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An efficient synthesis of 2*H*-indazoles via reductive cyclization of 2-nitrobenzylamines induced by low-valent titanium reagent

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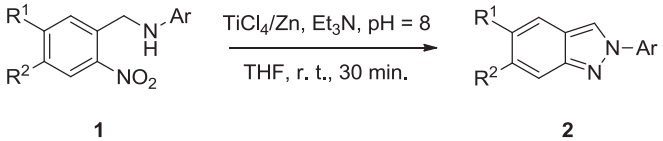
ABSTRACT

An efficient and improved synthesis of 2*H*-indazoles via reductive cyclization of 2-nitrobenzylamines induced by low-valent titanium reagent ($TiCl_4$/Zn) is described. In this reaction triethylamine (TEA) was used to control the pH value. This method has the advantages of easily accessible starting materials, convenient manipulation, higher yield, shorter reaction time, and wider substrate scope.

1. Introduction

Indazole is well known as an aza analogue of indole. The indazole unit has been found in pharmaceutical materials with a broad range of biological properties including antitumor,[1] anti-HIV,[2] antidepressant,[3] antimicrobial,[4] anti-inflammatory,[5] and contraceptive activities.[6] Considering the potent bioactivities of compounds containing 2*H*-indazole core, the development of new strategies for the efficient synthesis of 2*H*-indazole is needed. To construct this intriguing 2*H*-indazole scaffold, several synthetic methods have been developed from different starting materials.[7] Among them, reductive cyclization of 2-nitrobenzylamine attracts more attention because diverse starting materials are readily available. The reduction of 2-nitrobenzylamines with Sn, Zn, or Fe in acidic medium,[8] produced 2-substituted indazole byproduct in low yields. The reduction of 2-nitrobenzylamines and subsequent cyclization to 2-substituted indazoles were achieved by an electrochemical method, but this method requires special equipment.[9] A one-pot heterocyclization of 2-nitrobenzylamines in the presence of KOH and alcohol produced 3-alkoxy-2*H*-indazoles, however, only one 2-aryl-2*H*-indazole was mentioned with low yield.[10] Recently we reported the improved synthesis of 2-aryl-2*H*-indazoles via reductive cyclization of 2-nitrobenzylamines promoted by $SnCl_2 \cdot 2H_2O$,[11] This method has the advantages of a wide scope of substrates, however, the yields were unsatisfied. Although these methods have successfully led to a large repertoire of 2*H*-indazole synthetic routes, many of these still suffer from drawbacks such as unsatisfactory yields, long reaction time, and occurrence of side reactions. Therefore, the development of more efficient methods for the preparation of this kind of heterocyclic compounds is still an active research area.

Low-valent titanium reagents have an exceedingly high ability to promote reductive coupling reaction of carbonyl compounds and are attracting increasing interest in organic synthesis.[12] Many other functional groups can also be coupled.[13] Recently, we have focused on the synthesis of heterocyclic compounds such as quinazolin-4(3*H*)-ones,[14] pyrroles,[15] quinazoline-2,4-diones,[16] naphtho[1,2-*e*][1,3]oxazine,[17] benzothiazole,[18] and pyrrolo[1,2-*a*]quinazolin-5(1*H*)-one[19] induced by low-valent titanium reagent. However, most of the reported reactions mediated by a low-valent titanium reagent have been carried out in the presence of acid. Quite surprisingly, base controlled reactions with low-valent titanium reagents have not stimulated much interest so far. Recently, we reported the synthesis of indazol-3(2*H*)-ones form 2-nitrobenzamides induced by a low-valent titanium reagent in the presence of base (TEA),[20] in this paper we would like to describe a convenient base (TEA)-controlled protocol for the synthesis of 2*H*-indazoles induced by low-valent titanium reagent (Scheme 1).



1 2

Scheme 1. Synthesis of 2*H*-indazole **2**.

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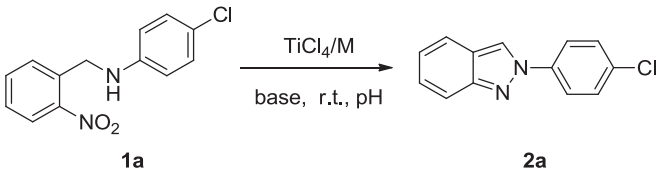
2. Results and discussion

On the basis of our previous experience, 4-chloro-*N*-(2-nitrobenzyl)aniline **1a** as a model substrate was investigated to establish the feasibility of the strategy and to optimize the reaction conditions for the synthesis of 2-(4-chlorophenyl)-2*H*-indazole (**2a**) (Scheme 2).



Scheme 2. Model reaction.

