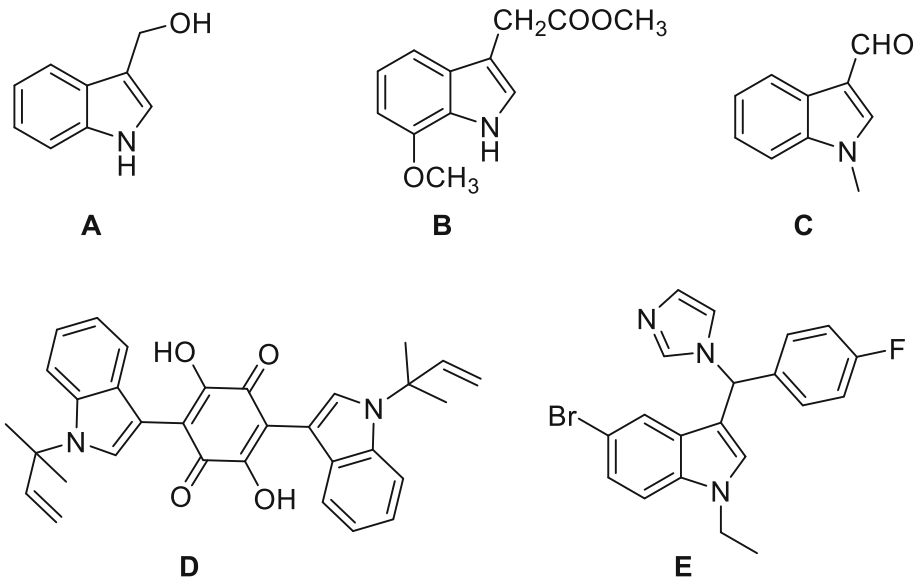
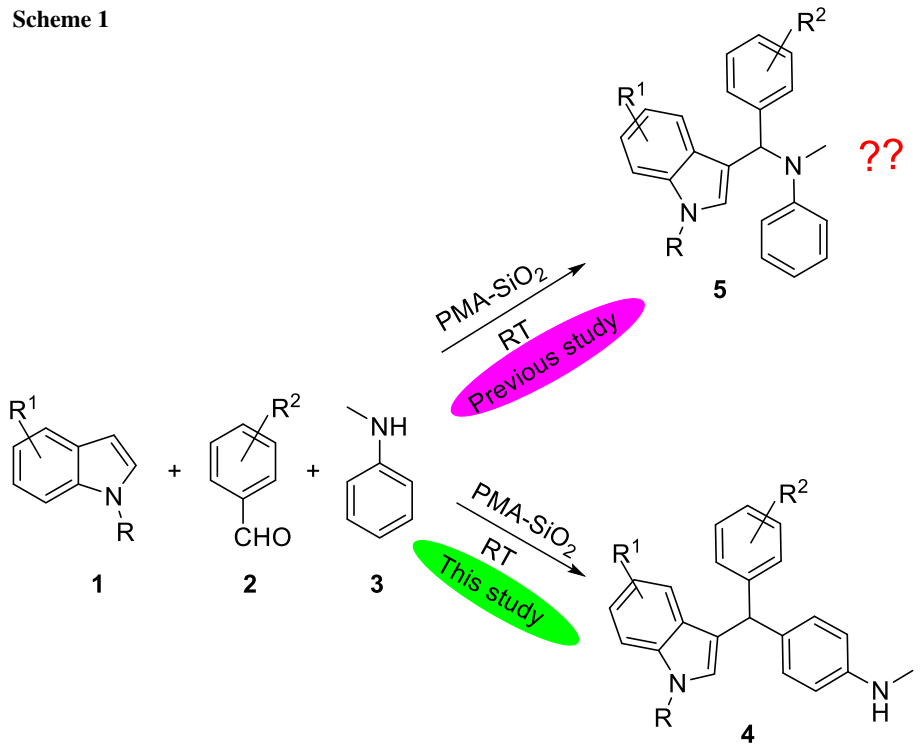


Fig. 1 Biologically active indoles derivatives

Scheme 1



Scheme 2. We also observed that electron-withdrawing and donating groups in indole and benzaldehyde have no effect in the product yield. A variety of *N*-substituted and *N*,*N*-disubstituted anilines were also used which produced products in good yield (**4n**–**4p** and **4q**, Scheme 2). The compounds synthesized were characterised by NMR, mass spectroscopy, and single-crystal X-ray crystallography (Fig. 2).

