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Synthesis of hydrogenated indazole derivatives starting with α,β-unsaturated ketones and hydrazine derivatives

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The reaction of hydrazine derivatives with α,β-unsaturated ketones, such as cyclohexenyl(phenyl)methanone and (*E*)-2-benzylidenecyclohexanone, were investigated.

The reaction between methylhydrazine and e.g., cyclohexenyl(phenyl)methanone was particularly interesting as 3a,4,5,6,7,7a-hexahydro-1-methyl-3-phenyl-1*H*-indazole was obtained as the major product together with 4,5,6,7-tetrahydro-2-methyl-3-phenyl-2*H*-indazole as a minor product.

1. Introduction

The pyrazole ring is an important central template for a wide variety of biologically active compounds including anti-inflammatory,[1] antidepressant[2] and YC-1 (guanylyl cyclase activator agents).[3] Some interesting pyrazoles are difficult to access and therefore, new and efficient methods for the construction of this heterocyclic system have recently attracted considerable attention.

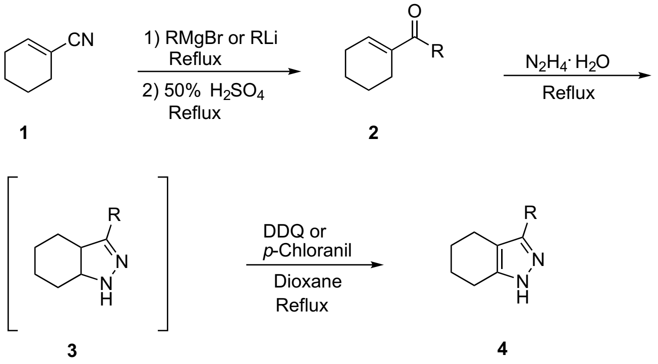
One interesting pyrazole variant is the tetrahydroindazole[4] containing a two-ring moiety that is known to be pharmacologically active e.g., against cancer[5] and inflammation.[6] Tetrahydroindazole was first prepared by Wallach as early as 1903[7] and since then, several approaches for the preparation of its derivatives have been developed. One of the most common methods for 3-aryl 4,5,6,7-tetrahydroindazoles[8] involves condensation of hydrazine derivatives with 1,3-diketones. Another general procedure utilizes 2-cyclohexenone derivatives as starting materials.[9] In addition, it has been reported that reaction between a hydrazone derivative and an aromatic aldehyde delivers 3-substituted 4,5,6,7-tetrahydroindazoles.[10] However, this purported approach failed in our hands. More recent syntheses involving the reaction of hydrazine with 2-fluorovinylcarbonyl derivatives have given pyrazole-fused ring systems.[11]

In the present paper, we describe a facile and efficient route towards various 3-substituted tetrahydroindazole derivatives by using α,β-unsaturated ketones as starting materials.

2. Results and discussion

The use of α,β-unsaturated ketones in organic synthesis for the production of heterocyclic compounds such as pyrazole derivatives has already been studied to a certain extent.[12–15]

Hence, we contemplated the conjugated cyano derivative, 1-cyanocyclohexene **1**,[16] as a readily available precursor to similar systems. The general synthetic approach for the preparation of



Scheme 1.

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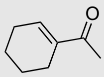
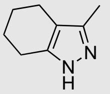
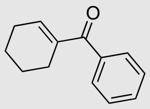
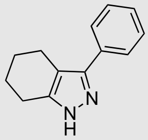
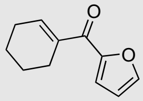
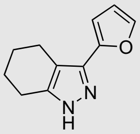
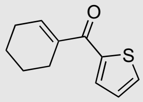
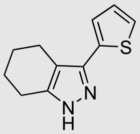
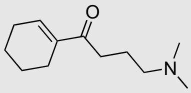
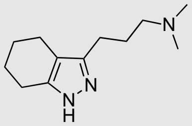
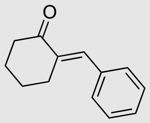
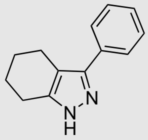
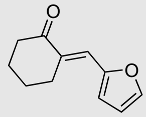
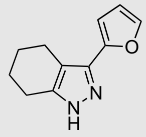
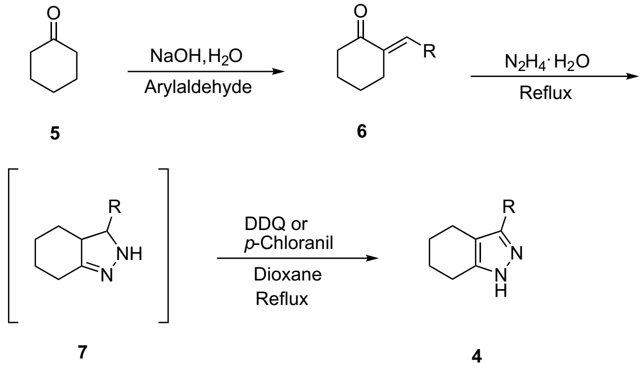
3-substituted 4,5,6,7-tetrahydroindazoles **4**[8,17,18] is summarized in Scheme 1.

Thus, compound **1** was treated with the appropriate Grignard or organo-lithium reagent, and after quenching with 50% H_2SO_4 the aqueous phase was refluxed overnight. The product obtained, the α,β-unsaturated ketone of type **2**,[19–21] was isolated by distillation giving 44–88% yields (Table 1). Cyclization of compounds **2** with hydrazine hydrate was carried out either neat or in alcoholic solvent (isopropanol or ethanol) under reflux. As indicated in Scheme 1 compounds **3** were not isolated but used directly. Selective dehydrogenation of **3** was carried out with DDQ or *p*-chloranil in dioxane at reflux, which gave the desired 3-substituted 4,5,6,7-tetrahydroindazole derivatives **4** after chromatography in 27–54% yield (Table 1). The isolation of 3-(3-dimethylaminopropyl) 4,5,6,7-tetrahydroindazole **4e** was achieved only by preparative HPLC, which subsequently proved to be unstable due to slow decomposition. The full aromatization of molecules of type **4** with DDQ in benzene to indazole has been recently reported.[9] However, in our hands, attempted aromatization with this reagent failed, as did more classical conditions (Pd/C, in hot decalin).