As shown in Table 1, we briefly examined the effect of different low-valent titanium systems and pH values on the success of the cyclization step. When substrate **1a** was reduced by $TiCl_4$/Zn and no base was added, no desired product **2a** was detected (Table 1, entry 1). When substrate **1a** was reduced with different low-valent titanium reagents in TEA and pH=8 (Table 1, entries 2–6), $TiCl_4$/Zn gave the best result of synthesis of **2a** (83% yield) (Table 1, entry 2). To further optimize reaction conditions, a similar test was carried out at pH value ranging from 5 to 9 with an increment of 1 each time. The yield of product **2a** was increased as pH value was increased from 5 to 8 (Table 1, entries 7–9 and 2). However, a further increase of pH value to 9 failed to improve the yield of product **2a** (Table 1, entry 10). Therefore, TEA and pH=8 was chosen as the reaction condition for all further synthesis of 2*H*-indazoles.

Table 1
Optimization of reaction conditions for the synthesis of **2a**

Entry	$TiCl_4$/M	Base/pH value	Isolated yield (%)
1	$TiCl_4$/Zn	No base/2	0
2	$TiCl_4$/Zn	TEA/8	83
3	$TiCl_4$/Fe	TEA/8	37
4	$TiCl_4$/Sm	TEA/8	66
5	$TiCl_4$/Mg	TEA/8	45
6	$TiCl_4$/Al	TEA/8	78
7	$TiCl_4$/Zn	TEA/5	60
8	$TiCl_4$/Zn	TEA/6	67
9	$TiCl_4$/Zn	TEA/7	74
10	$TiCl_4$/Zn	TEA/9	76

In order to apply this reaction to a library synthesis of 2*H*-indazoles, various 2-nitrobenzylamines were subjected to the reaction conditions and the results are summarized in Table 2.

As shown in Table 2, it can be seen that the proposed cyclization process proved to be suitable for substrates in which the 2-nitrobenzylamine was substituted with either electron-withdrawing group (such as halide group) or electron-donating group (such as methoxyl group). Also the reactions proved to be effective for substrates in which the *N*-aryl was substituted by not only aryl groups with either electron-withdrawing groups (such as halide groups) but also to electron-donating groups (such as alkyl groups).

To show the merit of the present work in comparison with reported results in the literature, we compared results of $SnCl_2 \cdot 2H_2O$ with reported reducing agent[11]in the synthesis of 2-aryl-2*H*-indazoles. As shown in Table 2, the $TiCl_4$/Zn/TEA system can act as a suitable reducing agent with respect to reaction times and yields of the products.

The structures of all products **2** were characterized by IR, ^1H NMR spectral data as well as HRMS analysis. The structure of **2w** was further confirmed by X-ray diffraction analysis.[21] The molecular structure of **2w** is shown in Fig. 1.

Table 2
Synthesis of 2*H*-indazoles **2** induced by low-valent titanium reagent

Entry	R^1	R^2	Ar	Compound	Yield (%)	Literature[11] yield (%)
1	H	H	4-ClC_6H_4	**2a**	83	—
2	H	H	3-$CH_3OC_6H_4$	**2b**	89	—
3	H	H	3-Cl–4-FC_6H_3	**2c**	81	—
4	H	H	C_6H_5	**2d**	87	88
5	H	H	4-$CH_3C_6H_4$	**2e**	83	40
6	H	H	4-$CH_3OC_6H_4$	**2f**	86	46
7	H	H	4-FC_6H_4	**2g**	80	65
8	H	H	4-BrC_6H_4	**2h**	85	85
9	H	H	3-Cl–4-$CH_3C_6H_3$	**2i**	88	71
10	H	H	3,4-$OCH_2OC_6H_3$	**2j**	82	—
11	Cl	H	3-$CH_3OC_6H_4$	**2k**	75	61
12	Cl	H	4-ClC_6H_4	**2l**	80	—
13	Cl	H	3-Cl–4-$CH_3C_6H_3$	**2m**	78	72
14	Cl	H	C_6H_5	**2n**	85	65
15	Cl	H	3-$CH_3C_6H_4$	**2o**	79	—
16	Cl	H	3-Cl–4-FC_6H_3	**2p**	86	60
17	Cl	H	4-FC_6H_4	**2q**	79	68
18	Cl	H	4-BrC_6H_4	**2r**	90	70
19	Cl	H	3-ClC_6H_4	**2s**	77	—
20	CH_3O	CH_3O	4-$CH_3OC_6H_4$	**2t**	78	—
21	CH_3O	CH_3O	3-ClC_6H_4	**2u**	83	—
22	CH_3O	CH_3O	4-BrC_6H_4	**2v**	87	—
23	CH_3O	CH_3O	4-FC_6H_4	**2w**	79	—
24	CH_3O	CH_3O	3-$CH_3C_6H_4$	**2x**	75	—
25	CH_3O	CH_3O	3-Cl–4-$CH_3C_6H_3$	**2y**	72	—

