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Ultrasound promoted mild and facile one-pot, three component synthesis of 2*H*-indazoles by consecutive condensation, C-N and N-N bond formations catalysed by copper-doped silica cuprous sulphate (CDSCS) as an efficient heterogeneous nano-catalyst

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Abstract:

An ultrasonic promoted facile and convenient one-pot three-component procedure for the synthesis of 2*H*-indazole derivatives using copper-doped silica cuprous sulphate (CDSCS) as a heterogeneous nano-catalyst has been described. In this approach, ultrasonic mediated reaction of different substituted 2-bromobenzaldehydes, structurally diverse primary amines, and tetrabutylammonium azide (TBAA) as an azide source in the presence of CDSCS in DMSO at room temperature furnishes 2*H*-indazoles in good to excellent yields. Utilizing ultrasonic irradiation techniques provided the dramatic improvements in terms of higher yields and shorter reaction times compared with conventional heating method.

Keywords: Ultrasound, One-pot three component, 2*H*-indazole, Heterogeneous nano-catalyst, Tetrabutylammonium azide (TBAA)

1. Introduction

Now a day, it is well realized that indazole and its related derivatives display a broad variety of biological activities. In this connection, the approved drugs such as lonidamine, bendacort, bendazac, granisetron, benzydamine, APINACA, axitinib and gamendazole were known to involve the indazole cores in their molecular scaffolds (Fig. 1) [1]. In addition to above

indazole-based approved drugs, other indazole derivatives were found to exhibit diverse biological activities like anti-tumour [2], anti-HIV [3], anti-microbial [4], anti-depressant [5], anti-platelet [6], neuroprotective sodium channel modulator [7], selective ligands for imidazoline I_2 [8], estrogen [9] and 5-HT_{1A} [10] receptors. Moreover, in the field of modern drug design and discovery, indazoles are known as useful bioisosters for indoles and benzimidazoles [11]. Indazole derivatives are also utilised in many industries including as optoelectronic chromophores used in fabrication of devices like OLEDs [12], dye-pigments [13] and agricultural purposes [14].

Despite the unique and remarkable medicinal profile of indazoles; however, a few facile and efficient approaches for the regioselective synthesis of N-substituted indazoles have been developed so far [15]. Nevertheless, most established protocols were devoted to achieve thermodynamically favoured 1*H*-indazole or complex mixture of 1*H*- and 2*H*-indazoles; whilst the facile and regioselective synthesis of 2*H*-indazoles is still remaining challenge [16].

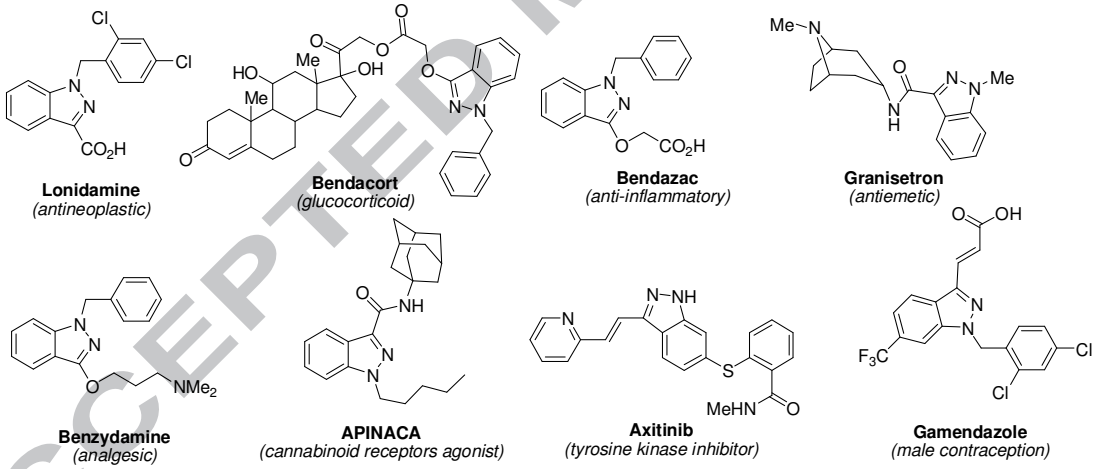


Fig.1. The structure of approved drugs having indazole cores and their corresponding pharmaceutical properties

To alleviate the problems associate with regioselectivity between 1*H*- vs 2*H*-indazoles, many useful approaches have been emerged in literatures to provide definite regioselective synthetic routes towards 2*H*-indazoles, comprising (i) base-catalysed reaction of 2-nitrobenzyl triphenylphosphonium bromide with Ar-N=C=O [17], (ii) reductive N-cyclisation of 2-nitroarylidine catalyzed by Rh complex [18], (iii) [3+2] sydnones and arynes

cycloaddition [19], (iv) Pd-catalysed reaction of 2-halophenylacetylene with hydrazine [20], (v) Fe-catalysed N–N bond formation from ArN_3 [21], (vi) DDQ–oxidised reaction of hydrazine and Baylis–Hillman adducts [22] and (vii) reaction of organozinc reagent with $ArN_2^+BF_4^-$ [23]. Despite the usefulness of the above protocols to access 2*H*-indazoles, however most of the existing methods are accompanied with several drawbacks such as requirement of multistep procedures for synthesis of starting materials, the use of precious metals or expensive ligands, non-regioselectivity, low tolerance of functionalities, harsh reaction conditions and non-recyclable catalysts.

