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Facile synthesis of 2*H*-indazole derivatives starting from the Baylis–Hillman adducts of 2-cyclohexen-1-one

Ka Young Lee, Saravanan Gowrisankar and Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, South Korea

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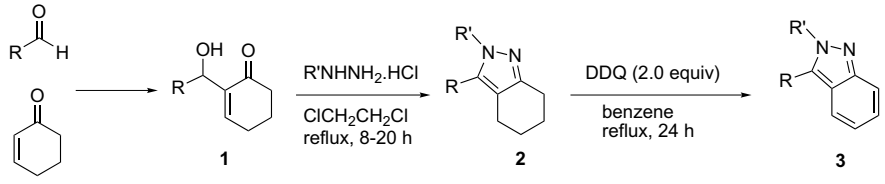
Abstract—Facile synthetic method of 2*H*-indazole derivatives was developed involving DDQ oxidation of pyrazoles, which were prepared starting from the Baylis–Hillman adducts of 2-cyclohexen-1-one.

The indazole nucleus is a pharmaceutically important structure and constitutes the key subunit in many drug substances with a broad range of pharmacological activities[1] including antitumor,[1b] antimicrobial,[1h] and antiplatelet,[1d] and anti-inflammatory activities.[1j] However, there is still a lack of general and efficient methodologies for the synthesis of *N*-substituted indazoles[2] although some of the reported methods could be used effectively.

Recently, we reported a regioselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles from Baylis–Hillman adducts.[3] A variety of Baylis–Hillman adducts derived from methyl vinyl ketone, ethyl vinyl ketone, 2-cyclohexen-1-one, and 2-cyclopenten-1-one was converted into the corresponding pyrazole derivatives.[3] If we could oxidize the cyclohexane moiety of the pyrazole **2**, which was derived from the Baylis–Hillman adduct of 2-cyclohexen-1-one, into aromatic nucleus we could open a new route toward the valuable 2*H*-indazole skeleton as shown in Scheme 1.

In order to oxidize the cyclohexane moiety of **2a** (entry 1 in Table 1) we tried some reaction conditions including the use of Pd/C, *p*-chloranil (tetrachloro-1,4-benzoquinone), and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).[4,5] Among the conditions, the DDQ-mediated oxidations gave the best results. Encouraged by the results, we synthesized pyrazole derivatives **2** according to the previous method[3,6] and examined the transformation into 2*H*-indazole derivatives **3**. As shown in Table 1, the pyrazoles **2a**–**g** was prepared in moderate yields (47–54%). The oxidation reaction of **2a**–**g** with DDQ (2.0 equiv) in benzene at refluxing temperature gave the desired 2*H*-indazole derivatives **3a**–**g** in moderate to good yields (69–80%).[7]

For the pyrazole **2f**, elimination of *tert*-butyl group was observed and indazole **3f′** was obtained as the major product (entry 6). During the DDQ oxidation of pyrazole **2h** (Scheme 2), which was produced from the Baylis–Hillman adduct of 4,4-dimethylcyclohex-2-en-1-one, we could not find any aromatized compound, which



Scheme 1.

Keywords: 2*H*-Indazoles; Baylis–Hillman adducts; DDQ; Pyrazoles; Carbazoles.
* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389; e-mail: kimjn@chonnam.ac.kr