We have also prepared molecules of type **4** by a method as outlined in Scheme 2, namely utilization of an α,β-unsaturated ketone **6**[23–27] (Table 1, entries 6 and 7). In this context, several papers are of interest when α,β-unsaturated ketone derivatives are reacted with hydrazine hydrate to obtain hexahydroindazoles.[14,15,28]

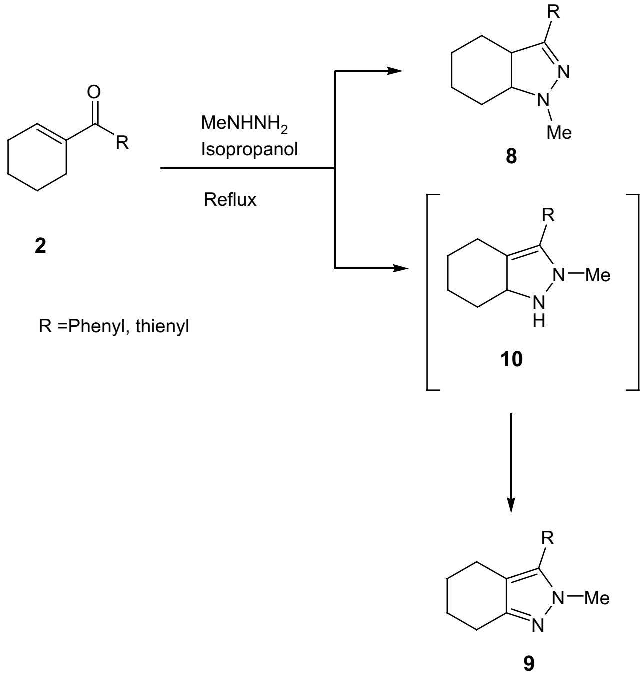
Table 1
Synthesis of 3-substituted tetrahydroindazoles **4**

Entry	Starting compound	Yield (%)	Product **4**	Yield (%)
1	 **2a**[21]	88	 **4a**[18]	54
2	 **2b**[22]	70	 **4b**[17]	31
3	 **2c**	55	 **4c**	45
4	 **2d**	53	 **4d**	27
5	 **2e**	44	 **4e**	—
6	 **6a**[23]	74	 **4b**	57
7	 **6b**[24]	70	 **4c**	49



Scheme 2.

Interestingly, when methylhydrazine was used as reagent and reacted with compound **2**, two types of products, **8**[29] and **9**,[30] were isolated after chromatography (Scheme 3, Table 2, entries 1 and 2).



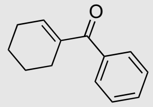
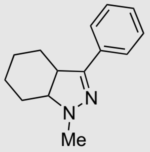
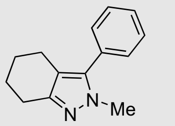
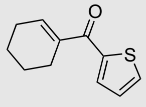
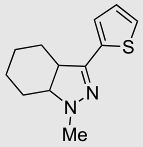
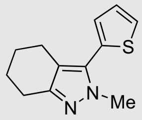
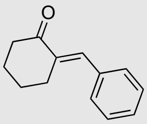
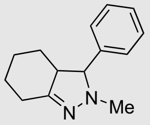
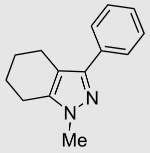
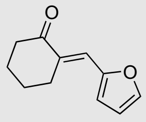
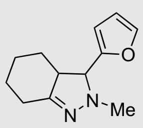
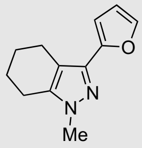
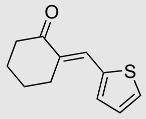
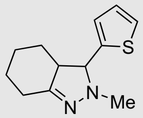
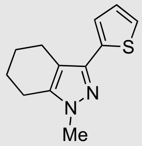
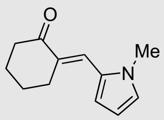
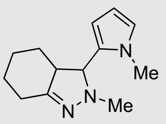
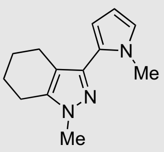
Scheme 3.

As shown in Scheme 3, we postulate that formation of 1-methylhexahydroindazoles **8** occurred by nucleophilic attack of the hydrazine-NH_2 on the ketone followed by cyclization. The other products, 2-methyltetrahydroindazoles **9**, indicate conjugate addition by hydrazine-NH_2 followed by cyclization to form the hexahydroindazole intermediates (presumably **10**), which easily undergo dehydrogenation to **9** (Scheme 3).

α,β-Unsaturated ketones **6b**[31,24] and **6d** reacted with methylhydrazine in the same manner to furnish two types of products, namely 2-methylhexahydroindazoles **11b** and **11d** and 1-methyltetrahydroindazoles **12b** and **12d**, respectively (Scheme 4, Table 2, entries 4 and 6). In contrast, when α,β-unsaturated ketones **6a** and **6c**[25] were used as starting materials only one isolable product was obtained in excellent yield, 2-methylhexahydroindazoles **11a**[32] and the respective **11c** (Scheme 4, Table 2, entries 3 and 5).

The results shown in Table 2 indicate that heteroatoms with electron pairs involved in resonance will promote two types of

Table 2
Reaction of α,β-unsaturated ketones **2** and **6** with methylhydrazine

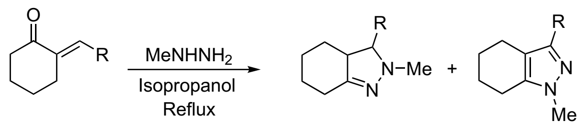
Entry	Starting compound	Yield (%)	Product	Yield (%)	Product	Yield (%)
1	 **2b**	70	 **8a**[29]	46	 **9a**[30]	21
2	 **2d**	53	 **8b**	51	 **9b**	23
3	 **6a**	74	 **11a**[32]	99	 **12a**[33]	—
4	 **6b**	70	 **11b**	26	 **12b**	17
5	 **6c**[25]	46	 **11c**	98	 **12c**	—
6	 **6d**	42	 **11d**	55	 **12d**	15

products. One product formed by nucleophilic attack of the hydrazine-NH_2 on the ketone and the other via Michael addition.

One significant difference between the ^{1}H NMR spectra of compounds **9a** and **12a** was observed in the aromatic region. The ^{13}C NMR spectra showed that the methyl carbon atom of compound **9a** resonated at 37.1 ppm whereas the corresponding carbon of compound **12a** resonated at 35.6 ppm. The CH_2 signals of **9a** were more constricted as compared with compound **12a**.

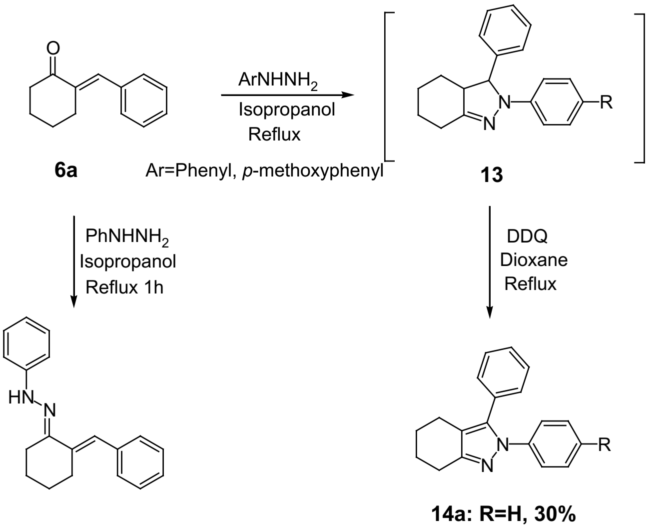
Moreover, when other substituted hydrazines such as phenylhydrazine or *p*-methoxyphenylhydrazine were used as reagents, with α,β-unsaturated ketone **6a**, isolation of hexahydroindazole derivatives of type **13**[34] was not possible by column chromatography. The crude materials from these steps were therefore used directly in the dehydrogenation step and delivered compounds **14**[8] (Scheme 5). Interestingly, Orlov and co-workers treated disubstituted α,β-unsaturated ketone derivatives with phenylhydrazine and obtained two type of products, 2-phenylhexahydroindazole derivatives and 1-phenyltetrahydroindazole derivatives.[35] In our hands, however, attempted isolation of molecules of type **13** failed, as did isolation of 1-phenyltetrahydroindazole derivatives.