In the last decade, the use of copper-based catalysts has extensively promoted the synthesis of 2*H*-indazoles. Among the copper catalysed synthesis of 2*H*-indazoles, the approaches in which generate 2-azidoimine have been privileged since utilizing the readily available starting materials. In this regard, the intramolecular N-N coupling reaction of the *in situ* generated 2-azidoimine through one-pot two-step process using CuO nanoparticles [24] or CuI-TMEDA [25] were reported to acquire 2*H*-indazoles. Moreover, the one-pot three component reactions (3CR) of 2-halobenzaldehydes, amines and sodium azide were established under Cu-based catalysts involving CuI-TMEDA [26] Cu(II)-hydrotalcite [27] Cu-complexed functionalised silica/starch composite [28] and nano-sized Cu_2O [29]. Notwithstanding of apparent profitableness of above protocols, however they still envisaged some disadvantages such as long reaction times, almost the homogeneity of the catalysts in media (except that of lit.[27, 28]), failure in recycling the catalyst and agglomeration of the nano-catalyst.

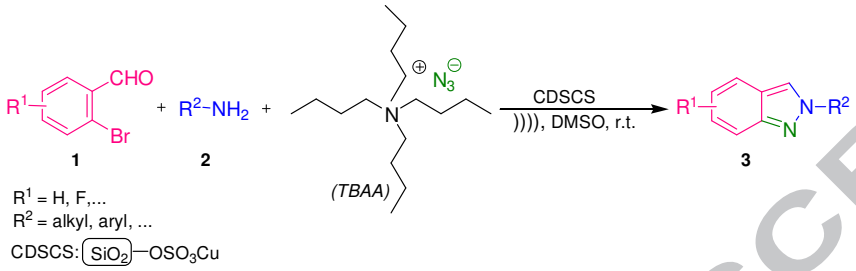
Undoubtedly, in recent years, the multi-component reactions (MCRs) have proved to be a powerful tool in organic chemistry offers incredible features such as ability to assemble a plenty of complex structures from simple and available starting materials, ease of experimental procedures, quantitative yields, lower environmental costs and atom economy [30].

Heterogeneous catalysts have received the particular attention owing to their remarkable economic and environmental benefits. Exploiting the heterogeneous catalysts often provides the simple experimental procedures, mild reaction conditions, recovery and reusability of the catalyst, the minimization of undesirable chemical wastes, and the production of large quantities of products by using a small amount of catalyst. Thus, the application of heterogeneous catalysts has an exact superiority over homogeneous catalyst [31].

Ultrasound-assisted organic synthesis has proved as a clean and advantageous approach in organic synthesis especially in the field of heterocyclic chemistry [32]. The ultrasonic effect induces very high local pressure and temperatures inside the bubbles (acoustic cavitation phenomenon) and enhances mass transfer and turbulent flow in the liquid [33]. This unique property of ultrasonic decisively affects the chemical reactivity through dissipation of energy. On the other hand, compared to conventional thermal heating, ultrasound irradiation has some important advantages: ultrasonification largely enhances the reaction rate and reduces the reaction times, improves yields, minimizes side product formation by providing the activation energy in micro environment, easier manipulation, increased selectivity, using small amounts of solvents, mild reaction condition and offers environmentally friendly and sustainable synthetic processes [34].

Silica-based catalysts are extremely important type of catalysts possessing the numerous advantages such as mild reaction conditions, cheapness, non-corrosive properties, high yields and selectivity, ease of handling, reusability by a simple flash filtration and also ease of preparation. Recently, we have reported the synthesis, characterization, and application of copper-doped silica cuprous sulfate (CDSCS) as an efficient heterogeneous nano-catalyst for various organic transformations [35-38]. In light of the unique biological activities of 2*H*-indazoles and also in continuation of our ongoing research in utilizing CDSCS in organic synthesis, hereby we would like to report an ultrasound promoted one pot, three component synthesis of 2*H*-indazoles through consecutive condensation, C-N and N-N bond formations

catalysed by CDSCS (Scheme 1). To the best of our knowledge, this approach is the first example of the synthesis of 2*H*-indazoles through a one-pot multicomponent coupling under ultrasonic irradiation and the use of tetrabutylammonium azide (TBAA) [CAS NO: 993-22-6] as an azide source.



Scheme 1. Synthesis of 2*H*-indazoles using CDSCS as a catalyst under ultrasonic irradiation.

2. Experimental

2.1. General

High-purity chemicals were purchased from Merck, Fluka, and Sigma-Aldrich. The fresh CDSCS was prepared due to our reported procedure [35]. Solvents were purified by using of standard procedures. Reactions were followed by TLC using SILG/UV 254 silica-gel plates. Column chromatography was performed on silica gel 60 (0.063-0.200 mm, 70-230 mesh; ASTM). Melting points were measured using Electrothermal IA 9000 melting point apparatus in open capillary tubes and are uncorrected. IR spectra were obtained using a Shimadzu FT-IR-8300 spectrophotometer. Ultrasonication was performed using a horn sonicator, Misonix model S-4000 (Qsonica LLC, Newtown, CT.) with a standard titanium tip diameters of ½" working at 20 kHz that was immersed directly into the reaction mixture. ^{1}H- and ^{13}C-NMR spectrum was recorded on Brüker Avance-DPX-250/400 spectrometer operating at 250/62.5 MHz, respectively. Chemical shifts are given in δ relative to tetramethylsilane (TMS) as an internal standard, coupling constants J are given in Hz. Abbreviations used for ^{1}H NMR signals are: s = singlet, d = doublet, t = triplet, m = multiplet. GC/MS was performed on a Shimadzu

GC/MS-QP 1000-EX apparatus (m/z; rel.%). Elemental analyses were performed on a Perkin–Elmer 240-B micro-analyzer.