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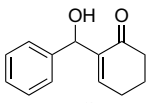
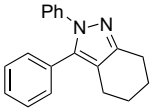
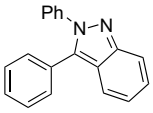
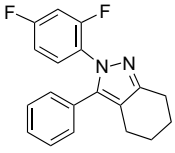
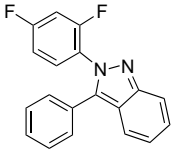
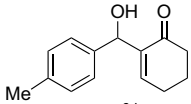
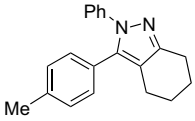
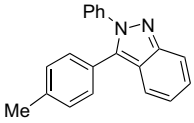
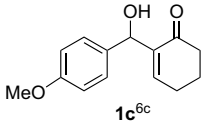
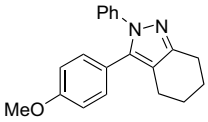
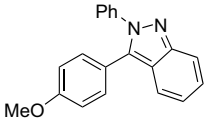
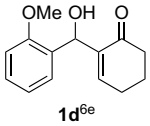
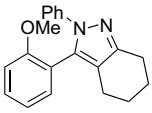
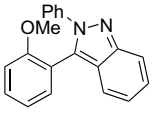
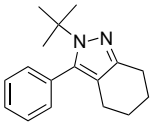
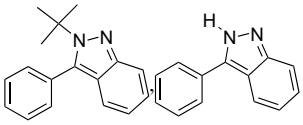
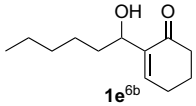
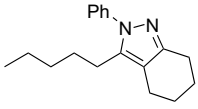
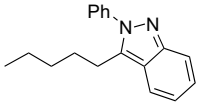
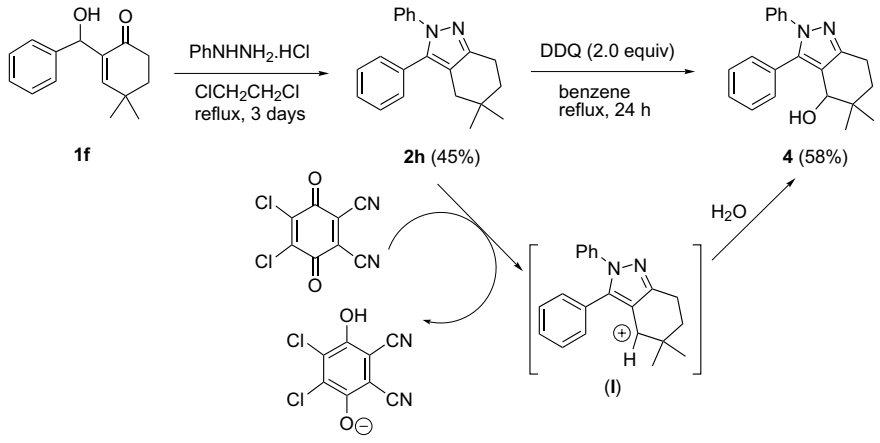
Table 1. Synthesis of 2*H*-indazole derivatives **3a–g**

Entry	B–H adduct **1**[a]	Pyrazole **2** (%)[b,c]	Indazole **3** (%)[c]
1	 **1a**[6b]	 **2a** (51)[3]	 **3a** (69)[2h]
2	**1a**	 **2b** (48)[3]	 **3b** (75)
3	 **1b**[6d]	 **2c** (50)	 **3c** (74)
4	 **1c**[6c]	 **2d** (54)	 **3d** (74)
5	 **1d**[6e]	 **2e** (48)	 **3e** (80)
6	**1a**	 **2f** (49)	 **3f** (20) **3f'** (57)
7	 **1e**[6b]	 **2g** (47)	 **3g** (69)

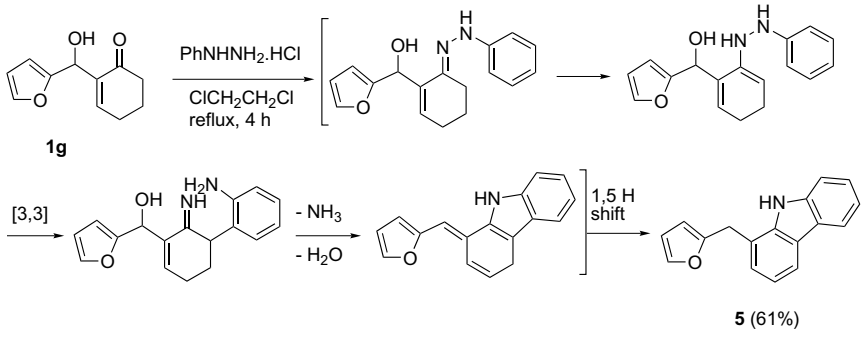
[a] B–H adducts were synthesized from the reaction of aldehydes and 2-cyclohexen-1-one with DMAP according to Ref. 6.
[b] Pyrazole derivatives were prepared from **1** and appropriate hydrazine derivatives according to Ref. 3.
[c] Isolated yields in parenthesis.