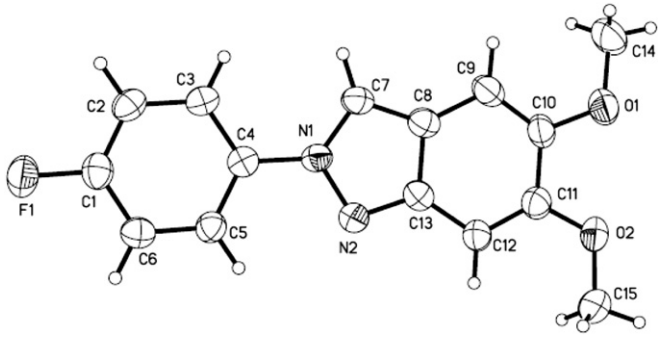
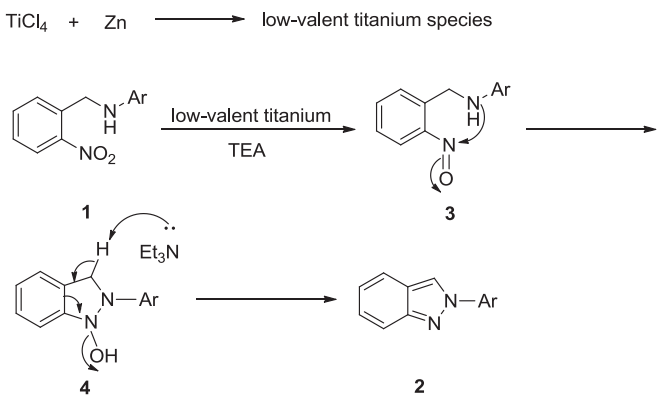


Fig. 1. The crystal structure of compound **2w**.

According to literature,[20] we suppose the following mechanism to explain this reaction. $TiCl_4$ is reduced by zinc dust to give low-valent titanium species. In the initial step, 2-nitrobenzylamine **1** was reduced by low-valent titanium reagent to 2-nitrosobenzylamine **3** in the presence of TEA. 2-Nitrosobenzylamine **3** then cyclized by the nucleophilic attack of the NH group onto the nitroso group giving intermediate **4**. Finally, the expected product **2** was produced by elimination of water in the presence of TEA (Scheme 3).



Scheme 3. Proposed mechanism for the synthesis of 2*H*-indazoles.

3. Conclusion

In summary, a series of 2-aryl-2*H*-indazoles were synthesized via reductive cyclization of 2-nitrobenzylamines induced by low-valent titanium reagent in the presence of TEA. The advantages of this new method are the easily accessible starting materials, convenient manipulation, shorter reaction time, and higher yields, and wider substrate scope.

4. Experimental section

4.1. General

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. All the reactions were conducted under N_2 atmosphere. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR and ^{13}C NMR were determined on Varian Inova-300 MHz spectrometer in DMSO-d_6 or $CDCl_3$ solution. *J* values are in hertz. Chemical shifts are expressed in parts per million downfield from internal standard TMS. HRMS analyses were carried out using TOF-MS or GCT-TOF instrument. X-ray diffractions were recorded on a Siemens P4 diffractometer.

4.2. General procedure for the synthesis of 2*H*-indazoles 2

$TiCl_4$ (0.44 mL, 4 mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (0.52 g, 8 mmol) in freshly distilled anhydrous THF (10 mL) at room temperature (rt) under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt, and then, 5 mL TEA was added; the pH was about 8 (the pH value was determined by pH test paper). A solution of 2-nitrobenzylamines (**1**) (1 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred at rt for 30 min. After this period, the thin layer chromatography (TLC) analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 18% HCl (15 mL) and extracted with $ClCH_2CH_2Cl$ (3×40 mL). The combined extracts were washed with water (3×40 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% ethanol to give pure 2*H*-indazoles (**2**).

*4.2.1. 2-(4-Chlorophenyl)-2H-indazole (**2a**).* Mp: 140–141 °C (lit.[7h] 141–142 °C). IR (KBr) *ν*: 1623, 1496, 1377, 1200, 1090, 949, 824, 751 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 7.11 (t, *J*=5.1 Hz, 1H, ArH), 7.30–7.34 (1H, m, ArH), 7.65 (d, *J*=3.0 Hz, 2H, ArH), 7.70 (d, *J*=6.0 Hz, 1H, ArH), 7.76 (d, *J*=6.3 Hz, 1H, ArH), 8.12 (d, *J*=6.3 Hz, 2H, ArH), 9.11 (s, 1H, C_3–H). HRMS [found: *m*/*z* 228.0451 (M^+), calcd for $C_{13}H_9^{35}ClN_2$: M, 228.0454].