2.2. Ultrasound promoted synthesis of 2*H*-indazole derivatives; General Procedure. In an open-capped cylindrical pyrex-glass (50 mL), was added a mixture of an appropriate 2-bromobenzaldehyde (10 mmol), proper primary amine (12 mmol), TBAA (15 mmol), and CDSCS (0.3 g, 0.05 mol%) in DMSO (10 mL) and the mixture was kept at room temperature and irradiated at 60W power (cup horn: 20 kHz) in ultrasonic apparatus. The progress of the reaction was monitored by TLC. After completion of the reaction (Table 5), then the reaction mixture was filtered to separate the catalyst and catalyst was washed with EtOAc (3 × 50 mL). The filtrate was then mixed with water (100 mL). The separated organic layer was washed with water (2 × 100 mL). Afterward, the organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude product was then purified by column chromatography on silica gel eluting with a mixture of *n*-hexane/EtOAc.

2.2.1. 2-Phenyl-2H-indazole (**3a**) [24]. White solid; yield: 1.79 g (92%); mp 81–82 °C; IR (KBr): 3100, 2945, 1652, 1567, 1470 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.16 (t, 1H, *J* = 7.8 Hz), 7.39 (t, 1H, *J* = 7.8 Hz), 7.48- 7.51 (m, 3H), 7.73 (d, 1H, *J* = 8.5 Hz), 7.81-7.86 (m, 2H), 7.97 (d, 1H, *J* = 8.5 Hz), 8.46 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 118.78, 120.84, 121.07, 121.79, 122.90, 123.34, 127.41, 128.77, 130.12, 141.86, 150.26; MS (EI): m/z (%) = 194 (15.7) [M^+]; Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.30; H, 5.12; N, 14.49.

2.2.2. 2-p-Tolyl-2H-indazole (**3b**) [24]. Yellow solid; yield: 1.87 g (90%); mp 101–102 °C; IR (KBr): 3065, 2958, 1633, 1538, 1447 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 2.26 (s, 3H), 7.11 (t, 1H, *J* = 7.5 Hz), 7.19 (t, 1H, *J* = 7.5 Hz), 7.29 (d, 2H, *J* = 8.6 Hz), 7.59 (d, 1H, *J* = 8.3 Hz), 7.80-7.89 (m, 3H), 8.49 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 22.60, 118.24, 120.93, 121.49, 122.71, 123.07, 126.82, 127.18, 131.36, 138.76, 139.50, 150.01; MS (EI): m/z (%) = 208 (16.5) [M^+]; Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.83; H, 5.92; N, 13.59.

2.2.3. 2-(4-Methoxyphenyl)-2H-indazole (**3c**) [24]. Brown solid; yield: 2.04 g (91%); mp 132–133 °C; IR (KBr): 3045, 2961, 1629, 1560, 1453, 1187 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 3.57 (s, 3H), 6.91 (d, 2H, *J* = 8.2 Hz), 7.15-7.22 (m, 2H), 7.42-7.48 (m, 2H), 7.89 (d, 2H, *J* = 8.2 Hz), 8.37 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 53.97, 115.72, 118.07, 120.75, 121.08,

122.45, 122.86, 123.16, 127.23, 134.91, 150.12, 159.90; MS (EI): m/z (%) = 224 (14.2) [M+]; Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.06; H, 5.31; N, 12.59.

2.2.4. 2-Mesityl-2H-indazole (**3d**) [26]. Pale-yellow oil; yield: 1.49 g (63%); IR (film): 3050, 2974, 1622, 1567, 1468 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.90 (s, 6H), 2.38 (s, 3H), 6.87 (s, 2H), 7.18-7.29 (m, 2H), 7.78-7.85 (m, 2H), 7.91 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 17.85, 22.16, 118.09, 120.98, 122.52, 122.76, 125.11, 126.68, 129.47, 135.81, 137.90, 139.73, 150.03; MS (EI): m/z (%) = 236 (18.7) [M+]; Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.47; H, 6.91; N, 11.98.

2.2.5. 2-(Naphthalen-1-yl)-2H-indazole (**3e**) [24]. White foam; yield: 2.10 g (86%); IR (KBr): 3100, 2956, 1635, 1582, 1469 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.21 (t, 1H, *J* = 7.9 Hz), 7.44 (t, 1H, *J* = 7.9 Hz), 7.54-7.62 (m, 5H), 7.71-7.75 (m, 2H), 7.86 (d, 1H, *J* = 8.1 Hz), 7.97 (d, 1H, *J* = 8.1 Hz), 8.32 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 118.37, 120.59, 122.71, 122.96, 123.58, 124.77, 125.39, 126.02, 126.90, 127.15, 127.74, 128.81, 129.70, 130.22, 135.07, 138.12, 149.93; MS (EI): m/z (%) = 244 (21.4) [M+]; Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.50; H, 5.06; N, 11.51.

2.2.6. Ethyl 4-(2H-indazol-2-yl)benzoate (**3f**) [26]. Pale-yellow solid; yield: 2.10 g (79%); mp 120–121 °C; IR (KBr): 3037, 2964, 1730, 1610, 1542, 1458 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.60 (t, 3H, *J* = 7.0 Hz), 4.57 (q, 2H, *J* = 7.0 Hz), 7.15 (t, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.78-7.86 (m, 2H), 7.94-8.05 (m, 2H), 8.14 (d, 2H, *J* = 8.2 Hz), 8.38 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 15.12, 60.27, 118.54, 120.03, 120.76, 121.29, 123.40, 126.61, 127.90, 129.52, 131.82, 144.10, 151.07, 166.75; MS (EI): m/z (%) = 266 (19.4) [M+]; Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.05; H, 5.18; N, 10.65.