Treatment of α,β-unsaturated ketone **6a** with phenylhydrazine in refluxing isopropanol for 1 h resulted in compound **15**[34,36] and in



6 **11** **12**

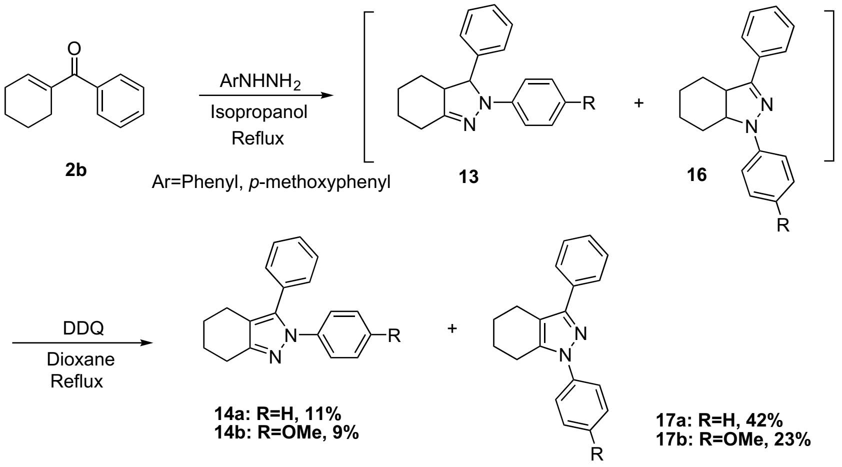
Scheme 4.



6a **13** **15**

14a: R=H, 30%
14b :R=OMe, 32%

Scheme 5.



Scheme 6.

this context, prolonged reflux time was needed to obtain cyclization (Scheme 5).

Reaction of compound **2b** and phenylhydrazine or *p*-methoxyphenylhydrazine delivered two products, **14**[8] and **17**,[37,17] which more easily separated by column chromatography (Scheme 6). The structure elucidation of these compounds could easily be verified by ^{1}H and ^{13}C NMR spectra. The precursors to **14** and **17**, the pair **13**[34] and **16**[38] could not be isolated by column chromatography. In the literature, several derivatives of hexahydroindazole (often obtained in good yields) have been reported when certain α,β-unsaturated ketone derivatives were reacted with phenylhydrazine.[34,35,39] Similarly, Katzenellenbogen co-workers have claimed the isolation of a hexahydroindazole in good yield.[12] We have not been able to reproduce this experiment when **6** or **2** were used as starting materials.

Dehydrogenation of 3-phenylhexahydroindazole derivatives of type **8a** and **11a** with 1 equiv DDQ or *p*-chloranil in dioxane, resulted in tetrahydroindazoles of type **12a**[33] and the respective **9a**[30] in good yield (100% respective 88%) without further purification. Furthermore, full aromatization of compounds **8a** and **11a** with 3.1 equiv DDQ in dioxane gave indazoles of type **18**[40] and the respective **19**[40] in excellent yield (Scheme 7). However, attempts at achieving full aromatization of compounds **14** and **17** under the same conditions failed.

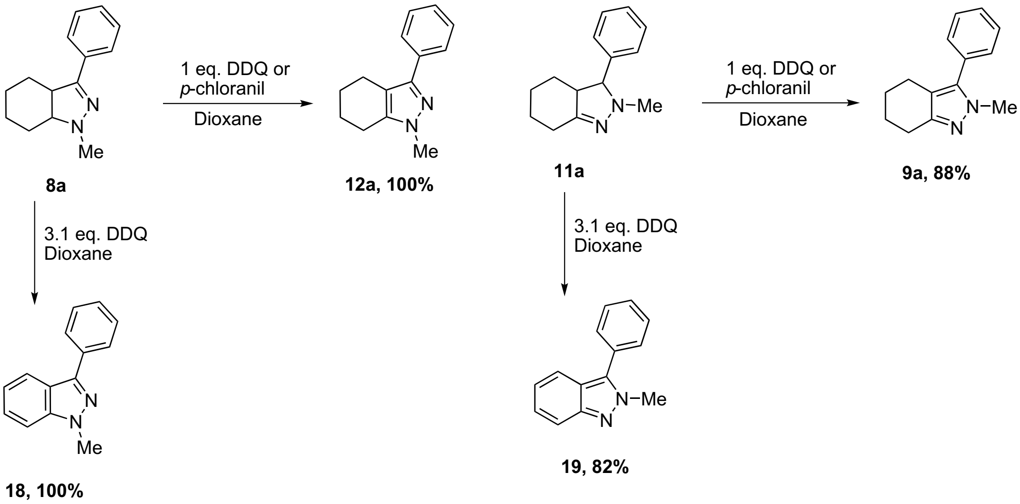
3. Conclusions

We have described the synthesis of 3-arylhexahydroindazole and 3-aryl tetrahydroindazole derivatives by using α,β-unsaturated ketones and hydrazine derivatives as reactants. Furthermore, we have shown that the dehydrogenation of 3-phenylhexahydroindazoles **8a** and **11a** with different equivalents of DDQ resulted in tetrahydroindazoles **12a** and **9a** and indazoles **18** and **19**, respectively, in excellent yields. However, attempts at achieving full aromatization of 3-aryltetrahydroindazoles of types **4**, **14** and **17** with an excess of DDQ failed.

4. Experimental

4.1. General experimental procedures

NMR spectroscopic data were recorded on a Bruker DPX 300 instrument operating at 300.1 MHz for ^{1}H and 75.5 MHz for ^{13}C, respectively, using the residual solvent signal as reference. Assignments are based on standard ^{1}H, ATP, ^{13}C high power decoupling (HPDEC) and 1D NOE-DIFF experiments. IR spectra were acquired on a Thermo Nicolet Avatar 330 FT-IR instrument. Preparative high-performance liquid chromatography (HPLC) with a C8 stationary phase and ammonium acetate acetonitrile/water buffer as



Scheme 7.

mobile phase and electrospray mass spectroscopy (ES/MS) were determined by Joakim Löfstedt, Karo Bio, Sweden. Chromatographic separations were performed on silica gel 60 (40–63 μm). HRMS determinations (FAB) were recorded by Einar Nilsson, University of Lund, Sweden. Elemental analyses were performed by LSM Lab, Uppsala, Sweden. Chemicals and solvents were obtained from commercial sources and used as received with the exception of THF, which was distilled from sodium and benzophenone and 1,4-dioxane and Et_2O, which were stored over sodium.

4.2. Cyclohex-1-enecarbonitrile (1)

This compound was prepared in two steps according to Refs. 16 and 41 and was purified by distillation at 85–90 °C/2 mmHg (119.5 °C/10 mmHg) to yield a colourless oil (26.4 g, 60.6%). IR (neat) 2935, 2864, 2213, 1673, 1449, 1437, 1424, 922 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.64–6.56 (m, 1H), 2.23–2.11 (m, 4H), 1.72–1.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 145.2 (CH), 119.8 (C), 112.4 (C), 26.6 (CH_2), 25.7 (CH_2), 21.4 (CH_2), 20.7 (CH_2).