A plausible mechanism is proposed for this reaction (Scheme 3). First, aldehyde and indole react in the presence of acidic PMA–SiO_2 to form intermediate **X** which in turn eliminate a molecule of H_2O to generate alkylideneindoleninium intermediate **Y**. Next, intermediate **Y** was attacked by the C-4 carbon of the *N*-methylaniline giving the intermediate **Z**, which on deprotonation gives the desired product **4**. Another mechanism could be possible for this reaction (path b). However, we ruled out the path b based on the following observations. With < 1.2 eq. of *N*-methylaniline, the reaction produced small amount of BIMs which can be possible only when intermediate **Y** forms. On the other hand, irrespective of the amount of *N*-methylaniline, we never obtained 4,4′-(phenylmethylene)bis(*N*-methylaniline) **7**. To gain more insight into the mechanism, we attempted to trap the alkylideneindoleninium intermediate **Y** with a nucleophilic species pyrazol-5-amine **8** and successfully obtained the trapped product **9** (22%) along with **4** (Scheme 3).

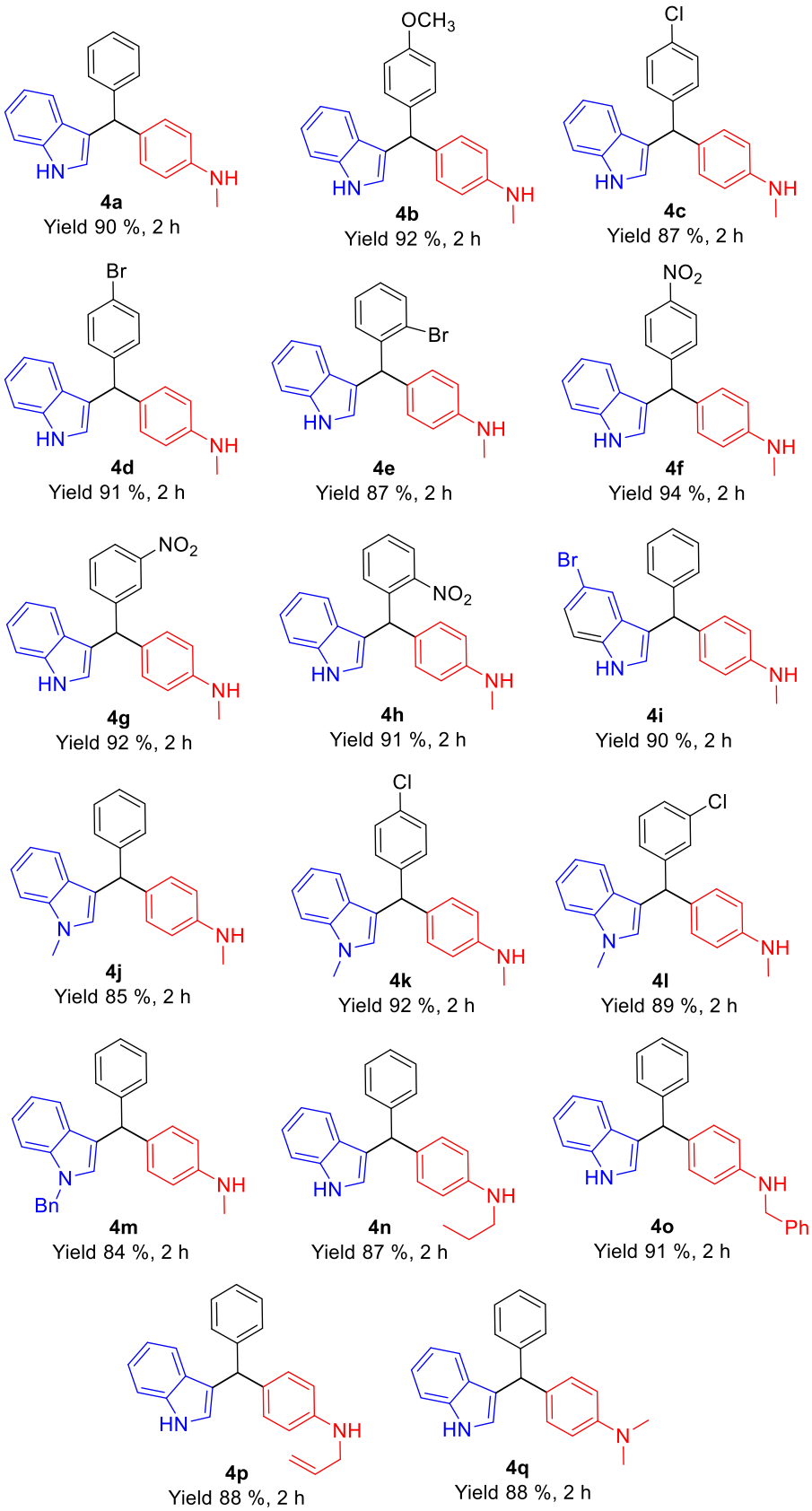
Conclusion

In conclusion, here, we assigned the revised structure of the product formed from the 3-component reaction of indole, aldehyde, and *N*-methylaniline catalyzed by PMA–SiO_2. The reaction describes an efficient synthetic technique for the preparation of 3-(α,α-diarylmethyl)indoles. The newly deduced structure **4** was established through NMR spectroscopy as well as single-crystal X-ray analysis of the products obtained. A mechanism is also established based on few observations, where alkylideneindoleninium ion functions as the key intermediate.