2.2.7. 2-(Pyridin-2-yl)-2H-indazole (**3g**) [24]. Yellow solid; yield: 1.82 g (93%); mp 105–106 °C; IR (KBr): 3047, 2959, 1598, 1513, 1436 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.15 (t, 1H, *J* = 7.5 Hz), 7.30-7.38 (m, 2H), 7.70 (t, 1H, *J* = 7.5 Hz), 7.86-7.90 (m, 2H), 7.96 (d, 1H, *J* = 8.0 Hz), 8.07 (d, 1H, *J* = 8.0 Hz), 8.51 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 114.35, 118.54, 120.91, 121.40, 122.39, 122.94, 123.88, 127.80, 138.42, 148.71, 150.67, 151.74; MS (EI): m/z (%) = 195 (13.7) [M+]; Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.95; H, 4.70; N, 21.60.

2.2.8. 2-(3,5-Dichlorophenyl)-2H-indazole (**3h**). Yellow solid; yield: 2.16 g (82%); mp 122–123 °C; IR (KBr): 3051, 2960, 1638, 1527, 1472, 1094 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.10-7.18 (m, 2H), 7.33-7.42 (m, 3H), 7.59 (d, 1H, *J* = 8.4 Hz), 7.87 (d, 1H, *J* = 8.4 Hz), 8.41 (s,

1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 116.28, 118.96, 120.30, 120.74, 122.70, 123.85, 127.33, 128.14, 136.23, 142.01, 149.93; MS (EI): m/z (%) = 262 (35.9) [M^+]; Anal. Calcd for $C_{13}H_8Cl_2N_2$: C, 59.34; H, 3.06; N, 10.65. Found: C, 59.45; H, 2.94; N, 10.72.

2.2.9. 2,2'-(4,4'-Oxybis(4,1-phenylene))bis(2H-indazole) (**3i**). White solid; yield: 3.62 g (90%); mp 246–247 °C; IR (KBr): 3080, 2977, 1636, 1520, 1458, 1227 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ = 6.90-7.01 (m, 4H), 7.15 (t, 2H, *J* = 7.8 Hz), 7.38 (t, 2H, *J* = 7.8 Hz), 7.63-7.74 (m, 6H), 7.80 (d, 2H, *J* = 8.1 Hz), 8.52 (s, 2H); ^{13}C NMR (250 MHz, DMSO-d_6): δ = 116.12, 118.60, 120.89, 121.47, 122.37, 122.91, 123.20, 126.79, 136.04, 147.33, 151.61; MS (EI): m/z (%) = 402 (31.6) [M^+]; Anal. Calcd for $C_{26}H_{18}N_4O$: C, 77.59; H, 4.51; N, 13.92. Found: C, 77.71; H, 4.58; N, 13.84.

2.2.10. 2-Butyl-2H-indazole (**3j**) [24]. Colorless oil; yield: 1.06 g (61%); IR (film): 3049, 2967, 2837, 1624, 1524, 1469 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (t, 3H, *J* = 7.0 Hz), 1.42-1.49 (m, 2H), 1.87-1.93 (m, 2H), 4.18 (t, 2H, *J* = 7.0 Hz), 7.10 (t, 1H, *J* = 7.6 Hz), 7.38 (t, 1H, *J* = 7.6 Hz), 7.68 (d, 1H, *J* = 8.3 Hz), 7.85 (d, 1H, *J* = 8.3 Hz), 8.04 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 12.96, 20.66, 33.05, 53.78, 117.91, 120.47, 121.82, 122.17, 123.04, 127.31, 149.80; MS (EI): m/z (%) = 174 (14.8) [M^+]; Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.71; H, 8.18; N, 16.15.

2.2.11. 2-(3-Phenylpropyl)-2H-[1,3]dioxolo[4,5-f]indazole (**3k**) [26]. Pale-yellow solid; yield: 2.38 g (85%); mp 117–118 °C; IR (KBr): 3046, 2973, 1625, 1539, 1446, 1230 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.41-2.47 (m, 2H), 2.70 (t, 2H, *J* = 7.4 Hz), 4.23 (t, 2H, *J* = 7.4 Hz), 5.68 (s, 2H), 6.90-7.01 (m, 2H), 7.12 (s, 1H), 7.23-7.41 (m, 4H), 8.01 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 30.18, 32.95, 53.27, 95.01, 106.34, 111.49, 117.87, 122.44, 126.70, 128.05, 128.91, 141.20, 145.86, 146.79, 150.06; MS (EI): m/z (%) = 280 (20.3) [M^+]; Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.97; H, 5.89; N, 10.11.

2.2.12. 2-(4-Ethylphenyl)-2H-[1,3]dioxolo[4,5-f]indazole (**3l**) [26]. Pale-yellow solid; yield: 2.34 g (88%); mp 161–162 °C; IR (KBr): 3050, 2982, 1614, 1536, 1461, 1223 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (t, 3H, *J* = 7.3 Hz), 2.62 (q, 2H, *J* = 7.3 Hz), 5.73 (s, 2H), 7.13 (s, 1H), 7.24 (s, 1H), 7.36-7.43 (m, 2H), 7.80 (d, 2H, *J* = 8.5 Hz), 8.12 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 16.14, 28.87, 97.05, 107.66, 111.50, 118.81, 120.01, 120.74, 129.37, 138.49, 143.76, 146.90, 147.72, 150.19; MS (EI): m/z (%) = 266 (18.9) [M^+]; Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.30; H, 5.41; N, 10.62.

2.2.13. 5-Fluoro-2-phenyl-2H-indazole (**3m**) [24]. Yellow solid; yield: 1.91 g (90%); mp 135–136 °C; IR (KBr): 3029, 2960, 1681, 1547, 1453, 1279 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.20 (d, 1H, *J* = 7.8 Hz), 7.41 (d, 1H, *J* = 7.8 Hz), 7.63-7.68 (m, 3H), 7.84-7.90 (m, 3H), 8.27 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 104.58, 118.15, 120.32, 120.81, 121.98, 123.01, 128.30, 129.76, 140.79, 148.10, 158.47; MS (EI): m/z (%) = 212 (13.6) [M^+]; Anal. Calcd for $C_{13}H_9FN_2$: C, 73.57; H, 4.27; N, 13.20. Found: C, 73.49; H, 4.34; N, 13.31.