*4.2.2. 2-(3-Methoxyphenyl)-2H-indazole (**2b**).* Mp: 46–47 °C. IR (KBr) *ν*: 3010, 2960, 2837, 1625, 1599, 1485, 1383, 1325, 1261, 1162, 1038, 861, 781, 679 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 3.87 (s, 3H, CH_3O), 7.01 (d, *J*=6.0 Hz, 1H, ArH), 7.10 (t, *J*=5.1 Hz, 1H, ArH), 7.31 (t, *J*=4.8 Hz, 1H, ArH), 7.48 (t, *J*=5.4 Hz, 1H, ArH), 7.65–7.67 (m, 2H, ArH), 7.71 (d, *J*=6.6 Hz, 1H, ArH), 7.76 (d, *J*=6.3 Hz, 1H, ArH), 9.11 (s, 1H, C_3–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 55.5, 105.8, 112.3, 113.7, 117.5, 121.0, 121.8, 122.2, 122.4, 126.9, 130.6, 141.1, 148.9, 160.2. HRMS [found: *m*/*z* 224.0951 (M^+), calcd for $C_{14}H_{12}N_2O$: M, 224.0950].

*4.2.3. 2-(3-Chloro-4-fluorophenyl)-2H-indazole (**2c**).* Mp: 130–132 °C. IR (KBr) *ν*: 3065, 1627, 1504, 1380, 1262, 1064, 956, 857, 755 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 7.12 (t, *J*=5.1 Hz, 1H, ArH), 7.33 (t, *J*=4.8 Hz, 1H, ArH) , 7.64–7.72 (m, 2H, ArH), 7.77 (d, *J*=6.0 Hz, 1H, ArH), 8.12–8.16 (m, 1H, ArH), 8.36–8.38 (m, 1H, ArH), 9.16 (s, 1H, C_3–H). HRMS [found: *m*/*z* 246.0358 (M^+), calcd for $C_{13}H_8^{35}ClFN_2$: M, 246.0360].

*4.2.4. 2-Phenyl-2H-indazole (**2d**).* Mp: 84–85 °C (lit.[11] 84–85 °C). IR (KBr) *ν*: 3066, 1626, 1593, 1518, 1494, 1464, 1407, 1378, 1349, 1314, 1250, 1231, 1201, 1143, 1129, 1073, 1044, 950, 907, 820, 780, 754, 685 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 7.11 (t, *J*=5.7 Hz, 1H, ArH), 7.32 (t, *J*=6.0 Hz, 1H, ArH), 7.46 (t, *J*=5.4 Hz, 1H, ArH), 7.59 (t, *J*=5.7 Hz, 2H, ArH), 7.72 (d, *J*=6.6 Hz, 1H, ArH), 7.77 (d, *J*=6.3 Hz, 1H, ArH), 8.10 (d, *J*=6.0 Hz, 2H, ArH), 9.12 (s, 1H, C_3–H). HRMS [found: *m*/*z* 194.0843 (M^+), calcd for $C_{13}H_{10}N_2$: M, 194.0844].

*4.2.5. 2-(4-Methylphenyl)-2H-indazole (**2e**).* Mp: 96–98 °C (lit.[11] 97–98 °C). IR (KBr) *ν*: 3039, 2946, 1624, 1522, 1453, 1418, 1392, 1378, 1346, 1311, 1258, 1230, 1196, 1146, 1126, 1108, 1047, 1017, 953, 822, 791, 756, 738 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 2.39 (s, 3H, CH_3), 7.09 (t, *J*=6.0 Hz, 1H, ArH), 7.30 (t, *J*=5.1 Hz, 1H, ArH), 7.38 (d, *J*=6.3 Hz, 2H, ArH), 7.71 (d, *J*=6.6 Hz, 1H, ArH), 7.77 (d, *J*=6.6 Hz, 1H, ArH), 7.96 (d, *J*=6.3 Hz, 2H, ArH), 9.02 (s, 1H, C_3–H). HRMS [found: *m*/*z* 208.1002 (M^+), calcd for $C_{14}H_{12}N_2$: M, 208.1000].

*4.2.6. 2-(4-Methoxyphenyl)-2H-indazole (**2f**).* Mp: 124–126 °C (lit.[11] 123–124 °C). IR (KBr) *ν*: 3010, 2959, 2836, 1626, 1609, 1520, 1458, 1437, 1396, 1382, 1340, 1315, 1302, 1244, 1177, 1127, 1108, 1046, 1028, 952, 837, 810, 779, 754, 729 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 3.87 (s, 3H, CH_3O), 7.02 (d, *J*=6.3 Hz, 2H, ArH), 7.11 (t, *J*=4.8 Hz, 1H, ArH), 7.32 (*J*=5.1 Hz, 1H, ArH), 7.70 (d, *J*=6.6 Hz, 1H, ArH), 7.791–7.81 (m, 3H, ArH), 8.31 (s, 1H, C_3–H). HRMS [found: *m*/*z* 224.9050 (M^+), calcd for $C_{14}H_{12}N_2O$: M, 224.9050].