Experimental

All the commercially available reagents were used as received. Melting points were determined in open capillary tubes with a Buchi-540 micro-melting point apparatus. IR spectra were recorded on a Perkin-Elmer system 2000 FT-IR spectrometer. Mass spectra (ESI-HRMS) were recorded on Agilent Accurate-Mass Q-TOF LC/MS 6520. NMR spectra were recorded on Bruker Avance DPX-300 and 500 NMR spectrometer with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts (δ) are quoted in ppm and coupling constants (J) are measured in Hertz (Hz). All the experiments were monitored by thin-

Scheme 2


4a
Yield 90 %, 2 h
4b
Yield 92 %, 2 h
4c
Yield 87 %, 2 h
4d
Yield 91 %, 2 h
4e
Yield 87 %, 2 h
4f
Yield 94 %, 2 h
4g
Yield 92 %, 2 h
4h
Yield 91 %, 2 h
4i
Yield 90 %, 2 h
4j
Yield 85 %, 2 h
4k
Yield 92 %, 2 h
4l
Yield 89 %, 2 h
4m
Yield 84 %, 2 h
4n
Yield 87 %, 2 h
4o
Yield 91 %, 2 h
4p
Yield 88 %, 2 h
4q
Yield 88 %, 2 h

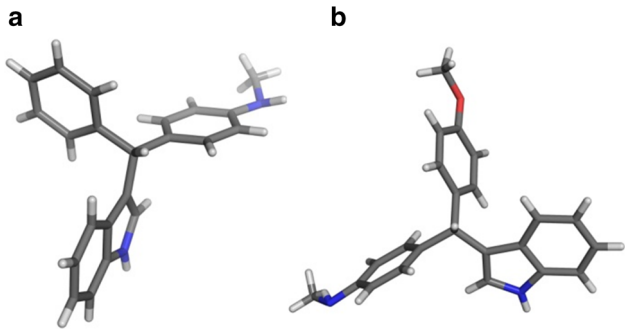


Fig. 2 Single-crystal X-ray structure of **4a** and **4b**

layer chromatography (TLC) on pre-coated silica-gel plates (Merck) and visualized under UV lamp at 254 nm for UV active materials. Further visualization was achieved by iodine vapour. Column chromatography was performed on silica gel (100–200 mesh, Merck) using ethyl acetate/hexane as eluent.

Preparation of PMA–SiO_2 catalyst [37]

To a solution of 100 mg $H_3PMo_{12}O_{40}$ (0.1 eq. by wt) in 5 cm^3, MeOH was added slowly 900 mg silica gel (0.9 eq. by wt, 100–200 mesh), and the mixture was stirred at room temperature for 6 h. Evaporation of MeOH under reduced pressure gave PMA–SiO_2 catalyst as dry yellowish powder.