2.2.14. 2-(3,4-Dimethylphenyl)-5-fluoro-2H-indazole (**3n**) [24]. Yellow solid; yield: 1.99 g (83%); mp 106–107 °C; IR (KBr): 3042, 2960, 1618, 1535, 1465, 1203 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 2.50 (s, 3H), 6.95-7.04 (m, 2H), 7.37-7.43 (m, 2H), 7.60 (d, 1H, *J* = 7.9 Hz), 7.79 (s, 1H), 8.16 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 20.23, 20.79, 104.06, 118.49, 119.01, 120.17, 120.94, 121.88, 122.58, 130.70, 137.12, 138.25, 138.71, 147.34, 158.10; MS (EI): m/z (%) = 240 (19.3) [M^+]; Anal. Calcd for $C_{15}H_{13}FN_2$: C, 74.98; H, 5.45; N, 11.66. Found: C, 75.10; H, 5.54; N, 11.74.

2.2.15. Ethyl 4-(5-fluoro-2H-indazol-2-yl)benzoate (**3o**) [26]. Pale-yellow solid; yield: 2.27 g (80%); mp 118–119 °C; IR (KBr): 3039, 2954, 1726, 1621, 1547, 1430, 1198 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.56 (t, 3H, *J* = 7.4 Hz), 4.51 (q, 2H, *J* = 7.4 Hz), 7.16-7.31 (m, 3H), 7.52-7.69 (m, 2H), 8.02 (d, 2H, *J* = 8.2 Hz), 8.26 (s, 1H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 14.95, 61.74, 103.6, 119.54, 120.08, 120.62, 120.97, 122.71, 130.23, 131.55, 143.70, 147.82, 158.29, 167.31; MS (EI): m/z (%) = 284 (14.4) [M^+]; Anal. Calcd for $C_{16}H_{13}FN_2O_2$: C, 67.60; H, 4.61; N, 9.85. Found: C, 67.75; H, 4.48; N, 9.96.

3. Results and discussion

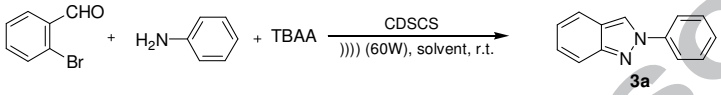
To optimize the reaction conditions, we examined the 3CR of 2-bromobenzaldehyde, aniline, and TBAA in the presence of catalytic amount of CDSCS as a sample reaction. In view of the immense importance of the solvent role in reaction progress, we first focused our attention on the choice of an appropriate solvent. For this purpose, we investigated the influence of various traditional solvents normally used in organic reactions (Table 1)

As can be seen from Table 1, the impact of several solvents involving polar protic, polar aprotic, nonpolar and a room temperature ionic liquid was assessed for preparation of 2-phenyl-2*H*-indazole (**3a**). Among the evaluated solvents, the use of DMSO gained the best result in terms of reaction time and yield, therefore this solvent was utilised for all next studied reactions (Table 1, entry 1). In addition, DMF, MeCN, THF and NMP also acquired good yields of **3a** (Table 1, entries 2-5). Whereas, nonpolar solvents such as toluene and *p*-xylene

(Table 1, entries 6 and 7) resulted the low yields of **3a**. Moreover, protic solvents like water, ethanol and PEG 400 afforded the moderate yields of the corresponding 2*H*-indazole. Surprisingly, [bmim]Br as a room temperature ionic liquid failed to yield the product after irradiation for 4h (Table 1, entry 11). In general, polar aprotic solvents achieve better yields of 2*H*-indazoles.

Table 1

Effect of solvents in synthesis of 2-phenyl-2*H*-indazole. [a]



Entry	Solvent	Time (h)	Yield [b] (%)
1	DMSO	1	92
2	DMF	1.5	80
3	MeCN	2.5	75
4	THF	2	66
5	NMP	1.5	78
6	Toluene	5	27
7	p-Xylene	5	30
8	EtOH	2.5	54
9	H_2O	3	48
10	PEG 400	3.5	50
11	[bmim]Br	4	NR[c]

[a] Reaction conditions: 2-bromobenzaldehyde (10 mmol), aniline (12 mmol), TBAA (15 mmol), CDSCS (0.3 g), and solvent (10 mL).
[b] Isolated yield.
[c] No reaction.

After identifying the proper solvent and the persistence of finding the other optimal conditions, the influence of ultrasound power intensity on the sample reaction was screened. In this regard, the sample reaction was carried out at different irradiation powers in the range of 20 to 80 W (Table 2).

As shown in Table 2, without exposing the reaction to ultrasound irradiation, the reaction was not achieved at all even after stirring for 48h at room temperature (Table 2, entry 1). However, as expected, the increase of ultrasonic power led to relatively higher yields of **3a** in shorter reaction time. The maximum yield of **3a** was obtained when the power was set to 60 W for an hour. The increased yield associated with increasing irradiation power, is attributed to abundance of active cavitation bubbles which result in higher maximum collapse temperature and accelerated the respective reaction. Moreover, by increasing the ultrasonic power (>70W) no apparent improvement was observed.