*4.2.7. 2-(4-Fluorophenyl)-2H-indazole (**2g**).* Mp: 102–103 °C (lit.[11] 102–104 °C). IR (KBr) *ν*: 3062, 1627, 1520, 1456, 1434, 1382, 1294, 1234, 1203, 1156, 1129, 1097, 1042, 1008, 951, 839, 816, 793, 779, 752 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.05 (t, *J*=5.1 Hz, 1H, ArH), 7.12–7.18 (m, 2H, ArH), 7.26 (t, *J*=6.0 Hz, 1H, ArH), 7.63 (d, *J*=6.0 Hz, 1H, ArH), 7.71 (d, *J*=6.3 Hz, 1H, ArH), 7.77–7.79 (m, 2H, ArH), 8.26 (s, 1H, C_3–H). HRMS [found: *m*/*z* 212.0748 (M^+), calcd for $C_{13}H_9FN_2$: M, 212.0750].

*4.2.8. 2-(4-Bromophenyl)-2H-indazole (**2h**).* Mp: 148–149 °C (lit.[11] 148–150 °C). IR (KBr) *ν*: 3062, 1627, 1520, 1456, 1434, 1382, 1294, 1234, 1203, 1156, 1129, 1097, 1042, 1008, 951, 839, 816, 793, 779, 752 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.12 (t, *J*=5.1 Hz, 1H, ArH), 7.33 (t, *J*=4.8 Hz, 1H, ArH), 7.64 (d, *J*=6.0 Hz, 2H, ArH), 7.69 (d, *J*=6.6 Hz, 1H, ArH), 7.78 (t, *J*=5.1 Hz, 3H, ArH), 8.37 (s, 1H, C_3–H). HRMS [found: *m*/*z* 271.9945 (M^+), calcd for $C_{13}H_9^{79}BrN_2$: M, 271.9949].

*4.2.9. 2-(3-Chloro-4-methylphenyl)-2H-indazole (**2i**).* Mp: 133–135 °C (lit.[11] 133–135 °C). IR (KBr) *ν*: 3057, 2942, 1628, 1606, 1580, 1520, 1499, 1446, 1415, 1377, 1336, 1275, 1231, 1208, 1149, 1128, 1058, 963, 877, 842, 811, 778, 709 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 2.41 (s, 3H, CH_3), 7.10–7.14 (m, 1H, ArH), 7.31–7.35 (m, 1H, ArH), 7.58 (d, *J*=6.3 Hz, 2H, ArH), 7.77 (d, *J*=6.3 Hz, 1H, ArH), 8.01 (dd, J_1=1.5 Hz, J_2=6.3 Hz, 1H, ArH), 8.20 (d, *J*=1.5 Hz, 1H, ArH), 9.16 (s, 1H, C_3–H). HRMS [found: *m*/*z* 242.0610 (M^+), calcd for $C_{14}H_{11}^{35}ClN_2$: M, 242.0611].

*4.2.10. 2-(3,4-Methylenedioxyphenyl)-2H-indazole (**2j**).* Mp: 114–116 °C. IR (KBr) *ν*: 3036, 2915, 2805, 1625, 1605, 1590, 1508, 1488, 1365, 1309, 1288, 1253, 1223, 1183, 1158, 1094, 1065, 930, 894, 865, 810, 780 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 6.12 (s, 2H, OCH_2O), 7.06 (s, 2H, ArH), 7.26 (s, 1H, ArH), 7.50–7.65 (m, 4H, ArH), 8.95 (s, 1H,

C_3–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 101.9, 102.0, 108.6, 113.8, 117.3, 120.8, 121.5, 122.0, 122.3, 126.5, 134.6, 146.9, 148.1, 148.6. HRMS [found: m/z 239.0815 $(M+H)^+$, calcd for $C_{14}H_{11}N_2O_2$: M+H, 239.0821].

*4.2.11. 5-Chloro-2-(3-methoxyphenyl)-2H-indazole (**2k**).* Mp: 97–98 °C (lit.[11] 97–99 °C). IR (KBr) ν: 3065, 2959, 2834, 1608, 1593, 1513, 1483, 1438, 1369, 1337, 1311, 1271, 1225, 1193, 1161, 1095, 1050, 1039, 966, 927, 867, 808, 771, 729 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 3.88 (s, 3H, CH_3O), 7.02–7.04 (m, 1H, ArH), 7.28–7.31 (m, 1H, ArH), 7.49 (t, J=5.1 Hz, 1H, ArH), 7.66 (d, J=6.0 Hz, 2H, ArH), 7.77 (d, J=6.9 Hz, 1H, ArH), 7.85 (d, J=1.2 Hz, 1H, ArH), 9.11 (s, 1H, C_3–H). HRMS [found: m/z 258.0560 (M^+), calcd for $C_{14}H_{11}^{35}ClN_2O$: M, 258.0560].