4.3. Cyclohex-1-enyl-phenyl-methanone (2b)[19,20]

This compound was prepared from phenylmagnesium bromide (107.5 mmol) and 1-cyanocyclohexene **1** (5 g, 46.7 mmol) in Et_2O (20 mL) according to Refs. 19 and 20. The crude product was purified by distillation at 128–132 °C/1–2 mmHg (120–125 °C/0.5 mmHg)[22] to yield a colourless oil (6.04 g, 69.5%). IR (neat) 3058, 2931, 2859, 1641, 1276, 1254, 699, 657 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63–7.60 (m, 2H), 7.51–7.37 (m, 3H), 6.60–6.55 (m, 1H), 2.46–2.38 (m, 2H), 2.30–2.21 (m, 2H), 1.78–1.61 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 198.3 (C), 144.1 (CH), 138.9 (2×C), 131.3 (CH), 129.2 (CH), 128.1 (CH), 26.2 (CH_2), 24.1 (CH_2), 22.1 (CH_2), 21.8 (CH_2).

4.4. Cyclohex-1-enyl-furan-2-yl-methanone (2c)

This compound was prepared from freshly prepared furyllithium (107.5 mmol) and 1-cyanocyclohexene **1** (5 g, 46.7 mmol) in THF (20 mL) according to the procedure given for compound **2b**. The crude product was purified by distillation at 135–139 °C/2 mmHg resulting in a yellow oil (4.5 g, 55%). IR (neat) 2932, 2860, 1627, 1561, 1464, 1284, 1012, 818 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54–7.51 (m, 1H), 7.00 (d, J=3.5 Hz, 1H), 6.91–6.86 (m, 1H), 6.44–6.41 (m, 1H), 2.36–2.28 (m, 2H), 2.26–2.17 (m, 2H), 1.69–1.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 184.1 (C), 152.3 (C), 146.4 (CH), 141.1 (CH), 138.4 (C), 118.9 (CH), 111.8 (CH), 26.2 (CH_2), 24.1 (CH_2), 22.1 (CH_2), 21.7 (CH_2). HRMS: (FAB) calcd for $C_{11}H_{12}O_2$ $[M+H]^+$ 177.0916, found 177.0907.

4.5. Cyclohex-1-enyl-thiophen-2-yl-methanone (2d)

This compound was prepared from freshly prepared 2-thienylmagnesium bromide (43.0 mmol) and 1-cyanocyclohexene **1** (2 g, 18.7 mmol) in Et_2O (10 mL) according to the procedure given for compound **2b**. The crude product was purified by distillation at 155–157 °C/2 mmHg resulting in a colourless oil (1.9 g, 53%). IR (neat) 2935, 2856, 1612, 1414, 1275, 1252, 1232, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61–7.56 (m, 2H), 7.11–7.06 (m, 1H), 6.79–6.74 (m, 1H), 2.43–2.36 (m, 2H), 2.32–2.23 (m, 2H), 1.77–1.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 189.4 (C), 143.6 (C), 140.3 (CH), 138.9 (C), 132.9 (CH), 132.8 (CH), 127.5 (CH), 26.0 (CH_2), 24.5 (CH_2), 22.1 (CH_2), 21.7 (CH_2). HRMS: (FAB) calcd for $C_{11}H_{12}OS$ $[M+H]^+$ 193.0687, found 193.0687.

4.6. 1-Cyclohex-1-enyl-ethanone (2a)

This compound was prepared from methylmagnesium bromide (3 M in ether, 65.4 mmol) and 1-cyanocyclohexene **1** (5 g, 46.7 mmol) in Et_2O (20 mL) according to the procedure given for compound **2b**. The crude product was purified by distillation at 84–89 °C/7 mmHg (65–69 °C/5 mmHg)[21] to yield a colourless oil (5.08 g, 88%). IR (neat) 3379, 2932, 1662, 1638, 1272, 1244, 1234, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.89–6.83 (m, 1H), 2.26–2.14 (m, 7H), 1.64–1.52 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 199.4 (C), 140.9 (CH), 139.8 (C), 26.2 (CH_2), 25.2 (CH_3), 23.0 (CH_2), 22.0 (CH_2), 21.6 (CH_2).

4.7. 1-Cyclohexenyl-4-(dimethylamino)butan-1-one (2e)

This compound was prepared from freshly prepared 3-dimethylaminopropylmagnesium bromide[42] (71.9 mmol) and 1-cyanocyclohexene **1** (3.35 g, 31.3 mmol) in THF (20 mL) according to the procedure given for compound **2b**. The crude product was purified by distillation at 138–145 °C/7 mmHg to yield a colourless oil (2.70 g, 44.2%). IR (neat) 2931, 2857, 2814, 2764, 1665, 1459, 1448, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88–6.82 (m, 1H), 2.61 (t, J=7.3 Hz, 2H), 2.30–2.09 (m, 12H), 1.79–1.66 (m, 2H), 1.61–1.48 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 201.3 (C), 139.6 (CH), 139.3 (C), 59.2 (CH_2), 45.4 (2×CH_3), 34.8 (CH_2), 26.1 (CH_2), 23.2 (CH_2), 22.6 (CH_2), 22.1 (CH_2), 21.7 (CH_2).

4.8. (*E*)-2-Benzylidenecyclohexanone (6a)[26,43,27]

This compound was prepared from cyclohexanone (25.8 ml, 250 mmol) and benzaldehyde (12.7 ml, 125 mmol) according to Ref. 23 and was purified by distillation at 145–155 °C/4 mmHg (122 °C/1 mmHg)[23] to yield a yellow oil (17.2 g, 74%), which solidified by cooling. IR (neat) 2939, 2863, 2835, 1672, 1594, 1490, 1140, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (t, J=2.1 Hz, 1H), 7.36–7.20 (m, 5H), 2.79–2.72 (m, 2H), 2.45 (t, J=6.7 Hz, 2H), 1.89–1.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 201.8 (C), 136.7 (C), 135.7 (C), 135.6 (CH), 130.4 (CH), 128.6 (CH), 128.4 (CH), 40.4 (CH_2), 29.0 (CH_2), 23.9 (CH_2), 23.4 (CH_2).

4.9. (*E*)-2-((Furan-2-yl)methylene)cyclohexanone (6b)

This compound was prepared from cyclohexanone (12.9 ml, 125 mmol) and 2-furaldehyde (10.1 ml, 122 mmol) according to Ref. 24. The crude product was recrystallized from ethanol to give **6b** (14.9 g, 70%) as a yellow solid. IR (neat) 3099, 2939, 2875, 1664, 1577, 1262, 1141, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55–7.52 (m, 1H), 7.39–7.36 (m, 1H), 6.62 (d, J=3.4 Hz, 1H), 6.51–6.47 (m, 1H), 2.94–2.87 (m, 2H), 2.49 (t, J=6.5 Hz, 2H), 1.94–1.76 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 200.5 (C), 152.5 (C), 144.6 (CH), 132.7 (C), 123.1 (CH), 116.2 (CH), 112.4 (CH), 40.0 (CH_2), 28.5 (CH_2), 23.3 (CH_2), 23.1 (CH_2).