Table 2

The influence of ultrasonic irradiation on the synthesis of 2-phenyl-2*H*-indazole. [a]

3a

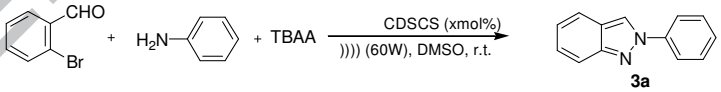
Entry	Power (W)	Time (h)	Yield [b] (%)
1	0	48	NR[c]
2	20	7	44
3	30	5	50
4	40	3	66
5	50	2	78
6	60	1	92
7	70	1	91
11	80	1	91

[a] Reaction conditions: 2-bromobenzaldehyde (10 mmol), aniline (12 mmol), TBAA (15 mmol), CDSCS (0.3 g), and DMSO (10 mL).
[b] Isolated yield.
[c] No reaction.

In another study, we investigated the relation between loading amounts of catalyst and reaction progress (Table 3). As shown in Table 3, the catalyst has undeniable role in reaction advancement, thus, in the absence of an active catalyst the reaction was failed to achieved at all (Table 3, entry 1). By increasing the loading catalyst amount, the reaction yields were gradually increased. An impressive activity of catalyst and the maximum yield of desired **3a** were observed when the loading catalyst amount was reached to 0.05 mol% (Table 3, entry 6). Practically, the yield remained unchanged when the used catalyst amount exceeded more than 0.05 mol% (Table 3, entries 7 and 8).

Table 3

Effect of catalyst loading in synthesis of 2-phenyl-2*H*-indazole. [a]



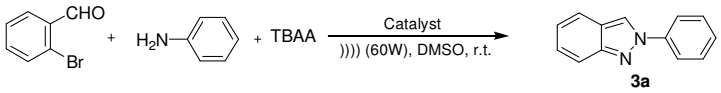
3a

Entry	CDSCS (mol%)	Time (h)	Yield [b] (%)
1	0	8	NR [c]
2	0.01	4	52
3	0.02	3	58
4	0.03	2.5	63
5	0.04	2	76
6	0.05	1	92
7	0.06	1	92
8	0.07	1	90

[a] Reaction conditions: 2-bromobenzaldehyde (10 mmol), aniline (12 mmol), TBAA (15 mmol), catalyst (xmol%), and DMSO (10 mL).
[b] Isolated yield.
[c] No reaction.

Table 4

Effect of catalyst type in synthesis of 2-phenyl-2*H*-indazole. [a]



3a

Entry	catalyst	Time (h)	Yield [b] (%)
1	$CuCl_2$	4	56
2	CuO	3	60
3	Cu_2O	3	64
4	$Cu(OAc)_2$	2.5	60
5	CuI	2	72
6	CuI-TMEDA [c]	1	80
7	CDSCS	1	92
8	$CuSO_4.5H2O$	4	54

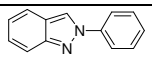
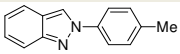
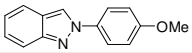
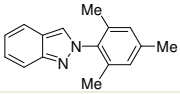
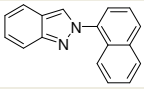
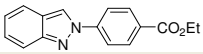
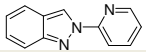
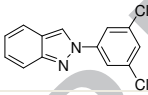
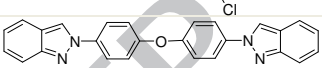
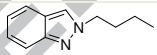
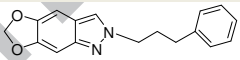
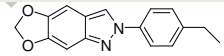
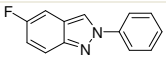
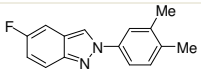
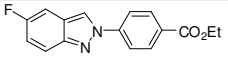
[a] Reaction conditions: 2-bromobenzaldehyde (10 mmol), aniline (12 mmol), TBAA (15 mmol), catalyst, and DMSO (10 mL).
[b] Isolated yield.
[c] N,N,N',N'-tetramethylethylenediamine.

In order to ascertain the catalytic potency of CDSCS in synthesis 2*H*-indazole under ultrasonic irradiation, we assayed the model reaction using other used copper catalysts under the optimized condition (Table 4). As depicted in Table 4, a higher yield of **3a** was obtained when CDSCS was employed (Table 4, entry 7). In addition to CDSCS, the combination of CuI-TMEDA [26] afforded a good yield of **3a**. Using the other catalysts, the satisfactory yields of the corresponding product were afforded, however the reactions required longer reaction time for completion. In general, it seems that $Cu^{(I)}$-catalysts demonstrate better catalytic activity compared with $Cu^{(II)}$-catalysts in 2*H*-indazole synthesis under ultrasonic irradiation.

With the optimal reaction conditions in hand, we screened the versatility and the scope of this protocol to other 2-bromobenzaldehyde and primary amine derivatives (Table 5). We have also undertaken the synthesis of 2*H*-indazoles utilising CDSCS as a catalyst under conventional heating protocol (DMSO at 120° C) and compared the results with ultrasonic mediated protocols. As illustrated in Table 5, the dramatic improvements in terms of higher yields and shorter reaction times were observed compared with conventional heating method.

Table 5

The synthesized 2*H*-indazoles using CDSCS under ultrasonic irradiation. [a]

Entry	Product No.	Product [a]	Sonication [b]		Conventional [c]	
			Time (h)	Yield [d] (%)	Time (h)	Yield [d] (%)
1	**3a**		1.0	92	12	85
2	**3b**		1.0	90	8	79
3	**3c**		0.75	91	5	80
4	**3d**		1.5	63	10	51
5	**3e**		1.0	86	7	64
6	**3f**		1.5	79	9	58
7	**3g**		1.5	93	7	81
8	**3h**		1.5	82	10	75
9	**3i**		2.0	90	11	82
10	**3j**		1.5	61	12	60
11	**3k**		0.75	85	8	80
12	**3l**		1.0	88	10	76
13	**3m**		0.75	90	6	78
14	**3n**		0.5	83	6	74
15	**3o**		1.0	87	7	80

[a] All products were characterized by ^{1}H and ^{13}C NMR, IR, CHN, and MS analysis.
[b] Reaction conditions: 2-bromobenzaldehydes (10 mmol), amines (12 mmol), TBAA (15 mmol), CDSCS (0.3 g), DMSO (10 mL), power (60 W), room temperature.
[c] Reaction conditions: 2-bromobenzaldehydes (10 mmol), amines (12 mmol), TBAA (15 mmol), CDSCS (0.3 g), DMSO (10 mL), heat (120 °C).
[d] Isolated yield.