*4.2.12. 5-Chloro-2-(4-chlorophenyl)-2H-indazole (**2l**).* Mp: 142–144 °C. IR (KBr) ν: 2925, 1513, 1259, 1191, 1046, 805, 715 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 7.30 (d, J=6.0 Hz, 1H, ArH), 7.66 (d, J=6.0 Hz, 2H, ArH), 7.76 (d, J=6.0 Hz, 1H, ArH), 7.86 (s, 1H, ArH), 8.11 (d, J=6.3 Hz, 2H, ArH), 9.11 (s, 1H, C_3–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 100.8, 107.4, 112.6, 116.1, 119.6, 120.3, 120.8, 121.2, 125.4, 133.5, 145.7, 147.0, 147.5. HRMS [found: m/z 262.0069 (M^+), calcd for $C_{14}H_8^{35}Cl_2N_2$: M, 262.0065].

*4.2.13. 5-Chloro-2-(3-chloro-4-methylphenyl)-2H-indazole (**2m**).* Mp: 160–162 °C (lit.[11] 159–161 °C). IR (KBr) ν: 3094, 2988, 2950, 1601, 1581, 1511, 1446, 1416, 1380, 1364, 1334, 1304, 1274, 1231, 1205, 1195, 1150, 1059, 1049, 994, 931, 877, 866, 848, 817, 806, 767, 734, 711, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 2.35 (s, 3H, CH_3), 7.17 (dd, J_1=1.5 Hz, J_2=7.2 Hz, 1H, ArH), 7.28 (d, J=6.3 Hz, 1H, ArH), 7.57 (s, 2H, ArH), 7.62 (d, J=6.9 Hz, 1H, ArH), 7.84 (s, 1H, ArH), 8.21 (s, 1H, C_3–H). HRMS [found: m/z 276.0220 (M^+), calcd for $C_{14}H_{10}^{35}Cl_2N_2$: M, 276.0221].

*4.2.14. 5-Chloro-2-phenyl-2H-indazole (**2n**).* Mp: 143–145 °C (lit.[11] 143–144 °C). IR (KBr) ν: 3063, 1627, 1596, 1509, 1462, 1405, 1371, 1323, 1298, 1286, 1230, 1199, 1177, 1140, 1072, 1051, 954, 930, 898, 872, 809, 769, 753, 728, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.24–7.26 (m, 1H, ArH), 7.42 (t, J=5.4 Hz, 1H, ArH), 7.53 (t, J=5.7 Hz, 2H, ArH), 7.68 (s, 1H, ArH), 7.73 (d, J=6.6 Hz, 1H, ArH), 7.88 (d, J=6.0 Hz, 2H, ArH), 8.35 (s, 1H, C_3–H). HRMS [found: m/z 228.0452 (M^+), calcd for $C_{13}H_9^{35}ClN_2$: M, 228.0454].

*4.2.15. 5-Chloro-2-(3-methylphenyl)-2H-indazole (**2o**).* Mp: 97–98 °C (lit.[11] 97–99 °C). IR (KBr) ν: 3030, 2921, 1626, 1606, 1590, 1508, 1489, 1364, 1309, 1288, 1253, 1223, 1173, 1158, 1141, 1093, 1059, 1050, 930, 893, 865, 810, 780, 732, 695 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 2.43 (s, 3H, CH_3), 7.28–7.30 (m, 2H, ArH), 7.46–7.50 (m, 1H, ArH), 7.77 (d, J=6.6 Hz, 1H, ArH), 7.84–7.87 (m, 2H, ArH), 7.92 (s, 1H, ArH), 9.05 (s, 1H, C_3–H). HRMS [found: m/z 242.0610 (M^+), calcd for $C_{14}H_{11}^{35}ClN_2$: M, 242.0611].

*4.2.16. 5-Chloro-2-(3-chloro-4-fluorophenyl)-2H-indazole (**2p**).* Mp: 140–141 °C (lit.[11] 140–142 °C). IR (KBr) ν: 3093, 1627, 1599, 1548, 1517, 1453, 1427, 1373, 1337, 1310, 1271, 1259, 1235, 1194, 1127, 1067, 1049, 965, 932, 877, 859, 804, 761, 716, 692 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 7.30–7.34 (m, 1H, ArH), 7.65 (t, J=6.6 Hz, 1H, ArH), 7.76 (t, J=5.4 Hz, 1H, ArH), 7.86 (s, 1H, ArH), 8.10–8.13 (m, 1H, ArH), 8.34–8.36 (m, 1H, ArH), 9.14 (s, 1H, C_3–H). HRMS [found: m/z 279.9969 (M^+), calcd for $C_{13}H_7^{35}Cl_2FN_2$: M, 279.9970].