Representative procedure for the synthesis of compound 4a

A mixture of indole (1 mmol), benzaldehyde (1 mmol), *N*-methylaniline (1.2 mmol), and PMA–SiO_2 (5%, w/w with respect to indole) was stirred at room temperature until the completion of the reaction. The reaction mixture was diluted with diethyl ether and filtered over a sintered funnel. The filtrate was concentrated and the crude product was purified by column chromatography using hexane/ethyl acetate as eluent and silica-gel 100–200 mesh.

Crystallographic data for compounds **4a** and **4b** have been deposited as CCDC-1839721 and -1839722, respectively, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, http://www.ccdc.cam.ac.uk/conts/retrieving.html.

4-[(1*H*-Indol-3-yl)(phenyl)methyl]-*N*-methylaniline (4a) Yield: 90% (281 mg); m.p.: 124–126 °C (128 °C [30]).

4-[(1*H*-Indol-3-yl)(4-methoxyphenyl)methyl]-*N*-methylaniline (4b) Yield: 92% (315 mg); m.p.: 156–158 °C (160 °C [30]).

4-[(4-Chlorophenyl)(1*H*-indol-3-yl)methyl]-*N*-methylaniline (4c, $C_{22}H_{19}ClN_2$) White solid; yield: 87% (301 mg); m.p.: 124–125 °C; R_f = 0.27 (hexane/EtOAc, 5:1); IR (KBr): $\bar{\nu}$ = 3414, 3047, 2925, 2855, 1615, 1456, 1091, 849, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (bs, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.23–7.20 (m, 3H), 7.18–7.13 (m, 3H), 7.02–6.99 (m, 3H), 6.55–6.52 (m, 3H), 5.52 (s, 1H), 3.13 (bs, 1H), 2.80 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7, 143.2, 136.6, 132.2, 131.6, 130.2, 129.6, 128.2, 126.8, 123.9, 122.0, 120.0, 119.9, 119.3, 112.4, 111.0, 47.3, 30.8 ppm; HRMS (ESI): exact mass calculated for $C_{22}H_{19}ClN_2$ ($[M + H]^+$) 347.1315, found 347.1319.

4-[(4-Bromophenyl)(1*H*-indol-3-yl)methyl]-*N*-methylaniline (4d) Yield: 91% (355 mg); m.p.: 142–144 °C (139 °C [30]).

4-[(2-Bromophenyl)(1*H*-indol-3-yl)methyl]-*N*-methylaniline (4e, $C_{22}H_{19}BrN_2$) Pink gummy; yield: 87% (340 mg); R_f = 0.26 (hexane/EtOAc, 5:1); IR (KBr): $\bar{\nu}$ = 3430, 3035, 2918, 2846, 1683, 1610, 1515, 1422, 1331, 1077, 739, 641 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (bs, 1H), 7.56 (dd, J = 1.2 Hz, 7.9 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 7.16–7.09 (m, 3H), 7.05–7.01 (m, 3H), 6.99–6.96 (m, 1H), 6.54–6.49 (m, 3H), 5.95 (s, 1H), 3.18 (bs, 1H), 2.79 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.6, 143.5, 136.7, 132.8, 131.1, 130.7, 129.9, 127.6, 127.1, 126.8, 125.0, 124.2, 122.0, 119.8, 119.6, 119.3, 112.3, 111.0, 47.0, 30.8 ppm; HRMS (ESI): exact mass calculated for $C_{22}H_{19}BrN_2$ ($[M + H]^+$) 391.0810, found 391.0813.

4-[(1*H*-Indol-3-yl)(4-nitrophenyl)methyl]-*N*-methylaniline (4f) Yield: 94% (335 mg); m.p.: 64–66 °C (63 °C [30]).