Using ultrasonic technique, in most cases, the reaction times shortened to around an hour or less and yields almost enhanced to excellent or quantitative amounts. Therefore, the results in

Table 5 confirm the advantage of ultrasonic method over conventional thermal method. This ultrasonic promoted protocol works well with structurally diverse aliphatic, aromatic, and heteroaromatic amines and tolerates different functional groups to afford the corresponding 2*H*-indazoles in good to excellent yields. The aromatic amines bearing electron-rich substituents were efficiently applied in the current protocol (Table 5, entries 2-4, 12 and 14). In addition, the sterically hindered amines like 2,4,6-trimethylbenzenamine was also successfully converted to the corresponding 2*H*-indazole in 63% yield (Table 5, entry 4). Heteroaromaic amines such as 2-aminopyridine was efficaciously applied under the optimized condition to afford **3g** in almost quantitative yield (Table 5, entry 7).

Aromatic amines with electron-deficient group such as CO_2Et provided the corresponding products **3f** and **3o** in 79 and 87% yields, respectively (Table 4, entries 6 and 15). The reaction of 4,4'-oxydibenzenamine with two equivalents of 2-bromobenzaldehyde afforded **3i** in an excellent yield (Table 5, entry 9). Under optimized reaction conditions, diverse aliphatic amines were readily reacted with 2-bromoaldehydes to produce the favourable yields of **3j** and **3k** (Table 5, entries 10 and 11). Furthermore, 6-bromobenzo[d][1,3]dioxole-5-carbaldehyde and 2-bromo-5-fluorobenzaldehyde were efficiently transformed to 2*H*-indzoles **3k-3o** under ultrasonic irradiation (Table 5, entries 11-15).

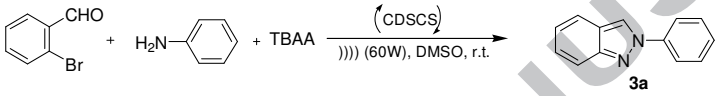
In addition to ultrasonic irradiation and catalytic performance of CDSCS which are main factors that influenced in progression of reaction; however, it is worthy to be mentioned that TBAA not only behaves as an azide source but also because of its phase transfer catalytic (PTC) nature can extensively promote the reaction.

The recoverability and reusability of heterogeneous catalyst is the important benefits and superiority over homogeneous catalysts from both environmental and economical standpoints. Thus, the recyclability and reusability of CDSCS were assessed under the optimized reaction conditions (Table 6). To this end, after the completion of the reaction, the catalyst was recycled from the reaction mixture through a sintered glass funnel and washed

successively with EtOAc (2 × 50 mL). The catalyst was then dried in a vacuum oven at 60 °C and tested for several sequential runs. The obtained results in Table 6 clearly confirm that CDSCS is a recyclable and reusable catalyst without any significant loss of its activity. In addition, the ICP analysis has demonstrated the reusability of the catalyst with extremely negligible desorption of active copper species from CDSCS. Based on the ICP analysis, the amount of leached copper from CDSCS is estimated about 0.006% after five consecutive runs which is an extremely negligible amount.

Table 6

The reusability of CDSCS for synthesis of 2-phenyl-2*H*-indazole under ultrasonic irradiation. [a]

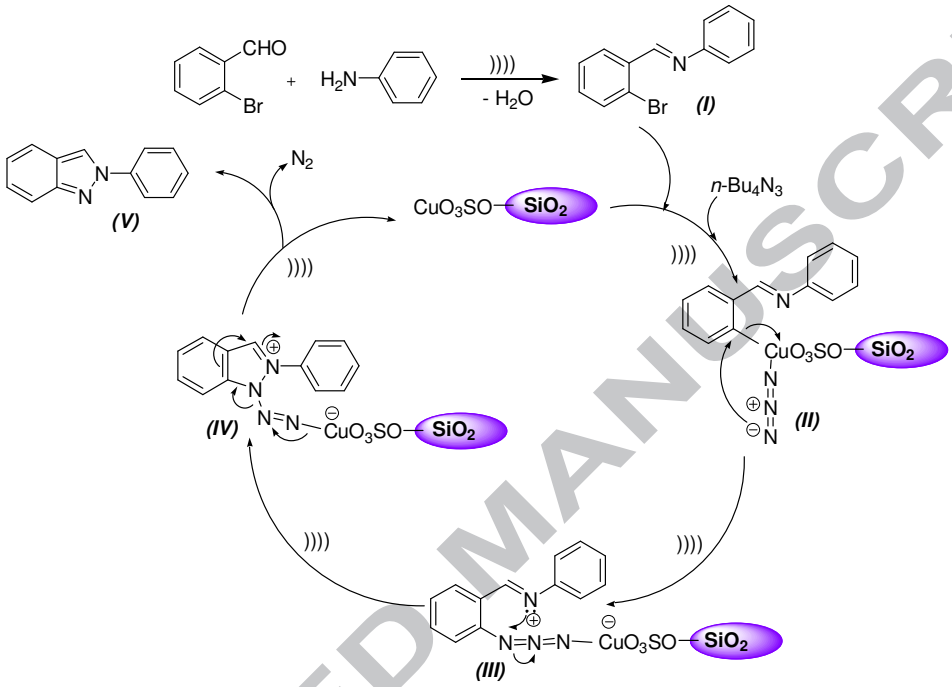


Run no. [b]	Time (h)	Yield [c] (%)
1	1	92
2	1	92
3	1.25	91
4	1.25	90
5	1.5	87

[a] Reaction conditions: 2-bromobenzaldehyde (10 mmol), aniline (12 mmol), TBAA (15 mmol), recovered CDSCS (0.3 g), DMSO (10 mL).
[b] The entry number corresponds to the trial number.
[c] Isolated yield.