*4.2.17. 5-Chloro-2-(4-fluorophenyl)-2H-indazole (**2q**).* Mp: 133–135 °C (lit.[11] 134–135 °C). IR (KBr) ν: 1609, 1517, 1431, 1404, 1370, 1292, 1238, 1197, 1153, 1095, 1050, 1010, 954, 930, 867, 831, 803, 769, 729, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.21–7.27 (m, 3H, ArH), 7.68(s, 1H, ArH), 7.72 (d, J=6.9 Hz, 1H, ArH), 7.83–7.86 (m, 2H, ArH), 8.29 (s, 1H, C_3–H). HRMS [found: m/z 246.0360 (M^+), calcd for $C_{13}H_8^{35}ClFN_2$: M, 246.0360].

*4.2.18. 2-(4-Bromophenyl)-5-chloro-2H-indazole (**2r**).* Mp: 150–152 °C (lit.[11] 150–152 °C). IR (KBr) ν: 3066, 1587, 1510, 1485, 1418, 1371, 1335, 1313, 1292, 1196, 1137, 1049, 1005, 952, 925, 852, 827, 801, 766, 724, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.26 (d, J=6.0 Hz, 1H, ArH), 7.64–7.66 (m, 3H, ArH), 7.71 (d, J=6.6 Hz, 1H, ArH), 7.77 (d, J=8.0 Hz, 2H, ArH), 8.32 (s, 1H, C_3–H). HRMS [found: m/z 305.9561 (M^+), calcd for $C_{13}H_8^{79}Br^{35}ClN_2$: M, 305.9559].

*4.2.19. 5-Chloro-2-(3-chlorophenyl)-2H-indazole (**2s**).* Mp: 142–144 °C (lit.[11] 143–144 °C). IR (KBr) ν: 3073, 1591, 1510, 1483, 1462, 1443, 1396, 1370, 1332, 1304, 1229, 1200, 1090, 1077, 1049, 925, 868, 835, 798, 747, 719, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.27 (d, J=3.6 Hz, 1H, ArH), 7.39 (d, J=5.4 Hz, 1H, ArH), 7.46 (t, J=5.4 Hz, 1H, ArH), 7.74–7.66 (m, 2H, ArH), 7.38 (t, J=6.0 Hz, 1H, ArH), 7.77 (d, J=5.4 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 8.34 (s, 1H, C_3–H). HRMS [found: m/z 262.0065 (M^+), calcd for $C_{13}H_8^{35}Cl_2N_2$: M, 262.0069].

*4.2.20. 5,6-Dimethoxy-2-(4-methoxyphenyl)-2H-indazole (**2t**).* Mp: 186–188 °C. IR (KBr) ν: 3060, 2960, 2835, 1608, 1595, 1513, 1485, 1439, 1369, 1377, 1311, 270, 1225, 1193, 1161, 1095, 1049, 1038, 965, 730, 867, 808, 770, 730, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 3.85 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 3.96 (s, 3H, CH_3O), 6.89 (s, 1H, ArH), 7.00 (d, J=6.0 Hz, 2H, ArH), 7.05 (s, 1H, ArH), 7.73 (d, J=5.4 Hz, 2H, ArH), 8.11 (s, 1H, C_3–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 56.0, 56.4, 96.3, 97.5, 115.0, 117.6, 119.7, 122.1, 134.7, 146.7, 148.7, 152.2, 159.1. HRMS [found: m/z 284.1161 (M^+), calcd for $C_{16}H_{16}N_2O_3$: M, 284.1161].

*4.2.21. 2-(3-Chlorophenyl)-5,6-dimethoxy-2H-indazole (**2u**).* Mp: 143–144 °C. IR (KBr) ν: 3135, 3011, 2960, 2835, 1625, 1592, 110, 1483, 1460, 1440, 1385, 1370, 1330, 1305, 1229, 1200, 1090, 1075, 1050, 920, 860, 834, 898, 746, 720, 694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 3.84 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 6.76 (s, 1H, ArH), 6.94 (s, 1H, ArH), 7.20 (d, J=6.0 Hz, 1H, ArH), 7.31 (t, J=6.3 Hz, 1H, ArH), 7.62 (d, J=6.0 Hz, 1H, ArH), 7.81 (s, 1H, ArH), 8.12 (s, 1H, C_3–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 56.1, 95.9, 97.0, 117.9, 118.0, 120.4, 127.1, 135.5, 141.7, 147.1, 149.0, 152.6. HRMS [found: m/z 288.0661 (M^+), calcd for $C_{15}H_{13}^{35}ClN_2O_2$: M, 288.0665].