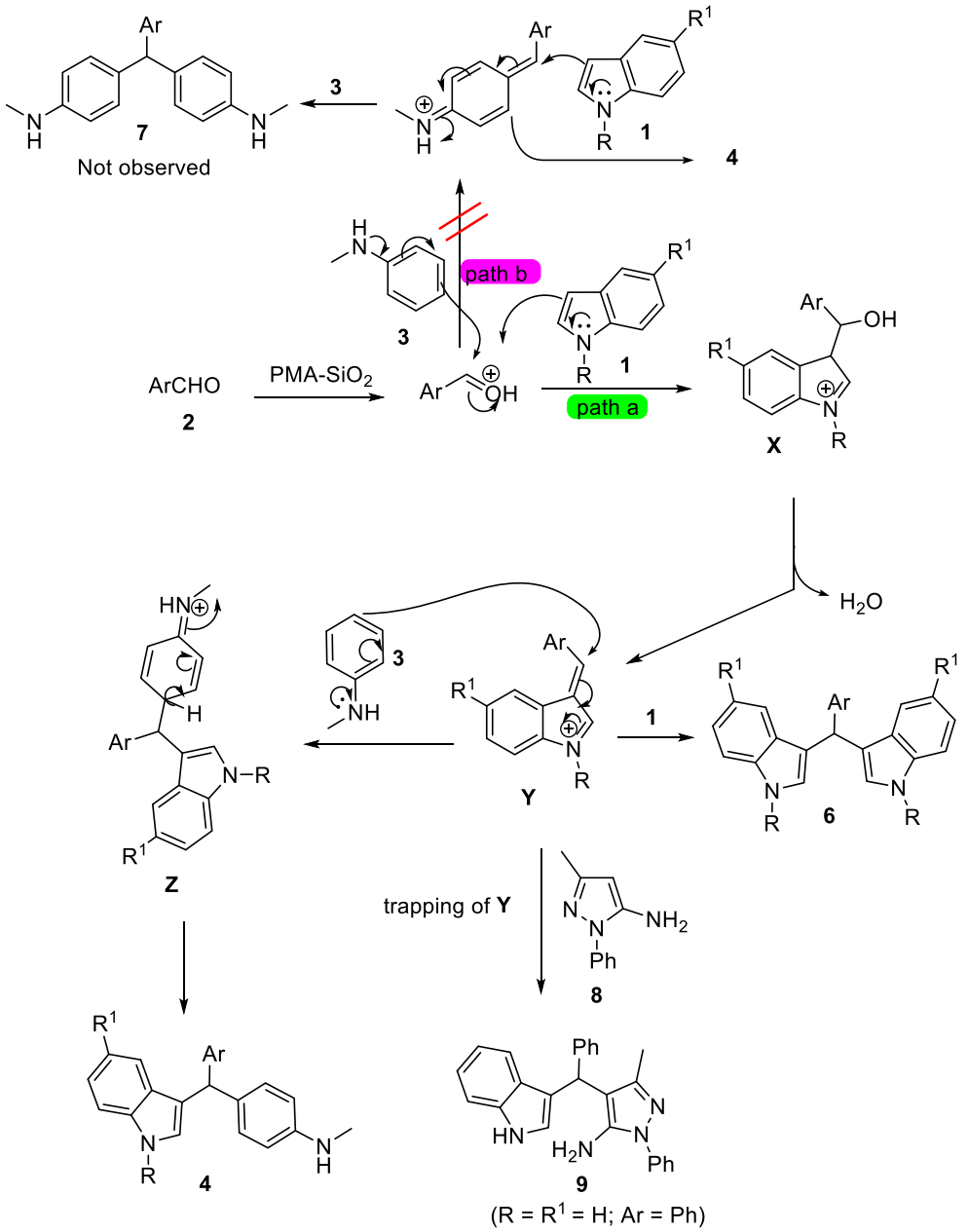
4-[(1*H*-Indol-3-yl)(3-nitrophenyl)methyl]-*N*-methylaniline (4g) Yield: 92% (328 mg); m.p.: 74–76 °C (64 °C [30]).

4-[(1*H*-Indol-3-yl)(2-nitrophenyl)methyl]-*N*-methylaniline (4h) Yield: 91% (325 mg); m.p.: 82–84 °C (71 °C [30]).