Due to literatures [24-29], a plausible mechanism for the preparation of 2*H*-indazole derivatives via one-pot 3CR of 2-bromobenzaldehydes, amines, and TBAA using CDSCS under ultrasonic irradiation was suggested (Scheme 2). According to this mechanism, a consecutive condensation, C–N and N–N bond formations were happened for synthesis of 2*H*-indazoles using the current protocol. The mechanism for synthesis of 2-phenyl-2*H*-indazole as a sample compound is shown in Scheme 2. Initially, the reaction occurred through the condensation of 2-bromobenzaldehyde with aniline to form the imine (I) as the main intermediate. The *in situ* generation of imine was evidently confirmed at the early stage of the reaction which simply can be identified by thin layer chromatography (TLC) or gas chromatography (GS) techniques through the comparison with pre-synthesized imine or provided authentic sample. In

continuation, TBAA was reacted with imine (I) in the presence of CDSCS to afford the intermediate (II) followed by reductive elimination to azide-copper complex (III) through C-N bond formation. Afterward, N-N bond formation via the intramolecular cyclization of (III) resulted in intermediate (IV). Eventually, the elimination of N_2 gas and dissociation of the catalyst led to 2*H*-indazole (V) as the ultimate product.



Scheme 2 . A plausible mechanism for the synthesis of 2*H*-indazole derivatives

4. Conclusion

In conclusion, we have developed an ultrasound promoted facile and convenient one-pot three-component procedure for the synthesis of 2*H*-indazole derivatives through consecutive condensation, C–N and N–N bond formations using CDSCS as a heterogeneous nano-catalyst. Utilizing ultrasonic irradiation techniques provided the dramatic improvements in terms of higher yields and shorter reaction times compared with conventional heating method in current research. The advantageous of this ultrasonic promoted approach involves the high yields of products, short reaction times, mild reaction conditions, low catalyst loading, using available precursors, ease of operation, the simplicity of separation, not requiring any

supplementary ligand, reusability of the catalyst minimization of by-products and chemical wastes. To the best of our knowledge, this method is the first example of one-pot 3CR of 2*H*-indazole through ultrasonic irradiation utilizing TBAA as a nitrogen source and CDSCS as a heterogeneous nano-catalyst.

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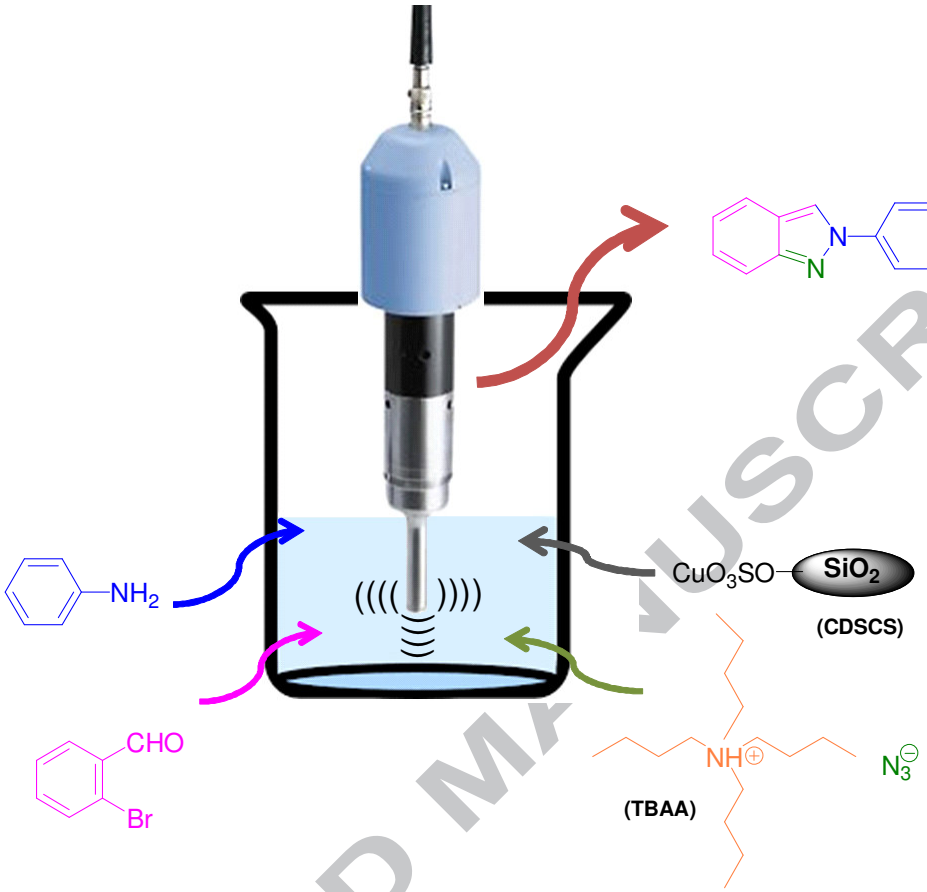

Highlights

- Ultrasound promoted facile three-component procedure to access 2*H*-indazoles.
- Under ultrasonic irradiation, the yields dramatically increased.
- Under ultrasonic irradiation, the reaction times considerably shortened.
- CDSCS is highly active and selective nano-catalyst for 2*H*-indazole synthesis.
- Reusability and inexpensive nature of the catalyst.