4.10. (*E*)-2-((Thiophen-2-yl)methylene)cyclohexanone (6c)[25]

Thiophene-2-carboxaldehyde (4.5 ml, 48.4 mmol) was added with stirring to a mixture of cyclohexanone (10 mL, 96.8 mmol) and NaOH (1.94 g, 48.4 mmol) in H_2O (40 mL). After stirring of the reaction mixture at room temperature overnight, the mixture was extracted with EtOAc (4×50 mL). The combined organic solvents were washed with water, dried with Na_2SO_4 and evaporated to yield **6c** (4.30 g, 46%) as a yellow oil, which solidified upon cooling. IR (neat) 3097, 2934, 2866, 1701, 1665, 1567, 1414, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (s, 1H), 7.46 (d, J=5.0 Hz, 1H), 7.29–7.25 (m, 1H), 7.09–7.04 (m, 1H), 2.80–2.73 (m, 2H), 2.45 (t, J=6.3 Hz, 2H), 1.88–1.75 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 200.5 (C), 139.2 (C), 133.3 (CH), 132.3 (C), 130.2 (CH), 129.6 (CH), 127.7 (CH), 40.0 (CH_2), 28.7 (CH_2), 23.3 (CH_2), 22.9 (CH_2).

4.11. (*E*)-2-((1-Methyl-1*H*-pyrrol-2-yl)methylene)-cyclohexanone (6d)

This compound was prepared from cyclohexanone (1.12 ml, 10.8 mmol) and 1-methylpyrrole-2-caboxaldehyde (0.60 g, 5.41 mmol) according to the procedure given for compound **6c** and was purified by dry flash chromatography (heptane/EtOAc, 0–60%) to yield **6d** (0.43 g, 42.3%) as a yellow oil. IR (neat) 3106, 2932, 2860, 1663, 1562, 1480, 1241, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65–7.61 (m, 1H), 6.83–6.80 (m, 1H), 6.57–6.52 (m, 1H), 6.27–6.23 (m, 1H), 2.77–2.70 (m, 2H), 2.50 (t, J=6.5 Hz, 2H), 1.94–1.76 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 200.4 (C), 130.1 (C), 129.7 (C), 126.9 (CH), 124.1 (CH), 115.3 (CH), 109.4 (CH), 39.8 (CH_2), 34.6 (CH_3), 29.1 (CH_2), 23.5 (CH_2), 23.1 (CH_2). HRMS: (FAB) calcd for $C_{12}H_{15}NO$ $[M+H]^+$ 190.1232, found 190.1229.

4.12. 3-Furan-2-yl-4,5,6,7-tetrahydro-1*H*-indazole (4c)

A solution of compound **2c** or **6b** (1 equiv) and hydrazine hydrate (5 equiv) was heated at reflux overnight. The solution was allowed to cool to room temperature and removal of water was achieved by co-evaporation with MeCN resulting in an oil. The residue was dissolved in dry dioxane and *p*-chloranil or DDQ (1.1 equiv) was added. After an exothermic reaction, the mixture was refluxed for 6 h and then allowed to reach room temperature. KOH (20% aq) and DCM were added to the reaction mixture, which finally was stirred for 30 min. The solvent was separated and the aqueous phase extracted with more DCM. The combined organic solvents were dried (Na_2SO_4) and evaporated to give an oily residue. The crude product was purified by column chromatography on silica with 0–30% Et_2O in CH_2Cl_2, which gave 1.56 g (49%) of the desired product **4c**. IR (neat) 3128, 3072, 2928, 2852, 1444, 1171, 1153, 993, 728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.18 (br s, 1H), 7.41–7.38 (m, 1H), 6.52 (d, J=3.3 Hz, 1H), 6.45–6.42 (m, 1H), 2.71–2.57 (m, 4H), 1.85–1.72 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 148.7 (C), 142.9 (C), 141.3 (CH), 137.8 (C), 112.4 (C), 111.1 (CH), 106.0 (CH), 23.2 (CH_2), 22.7 (CH_2), 21.8 (CH_2), 21.3 (CH_2). Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.4; H, 6.7; N, 14.4.

4.13. 3-Thiophen-2-yl-4,5,6,7-tetrahydro-1*H*-indazole (4d)

This compound was prepared from compound **2d** (1.9 g, 9.89 mmol) and hydrazine hydrate (2.40 ml, 49.5 mmol) using the same procedure given for **4c** but with ethanol as solvent. The product was obtained as a yellow solid (0.54 g, 27%). IR (neat) 3128, 3073, 2923, 2843, 1586, 1225, 906, 728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.96 (br s, 1H), 7.14 (d, J=3.6 Hz, 1H), 7.06 (d, J=5.1 Hz, 1H), 6.89 (dd, J=5.1 and 3.6 Hz, 1H), 2.52 (t, J=5.6 Hz, 2H), 2.38 (t, J=5.6 Hz, 2H), 1.70–1.51 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 142.3 (C), 141.5 (C), 136.5 (C), 127.3 (CH), 123.9 (CH), 123.6 (CH), 112.3 (C), 23.3 (CH_2), 22.5 (CH_2), 21.7 (CH_2), 21.6 (CH_2). Calcd for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71. Found: C, 64.8; H, 5.9; N, 13.6.

4.14. 3-Phenyl-4,5,6,7-tetrahydro-1*H*-indazole (4b)[8,17]

This compound was prepared from compounds **2b** or **6a** using the same procedure given for **4c**. The product was obtained as yellow solid (0.67 g, 31%). IR (neat) 3128, 3065, 2926, 2849, 1594, 1444, 1109, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.90 (br s, 1H), 7.56 (d, J=7.6 Hz, 2H), 7.32–7.15 (m, 3H), 2.68–2.59 (m, 2H), 2.56–2.46 (m, 2H), 1.79–1.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 144.6 (C), 144.4 (C), 132.9 (C), 128.7 (CH), 127.5 (CH), 126.7 (CH), 113.1 (C), 23.7 (CH_2), 22.7 (CH_2), 22.3 (CH_2), 22.2 (CH_2).

4.15. 3-Methyl-4,5,6,7-tetrahydro-1*H*-indazole (4a)[18]

This compound was prepared from compound **2a** (5.0 g, 40.3 mmol) and hydrazine hydrate (9.80 mL, 202 mmol) using the same procedure given for **4c** but with ethanol as solvent. The crude product was purified by distillation at 115–129 °C/2 mmHg to yield yellow oil (2.96 g, 54%). IR (neat) 3150, 2919, 2841, 1601, 1440, 1319, 845, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 2.56 (t, J=5.6 Hz, 2H), 2.32 (t, J=5.6 Hz, 2H), 2.11 (s, 3H), 1.76–1.61 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 144.0 (C), 140.6 (C), 113.0 (C), 23.4 (CH_2), 23.0 (CH_2), 22.3 (CH_2), 20.0 (CH_2), 10.6 (CH_3).