4-[(5-Bromo-1*H*-indol-3-yl)(phenyl)methyl]-*N*-methylaniline (4i, $C_{22}H_{19}BrN_2$) Pink solid; yield: 90% (351 mg); m.p.: 97 °C; R_f = 0.29 (hexane/EtOAc, 5:1); IR (KBr): $\bar{\nu}$ = 3420, 3024, 2925, 2855, 1622, 1517, 1318, 1174, 1096, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (bs, 1H), 7.42–7.16 (m, 8H), 7.04 (d, J = 8.3 Hz, 2H), 6.58 (d, J = 6.4 Hz, 3H), 5.53 (s, 1H), 3.70 (bs, 1H), 2.83 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6, 144.2, 135.2, 132.5, 130.1, 129.6, 128.8, 128.7, 128.4, 128.2, 126.1, 125.1, 124.8, 122.3, 120.2, 112.5, 47.6, 30.9 ppm; HRMS (ESI): exact mass calculated for $C_{22}H_{19}BrN_2$ ($[M + H]^+$) 391.0810, found 391.0816.

***N*-Methyl-4-[(1-methyl-1*H*-indol-3-yl)(phenyl)methyl]aniline (4j, $C_{23}H_{22}N_2$)** Brown solid; yield: 85% (277 mg); m.p.: 130–131 °C; R_f = 0.3 (hexane/EtOAc, 5:1); IR (KBr): $\bar{\nu}$ = 3401, 3053, 3019, 2926, 2873, 1742, 1614, 1520, 1055,

Scheme 3



1011, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.47 (d, J = 1.7 Hz, 1H), 7.22–7.19 (m, 4H), 7.16–7.10 (m, 5H), 7.01–6.99 (m, 1H), 6.92–6.89 (m, 1H), 6.40 (d, J = 8.4 Hz, 1H), 6.34 (s, 1H), 5.44 (s, 1H), 4.05 (bs, 1H), 3.63 (s, 3H), 2.78 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.5, 144.2, 139.0, 137.4, 134.5, 130.0, 128.8, 128.6, 128.2, 127.3, 126.1, 121.6, 120.0, 118.8, 118.4, 109.8, 109.1, 47.4, 32.7, 31.1 ppm; HRMS (ESI): exact mass calculated for $C_{23}H_{22}N_2$ ($[M + H]^+$) 327.1861, found 327.1868.

4-[(4-Chlorophenyl)(1-methyl-1*H*-indol-3-yl)methyl]-*N*-methylaniline (4k, $C_{23}H_{21}ClN_2$) Yellow solid; yield: 92% (331 mg); m.p.: 72–73 °C; R_f = 0.5 (hexane/EtOAc, 4:1); IR (KBr): $\bar{\nu}$ = 3421, 2933, 2870, 2839, 1738, 1612, 1471, 1025, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 1.4 Hz, 1H), 7.20–7.18 (m, 3H), 7.17–7.14 (m, 2H), 7.01–6.95 (m, 3H), 6.53 (d, J = 8.5 Hz, 2H), 6.39 (s, 1H), 5.52 (s, 1H), 3.67 (s, 4H, NCH_3 and NH), 2.79 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.7, 143.4, 137.4, 132.4, 131.5, 130.2, 129.6, 128.6, 128.2, 127.2, 121.6, 120.0, 118.8, 118.5,

112.3, 109.1, 47.3, 32.6, 30.8 ppm; HRMS (ESI): exact mass calculated for $C_{23}H_{21}ClN_2$ ($[M + H]^+$) 361.1472, found 361.1462.

4-[(3-Chlorophenyl)(1-methyl-1*H*-indol-3-yl)methyl]-*N*-methylaniline (4l, $C_{23}H_{21}ClN_2$) Brown solid; yield: 89% (320 mg); m.p.: 92–94 °C; $R_f = 0.33$ (hexane/EtOAc, 5:1); IR (KBr): $\bar{\nu}$ = 3435, 2928, 2858, 2831, 1629, 1245, 1068, 1020, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.28 (d, J = 8.2 Hz, 1H), 7.25–7.15 (m, 5H), 7.12 (d, J = 6.3 Hz, 1H), 7.02 (d, J = 7.9 Hz, 2H), 6.98 (t, J = 7.9 Hz, 1H), 6.55 (d, J = 7.6 Hz, 2H), 6.42 (s, 1H), 5.52 (s, 1H), 3.69 (s, 4H, NCH_3 and NH), 2.81 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.7, 147.0, 137.4, 134.0, 132.1, 129.6, 129.4, 128.9, 128.6, 127.2, 127.1, 126.2, 121.6, 119.9, 118.8, 118.2, 112.4, 109.1, 47.6, 32.7, 30.8 ppm; HRMS (ESI): exact mass calculated for $C_{23}H_{21}ClN_2$ ($[M + H]^+$) 361.1472, found 361.1478.