*4.2.22. 2-(4-Bromophenyl)-5,6-dimethoxy-2H-indazole (**2v**).* Mp: 156–158 °C. IR (KBr) ν: 2957, 2834, 1628, 1520, 1456, 1435, 1383, 1292, 1234, 1204, 1156, 1130, 1096, 1040, 1007, 950, 815, 794, 779, 752, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 3.93 (s, 3H, CH_3O), 3.97 (s, 3H, CH_3O), 6.86 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.60 (d, J=6.6 Hz, 2H, ArH), 7.72 (d, J=6.0 Hz, 2H, ArH), 8.16 (s, 1H, C_3–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 56.1, 59.9, 97.0, 117.9, 119.2, 120.5, 121.5, 132.8, 139.7, 147.0, 148.9, 152.5. HRMS [found: m/z 332.0160 (M^+), calcd for $C_{15}H_{13}^{79}BrN_2O_2$: M, 332.0160].

*4.2.23. 2-(4-Fluorophenyl)-5,6-dimethoxy-2H-indazole (**2w**).* Mp: 106–108 °C. IR (KBr) ν: 3060, 3135, 3010, 2955, 2836, 1625, 1520, 1456, 1434, 1382, 1294, 1234, 1203, 1155, 1129, 1098, 1044, 950, 840, 815, 792, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 3.91 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3O), 6.86 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.16 (t, J=6.3 Hz, 2H, ArH), 7.76–7.79 (m, 2H, ArH), 8.11 (s, 1H, C_3–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 56.1, 95.9, 97.1, 116.4, 116.7, 117.7, 119.5, 121.9, 122.0, 137.1, 146.9, 148.7, 152.3, 160.1, 163.3. HRMS [found: m/z 273.1034 $(M+H)^+$, calcd for $C_{15}H_{14}FN_2O_2$: M+H, 273.1039].

*4.2.24. 5,6-Dimethoxy-2-(3-methylphenyl)-2H-indazole (**2x**).* Mp: 110–112 °C. IR (KBr) ν: 3030, 2921, 2835, 1625, 1605, 1590, 1508,

1488, 1365, 1309, 1288, 1253, 1223, 1173, 1158, 1142, 1094, 1059, 1051, 930, 894, 865, 810, 780, 732, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 2.43 (s, 3H, CH_3), 3.91 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3O), 6.86 (s, 1H, ArH), 7.05 (s, 1H, ArH), 7.13 (d, J=5.4 Hz, 1H, ArH), 7.34 (t, J=6.0 Hz, 1H, ArH), 7.57 (d, J=6.0 Hz, 1H, ArH), 7.69 (s, 1H, ArH), 8.18 (s, 1H, C_3–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.7, 56.1, 96.0, 97.2, 117.3, 117.5, 119.5, 121.1, 128.1, 139.9, 140.7, 146.7, 148.62, 152.18. HRMS [found: m/z 269.1285 $(M+H)^+$, calcd for $C_{16}H_{17}N_2O_2$: M+H, 269.1290].

*4.2.25. 2-(3-Chloro-4-methylphenyl)-5,6-dimethoxy-2H-indazole (**2y**).* Mp: 121–123 °C. IR (KBr) ν: 3028, 2920, 2832, 1628, 1607, 1590, 1508, 1480, 1365, 1310, 1288, 1250, 1223, 1176, 1154, 1142, 1094, 1045, 930, 897, 868, 788, 734 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 2.35 (s, 3H, CH_3), 3.79 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 6.95–7.00 (m, 2H, ArH), 7.50 (s, 1H, ArH), 7.86 (s, 1H, ArH), 8.05 (s, 1H, ArH), 8.80 (s, 1H, C_3–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 24.4, 60.8, 60.9, 100.9, 102.7, 114.7, 122.6, 123.0, 124.6, 125.5, 137.4, 139.1, 144.5, 151.3, 153.5, 157.4. HRMS [found: m/z 303.0895 $(M+H)^+$, calcd for $C_{16}H_{16}^{35}ClN_2O_2$: M, 303.0900].

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Supplementary data

Supplementary data related to this article can be found in the online version, at doi:10.1016/j.tet.2012.03.043.

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21. Crystallographic data for the structures of **2w** have been deposited at the Cambridge Crystallographic Data Centre, deposit number is CCDC 869942. Copies of available material can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).The single-crystal growth was carried out in ethanol solutions at rt. Intensity data were collected on a Siemens P4 diffractometer with graphite monochromated Mo Kα radiation (λ=0.71075 Å) using the ω scan mode with $3.02°<\theta<25.50°$.Crystal data for **2w**: empirical formula $C_{15}H_{13}FN_2O_2$, yellow, crystal dimension 0.75×0.30×0.20 mm, orthorhombic, space group *Pbca*, a=11.5483(18) Å, b=13.452(2) Å, c=33.213(5) Å, α=90°, β=90°, γ=90°. V=5159.4(14) $Å^3$, M_r=272.27, Z=16, D_c=1.402 Mg/m^3, μ(Mo Kα)=0.104 mm^{-1}, $F(000)$=2272, S=1.275, R_1=0.1070, wR_2=0.2372.