4.16. Dimethyl-[3-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-propyl]-amine (4e)

This compound was prepared from compound **2e** (2.7 g, 13.8 mmol) and hydrazine hydrate (4 ml, 82.8 mmol) using the same procedure given for **4c**. The crude product was purified by preparative HPLC. The product **4e** decomposed slowly due to its instability and no yield could be measured. IR (neat) 3202, 3151, 2928, 2852, 2778, 1588, 1443, 1040 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.06 (br s, 1H), 2.66–2.59 (m, 4H), 2.51 (t, J=6.7 Hz, 2H), 2.44–2.35 (m, 8H), 1.92–1.84 (m, 2H), 1.81–1.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9 (C), 143.4 (C), 112.6 (C), 59.1 (CH_2), 44.7 (CH_3), 25.2 (CH_2), 23.8 (CH_2), 23.4 (CH_2), 23.1 (CH_2), 22.6 (CH_2), 20.2 (CH_2).

4.17. 3,3a,4,5,6,7-Hexahydro-2-methyl-3-phenyl-2*H*-indazole (11a)

To a solution of **6a** (1.0 g, 5.38 mmol) in isopropanol (20 mL), methylhydrazine (2.3 mL, 43.0 mmol) was added and the mixture heated at reflux overnight. The product was obtained after evaporation as a yellow oil (1.14 g, 99%). IR (neat) 2930, 2856, 2780, 1493, 1445, 1163, 749, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35–7.17 (m, 5H), 3.33 (d, J=12.9 Hz, 1H), 2.69–2.51 (m, 5H), 2.11–1.66 (m, 4H), 1.47–1.12 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 156.5 (C), 140.4 (C), 128.7 (CH), 127.7 (CH), 127.4 (CH), 80.6 (CH), 55.4 (CH), 42.4 (CH_3), 31.3 (CH_2), 27.7 (CH_2), 25.8 (CH_2), 24.5 (CH_2). HRMS: (FAB) calcd for $C_{14}H_{18}N_2$ $[M+H]^+$ 215.1548, found 215.1545.

4.18. 3,3a,4,5,6,7-Hexahydro-2-methyl-3-(thiophen-2-yl)-2*H*-indazole (11c)

This compound was prepared from compound **6c** (0.2 g, 1.04 mmol) and methylhydrazine (0.44 ml, 8.33 mmol) using the same procedure given for **11a**. The product was obtained after evaporation as a dark yellow oil (0.22 g, 98%). IR (neat) 2931, 2856, 2783, 1707, 1625, 1445, 824, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.24 (dd, J=4.7 and 1.4 Hz, 1H), 7.00–6.94 (m, 2H), 3.67 (d, J=12.7 Hz, 1H), 2.75 (s, 3H), 2.68–2.58 (m, 2H), 2.18–2.04 (m, 2H), 2.01–1.92 (m, 1H), 1.89–1.80 (m, 2H), 1.38–1.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.1 (C), 143.8 (C), 126.9 (CH), 125.1 (CH), 124.8 (CH), 75.7 (CH), 55.7 (CH), 42.5 (CH_3), 31.1 (CH_2), 27.6 (CH_2), 25.7 (CH_2), 24.4 (CH_2). HRMS: (FAB) calcd for $C_{12}H_{16}N_2S$ $[M+H]^+$ 221.1112, found 221.1115.

4.19. Synthesis of compounds (11b) and (12b)

These compounds were prepared from compound **6b** (0.5 g, 2.84 mmol) and methylhydrazine (1.21 mL, 22.7 mmol) using the same procedure given for **11a**. The crude product was purified by HPLC to yield product **11b** (150 mg, 25.9%) as a yellow oil and product **12b** (100 mg, 17.4%) also as a yellow oil.

*4.19.1. 3-(Furan-2-yl)-3,3a,4,5,6,7-hexahydro-2-methyl-2H-indazole (**11b**)*

IR (neat) 2933, 2858, 2780, 1614, 1447, 1149, 1009, 743 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.38–7.35 (m, 1H), 6.35–6.31 (m, 1H), 6.26 (d, J=3.1 Hz, 1H), 3.46 (d, J=12.7 Hz, 1H), 3.09–2.95 (m, 1H), 2.74 (s, 3H), 2.65–2.54 (m, 1H), 2.19–2.03 (m, 2H), 2.00–1.91 (m, 1H), 1.87–1.78 (m, 1H), 1.53–1.18 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 157.1 (C), 152.4 (C), 142.5 (CH), 110.3 (CH), 107.6 (CH), 72.8 (CH), 51.5 (CH), 42.6 (CH$_3$), 31.6 (CH$_2$), 27.6 (CH$_2$), 25.8 (CH$_2$), 24.5 (CH$_2$). HRMS: (FAB) calcd for $C_{12}H_{16}N_2O$ [M+H]$^+$ 205.1341, found 205.1339.

*4.19.2. 3-(Furan-2-yl)-4,5,6,7-tetrahydro-1-methyl-1H-indazole (**12b**)*

IR (neat) 3116, 2932, 2853, 1440, 1297, 1160, 1009, 729 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.43 (d, J=1.7 Hz, 1H), 6.50 (d, J=3.3 Hz, 1H), 2.44 (dd, J=3.3 and 1.7 Hz, 1H), 3.76 (s, 3H), 2.64 (t, J=5.9 Hz, 2H), 2.56 (t, J=5.9 Hz, 2H), 1.89–1.71 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 149.3 (C), 141.4 (CH), 139.7 (C), 139.6 (C), 113.4 (C), 111.1 (CH), 105.9 (CH), 35.7 (CH$_3$), 22.9 (CH$_2$), 22.5 (CH$_2$), 21.6 (CH$_2$), 21.5 (CH$_2$). HRMS: (FAB) calcd for $C_{12}H_{14}N_2O$ [M+H]$^+$ 203.1184, found 203.1185.

4.20. Synthesis of compounds (11d) and (12d)

These compounds were prepared from compound **6d** (0.1 g, 0.53 mmol) and methylhydrazine (0.22 mL, 4.23 mmol) using the same procedure given for **11a**. The crude product was purified by column chromatography on silica (heptane/EtOAc) to yield product **11d** (63 mg, 54.9%) as a yellow oil and product **12d** (17 mg, 15%) also as a yellow oil.

*4.20.1. 3,3a,4,5,6,7-Hexahydro-2-methyl-3-(1-methyl-1H-pyrrol-2-yl)-2H-indazole (**11d**)*

IR (neat) 2931, 2856, 2777, 1624, 1497, 1446, 1291, 708 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.59 (t, J=2.2 Hz, 1H), 6.13–6.04 (m, 2H), 3.67 (s, 3H), 2.70–2.57 (m, 5H), 2.22–2.05 (m, 2H), 2.02–1.92 (m, 1H), 1.88–1.79 (m, 1H), 1.53–1.18 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 156.8 (C), 129.1 (C), 123.8 (CH), 109.2 (CH), 107.0 (CH), 73.4 (CH$_3$), 52.8 (CH), 42.4 (CH$_3$), 35.1 (CH), 32.2 (CH$_2$), 27.8 (CH$_2$), 25.9 (CH$_2$), 24.6 (CH$_2$). HRMS: (FAB) calcd for $C_{13}H_{19}N_3$ [M+H]$^+$ 218.1657, found 218.1658.