4-[(1-Benzyl-1*H*-indol-3-yl)(phenyl)methyl]-*N*-methylaniline (4m) Yield: 84% (337 mg) [38].

4-[(1*H*-Indol-3-yl)(phenyl)methyl]-*N*-propylaniline (4n, $C_{24}H_{24}N_2$) Brown gummy product; yield: 87% (296 mg); $R_f = 0.45$ (hexane/EtOAc, 5:1); IR (KBr): $\bar{\nu}$ = 3414, 3057, 2925, 2853, 1615, 1517, 1456, 1384, 1320, 1248, 1175, 1094, 1011, 807, 742, 699, 606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.93 (bs, 1H), 7.33–7.12 (m, 8H), 7.03–6.95 (m, 3H), 6.55–6.52 (m, 3H), 5.55 (s, 1H), 3.18 (bs, 1H), 3.04 (t, J = 7.2 Hz, 2H), 1.68–1.56 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.7, 144.7, 136.6, 132.8, 129.8, 128.4, 128.1, 127.0, 125.9, 123.9, 121.9, 120.5, 120.0, 119.2, 112.7, 110.9, 47.9, 46.0, 22.7, 11.7 ppm; HRMS (ESI): exact mass calculated for $C_{24}H_{24}N_2$ ($[M + H]^+$) 341.2018, found 341.2017.

4-[(1*H*-Indol-3-yl)(phenyl)methyl]-*N*-benzylaniline (4o, $C_{28}H_{24}N_2$) Brown solid; yield: 91% (354 mg); $R_f = 0.4$ (hexane/EtOAc, 5:1); m.p.: 140–142 °C; IR (KBr): $\bar{\nu}$ = 3438, 3389, 3016, 2926, 2853, 2346, 1617, 1519, 1450, 1321, 1274, 1218, 1180, 1090, 1030, 930, 844, 802, 748, 693, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (bs, 1H), 7.37–7.14 (m, 13H), 7.05–6.96 (m, 3H), 6.95–6.57 (m, 3H), 5.57 (s, 1H), 4.29 (s, 2H), 3.38 (bs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4, 144.6, 139.4, 136.6, 133.2, 129.7, 128.9, 128.6, 128.1, 127.6, 127.2, 127.0, 125.9, 123.9, 121.9, 120.4, 120.0, 119.2, 112.8, 110.9, 48.6, 47.9 ppm; HRMS (ESI): exact mass calculated for $C_{28}H_{24}N_2$ ($[M + H]^+$) 389.2018, found 389.2016.

4-[(1*H*-Indol-3-yl)(phenyl)methyl]-*N*-allylaniline (4p, $C_{24}H_{22}N_2$) White gummy product; yield: 88% (298 mg); $R_f = 0.4$ (hexane/EtOAc, 5:1); IR (KBr): $\bar{\nu}$ = 3415, 2924, 2855, 1615, 1517, 1457, 1408, 1319, 1265, 1123, 919, 804, 742, 700, 606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.86 (bs, 1H), 7.28–7.10 (m, 8H), 7.03–6.93 (m, 3H), 6.55–6.50 (m, 3H), 5.99–5.86 (m, 1H), 5.54 (s, 1H), 5.28–5.22 (m, 1H), 5.15–5.13 (m, 1H), 4.42 (bs, 1H), 3.71 (d, J = 5.7 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.2, 144.6, 136.6, 135.5, 133.2, 129.7, 128.9, 128.1, 127.0, 125.9, 124.0, 121.9, 120.4, 120.0, 119.2, 116.2, 113.0, 111.0, 47.9, 46.8 ppm; HRMS (ESI): exact mass calculated for $C_{24}H_{22}N_2$ ($[M + H]^+$) 339.1861, found 339.1863.

4-[(1*H*-Indol-3-yl)(phenyl)methyl]-*N*,*N*-dimethylaniline (4q) Yield: 88% (287 mg); m.p.: 152–154 °C (162 °C [30]).

4-[(1*H*-Indol-3-yl)(phenyl)methyl]-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (9) Yield: 22% (83 mg); m.p.: 210–212 °C (211–214 °C [9]).

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