*4.20.2. 4,5,6,7-Tetrahydro-1-methyl-3-(1-methyl-1H-pyrrol-2-yl)-1H-indazole (**12d**)*

IR (neat) 3100, 2931, 2852, 1691, 1578, 1493, 1458, 715 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.65 (t, J=2.2 Hz, 1H), 6.29–6.25 (m, 1H), 6.18–6.14 (m, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 2.58 (q, J=5.8 Hz, 4H), 1.91–1.69 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 141.2 (C), 139.3 (C), 126.3 (C), 123.7 (CH), 114.6 (C), 109.4 (CH), 107.4 (CH), 36.1 (CH$_3$), 35.6 (CH$_3$), 23.2 (CH$_2$), 22.6 (CH$_2$), 22.0 (CH$_2$), 21.6 (CH$_2$). HRMS: (FAB) calcd for $C_{13}H_{17}N_3$ [M+H]$^+$ 216.1501, found 216.1497.

4.21. Synthesis of compounds (8a) and (9a)

These compounds were prepared from compound **2b** (0.51 g, 2.74 mmol) and methylhydrazine (1.17 mL, 21.94 mmol) using the same procedure given for compound **11a**. The crude product was purified by column chromatography on silica (heptane/EtOAc), which gave 0.27 g (46%) of product **8a** as a yellow oil and 0.12 g (20.6%) of product **9a** also as a yellow oil.

*4.21.1. 3a,4,5,6,7,7a-Hexahydro-1-methyl-3-phenyl-1H-indazole (**8a**)*[29]

IR (neat) 2931, 2859, 2783, 1496, 1443, 1175, 1117, 928, 758 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.68–7.61 (m, 2H), 7.42–7.30 (m, 3H), 2.91 (s, 3H), 2.74–2.59 (m, 1H), 2.54–2.44 (m, 1H), 2.37–2.11 (m, 2H), 1.97–1.83 (m, 2H), 1.67–1.21 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 157.7 (C), 133.5 (C), 128.9 (CH), 128.5 (CH), 126.6 (CH), 76.0 (CH), 52.1 (CH), 41.3 (CH$_3$), 28.8 (CH$_2$), 28.3 (CH$_2$), 25.9 (CH$_2$), 24.3 (CH$_2$). HRMS: (FAB) calcd for $C_{14}H_{18}N_2$ [M+H]$^+$ 215.1548, found 215.1547.

4.22. Synthesis of compounds (8b) and (9b)

These compounds were prepared from compound **2d** (0.1 g, 0.52 mmol) and methylhydrazine (0.22 mL, 4.17 mmol) using the same procedure given for compound **11a**. The crude product was purified by column chromatography on silica (heptane/EtOAc) to yield product **8b** (58.4 mg, 51%) as a brown oil and product **9b** (26 mg, 23%) as a dark yellow oil.

*4.22.1. 3a,4,5,6,7,7a-Hexahydro-1-methyl-3-(thiophen-2-yl)-1H-indazole (**8b**)*

IR (neat) 2933, 2859, 2786, 1733, 1443, 1119, 845, 701 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.33–7.26 (m, 2H), 7.06–7.00 (m, 1H), 2.88 (s, 3H), 2.67–2.48 (m, 2H), 2.35–2.22 (m, 1H), 2.18–2.09 (m, 1H), 1.97–1.85 (m, 2H), 1.63–1.47 (m, 2H), 1.40–1.25 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 148.2 (C), 136.9 (C), 127.4 (CH), 126.5 (CH), 125.8 (CH), 76.0 (CH), 52.5 (CH), 41.2 (CH$_3$), 28.8 (CH$_2$), 28.1 (CH$_2$), 25.8 (CH$_2$), 24.4 (CH$_2$). HRMS: (FAB) calcd for $C_{12}H_{16}N_2S$ [M]$^+$ 220.1034, found 220.1030.

*4.22.2. 4,5,6,7-Tetrahydro-2-methyl-3-(thiophen-2-yl)-2H-indazole (**9b**)*

IR (neat) 2928, 2854, 1656, 1443, 1411, 1372, 1058, 846, 698 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.34 (dd, J=5.1 and 1.2 Hz, 1H), 7.08–7.04 (m, 1H), 7.03–7.00 (m, 1H), 3.82 (s, 3H), 2.62 (t, J=6.1 Hz, 2H), 2.48 (t, J=6.1 Hz, 2H), 1.81–1.63 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 148.3 (C), 133.0 (C), 131.4 (C), 127.5 (CH), 127.2 (CH), 126.5 (CH), 116.0 (C), 37.6 (CH$_3$), 23.6 (CH$_2$), 23.4 (2×CH$_2$), 21.6 (CH$_2$). HRMS: (FAB) calcd for $C_{12}H_{14}N_2S$ [M+H]$^+$ 219.0956, found 219.0960.

4.23. 4,5,6,7-Tetrahydro-1-methyl-3-phenyl-1*H*-indazole (12a)[33]

Compound **8a** (0.14 g, 0.65 mmol) was dissolved in dry dioxane (40 mL) and *p*-chloranil (0.16 g, 0.65 mmol) was added. The reaction mixture was heated at reflux temperature overnight. The resulting black solution was allowed to reach room temperature and then 20% aq KOH was added. The reaction mixture was extracted with ether (3×60 mL) and the combined organic extracts were washed with water, dried (Na$_2$SO$_4$) and evaporated to give **12a** as a brown oil (0.14 g, 100%). IR (neat) 3059, 2929, 2852, 1732, 1443, 1371, 770, 695 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.68–7.61 (m, 2H), 7.35–7.27 (m, 2H), 7.23–7.16 (m, 1H), 3.69 (s, 3H), 2.63 (t, J=6.1 Hz, 2H), 2.51 (t, J=6.1 Hz, 2H), 1.82–1.62 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 147.1 (C), 139.9 (C), 134.4 (C), 128.5 (CH), 127.1 (CH), 126.7 (CH), 113.8 (C), 35.6 (CH$_3$), 23.4 (CH$_2$), 22.5 (2×CH$_2$), 21.7 (CH$_2$). HRMS: (FAB) calcd for $C_{14}H_{16}N_2$ [M+H]$^+$ 213.1392, found 213.1392.

4.24. 4,5,6,7-Tetrahydro-2-methyl-3-phenyl-2*H*-indazole (9a)[30]

This compound was prepared from compound **11a** (0.3 g, 1.4 mmol) and DDQ (0.3 g, 1.4 mmol) using the same procedure given for **12a**. The product was obtained without further purification as a dark yellow oil (0.26 g, 88%). IR (neat) 3057, 2928, 2852, 1678, 1489, 1371, 760, 698 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.42–7.24 (m, 5H), 3.71 (s, 3H), 2.64 (t, J=6.2 Hz, 2H), 2.40 (t, J=6.2 Hz, 2H), 1.84–1.62 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 148.2 (C), 139.8 (C), 130.6 (C), 129.2 (CH), 128.7 (CH), 128.2 (CH), 114.9 (C), 37.1 (CH$_3$), 23.7 (CH$_2$), 23.5 (CH$_2$), 23.4 (CH$_2$), 21.3 (CH$_2$). HRMS: (FAB) calcd for $C_{14}H_{16}N_2$ [M+H]$^+$ 213.1392, found 213.1392.

4.25. 2-Methyl-3-phenyl-2*H*-indazole (19)[40]

This compound was prepared from compound **11a** (0.25 g, 1.17 mmol) and DDQ (0.82 g, 3.62 mmol) using the same procedure given for **12a**. The crude product was purified by column chromatography (heptane/EtOAc) to yield **19** (0.20 g, 82%) as a brown oil. IR (neat) 2926, 2851, 1677, 1489, 1444, 1371, 760, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62–7.57 (m, 1H), 7.47–7.37 (m, 5H), 7.21–7.14 (m, 2H), 6.97–6.90 (m, 1H), 4.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.0 (C), 136.0 (C), 129.7 (C), 129.5 (CH), 129.0 (CH), 128.7 (CH), 126.2 (CH), 121.8 (CH), 121.2 (C), 120.1 (CH), 117.0 (CH), 38.5 (CH_3). HRMS: (FAB) calcd for $C_{14}H_{12}N_2$ $[M+H]^+$ 209.1079, found 209.1071.

4.26. 1-Methyl-3-phenyl-1*H*-indazole (18)[40]

This compound was prepared from compound **8a** (0.14 g, 0.65 mmol) and DDQ (0.46 g, 2.02 mmol) using the same procedure given for **12a**. The product was obtained without further purification as a brown oil (0.13 g, 100%). IR (neat) 3055, 2933, 1736, 1494, 1471, 779, 745, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95–7.83 (m, 3H), 7.44–7.25 (m, 5H), 7.15–7.06 (m, 1H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.8 (C), 141.6 (C), 133.8 (C), 128.9 (CH), 127.9 (CH), 127.5 (CH), 126.4 (CH), 121.7 (C), 121.5 (CH), 121.1 (CH), 109.3 (CH), 35.6 (CH_3). HRMS: (FAB) calcd for $C_{14}H_{12}N_2$ $[M+H]^+$ 209.1079, found 209.1074.

4.27. Synthesis of compounds (14a) and (17a) from compound (2b)

These compounds were prepared from compound **2b** (0.5 g, 2.69 mmol) and phenylhydrazine (2.1 mL, 21.5 mmol) using the same procedure given for **4c** but with isopropanol (20 mL) as solvent. The crude product was purified by column chromatography on silica (EtOAc/heptane, 0–30%), which gave 0.31 g (42.1%) of the desired product **17a**. A second product **14a** was isolated in small amount (80 mg, 10.9%).

*4.27.1. 4,5,6,7-Tetrahydro-1,3-diphenyl-1H-indazole (**17a**)*[37,17]

IR (neat) 3054, 2934, 2841, 1595, 1498, 1368, 760, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78–7.68 (m, 2H), 7.52–7.19 (m, 8H), 2.79–2.63 (m, 4H), 1.84–1.69 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 149.2 (C), 140.1 (C), 139.9 (C), 134.2 (C), 129.2 (CH), 128.6 (CH), 127.5 (CH), 127.1 (CH), 126.9 (CH), 123.6 (CH), 115.7 (C), 24.1 (CH_2), 23.2 (CH_2), 22.9 (CH_2), 22.7 (CH_2).

*4.27.2. 4,5,6,7-Tetrahydro-2,3-diphenyl-2H-indazole (**14a**)*[8]

This compound was prepared from compound **6a** (0.5 g, 2.69 mmol) and phenylhydrazine (2.1 mL, 21.5 mmol) using the same procedure given for **4c** but with isopropanol (20 mL) as solvent. The crude product was purified by column chromatography on silica (EtOAc/heptane), which gave 0.22 g (30.3%) of the desired product **14a**. IR (neat) 2933, 2857, 1595, 1492, 1444, 1366, 761, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–7.05 (m, 10H), 2.74 (t, J=6.2 Hz, 2H), 2.51 (t, J=6.2 Hz, 2H), 1.86–1.63 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 150.3 (C), 140.3 (C), 138.6 (C), 130.8 (C), 129.3 (CH), 128.8 (CH), 128.5 (CH), 127.8 (CH), 126.7 (CH), 124.9 (CH), 116.9 (C), 23.6 ($2\times CH_2$), 23.4 (CH_2), 21.5 (CH_2).

4.28. 4,5,6,7-Tetrahydro-2-(4-methoxyphenyl)-3-phenyl-2*H*-indazole (14b)

This compound was prepared from compound **6a** (0.29 g, 1.56 mmol) and *p*-methoxyphenylhydrazine (1.08 g, 7.80 mmol) using the same procedure given for **4c** but with isopropanol (30 mL) as solvent. The crude product was purified by column chromatography on silica (EtOAc/heptane, 0–30%), which gave 152 mg (32.1%) of the desired product **14b**. IR (neat) 2931, 2838, 1515, 1442, 1247, 1030, 833, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.17 (m, 3H), 7.11–7.06 (m, 4H), 6.74–6.69 (m, 2H), 3.70 (s, 3H), 2.73 (t, J=6.3 Hz, 2H), 2.52 (t, J=6.3 Hz, 2H), 1.85–1.79 (m, 2H), 1.73–1.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3 (C), 150.0 (C), 138.5 (C), 133.9 (C), 131.0 (C), 129.3 (CH), 128.4 (CH), 127.7 (CH), 126.3 (CH), 116.4 (C), 114.0 (CH), 55.5 (CH_3), 23.7 ($2\times CH_2$), 23.5 (CH_2), 21.7 (CH_2). HRMS: (FAB) calcd for $C_{20}H_{20}N_2O$ $[M+H]^+$ 305.1654, found 305.1659.

4.29. Synthesis of compounds (14b) and (17b) from compound (2b)

These compounds were prepared from compound **2b** (0.53 g, 2.85 mmol) and *p*-methoxyphenylhydrazine (2.49 g, 14.2 mmol) using the same procedure given for **4c** but with isopropanol (20 mL) as solvent. The crude product was purified by column chromatography on silica (EtOAc/heptane, 0–30%), which gave 135 mg (23.2%) of the desired product **17b**. A second product **14b** was isolated in small amount (80 mg, 9.2%).

*4.29.1. 4,5,6,7-Tetrahydro-1-(4-methoxyphenyl)-3-phenyl-1H-indazole (**17b**)*

IR (neat) 3060, 2932, 2837, 1511, 1464, 1443, 1244, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85–7.81 (m, 2H), 7.48–7.44 (m, 2H), 7.43–7.39 (m, 2H), 7.33–7.29 (m, 1H), 6.99–6.96 (m, 2H), 3.84 (s, 3H), 2.84–2.79 (m, 2H), 2.72–2.68 (m, 2H), 1.86–1.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6 (C), 148.7 (C), 139.8 (C), 134.3 (C), 133.4 (C), 128.5 (CH), 127.3 (CH), 127.0 (CH), 125.2 (CH), 115.1 (C), 114.3 (CH), 55.6 (CH_3), 23.7 (CH_2), 23.3 (CH_2), 22.8 (CH_2), 22.7 (CH_2). HRMS: (FAB) calcd for $C_{20}H_{20}N_2O$ $[M+H]^+$ 305.1654, found 305.1652.

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