might be produced by the combination of oxidation and methyl group migration. Instead, we obtained alcohol derivative **4** in 58% yield. The plausible mechanism for the formation of **4** is depicted in Scheme 2. As reported, the DDQ oxidation involved the hydride transfer from substrate to DDQ to form the carbocationic species as the first step.[4,5] For the substrate **2h** hydride abstraction at the 4-position occurred selectively to generate the carbocationic intermediate (**I**). The intermediate (**I**) could be stabilized by the nearby enamine moiety and could be formed selectively, which in turn react with moisture in the reaction mixture to produce the hydroxylated compound **4**. The position of OH group of **4** could be easily assigned from its ^{1}H NMR spectrum by the disappearance of the singlet methylene peak (δ = 2.38 ppm, –CH_2– at 4-position) of **2h**.[7] In addition, disappearance of OH peak (d, δ = 1.74 ppm) and the change of the doublet (H-4, δ = 4.17 ppm) into singlet with D_2O treatment showed the position of OH as correct.[7]

Unfortunately, we could not obtain the corresponding pyrazole derivative in the reaction of **1g** and phenylhydrazine hydrochloride. Instead, carbazole compound **5** was prepared in 61% yield by following the mechanism proposed in Scheme 3.[8] Consecutive



Scheme 2.



Scheme 3.

formation of the corresponding hydrazone, conversion to carbazole skeleton by following the typical Fischer indole synthesis mechanism,[8] and finally 1,5-hydrogen shift might generate the carbazole derivative **5**. However, we could not explain the differences for the synthesis of pyrazoles between **1g** and **1a**–**e** at this stage.

In summary, we disclosed a new procedure for the preparation of 2*H*-indazole derivatives starting from the Baylis–Hillman adducts of 2-cyclohexen-1-one by using DDQ oxidation procedure.

Acknowledgements

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7. Typical experimental procedure and spectroscopic data of the prepared compounds are as follows. Synthesis of compound **3a**: A mixture of pyrazole **2a** (130 mg, 0.47 mmol) and DDQ (216 mg, 0.95 mmol) in benzene (5 mL) was heated to reflux for 24 h. After removal of solvent and chromatographic purification process (hexanes/ether, 20:1) we obtained **3a** as a white solid, 88 mg (69%).
Compound **3a**: 69%; white solid, mp 106–107 °C; IR (KBr) 3059, 1624, 1597, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09–7.15 (m, 1H), 7.32–7.45 (m, 11H), 7.70 (dt, J = 8.4 and 1.2 Hz, 1H), 7.81 (dt, J = 8.7 and 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 117.93, 120.68, 121.92, 122.68, 126.18, 127.16, 128.41, 128.47, 128.92, 129.14, 129.84, 130.07, 135.56, 140.40, 149.17; Mass (70 eV) *m/z* (rel. intensity) 51 (10), 77 (24), 134 (33), 269 (92), 270 (M^+, 100).
Compound **3b**: 75%; white solid, mp 160–161 °C; IR (KBr) 3059, 1608, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.81–6.89 (m, 1H), 6.94–7.01 (m, 1H), 7.11–7.17 (m, 1H), 7.31–7.42 (m, 6H), 7.52–7.60 (m, 1H), 7.72 (dt, J = 8.4 and 0.9 Hz, 1H), 7.78 (dt, J = 9.0 and 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 104.92, 105.24, 105.27, 105.59, 111.99, 112.04, 112.29, 112.34, 117.91, 120.70, 121.06, 122.96, 125.01, 125.06, 125.17, 125.22, 127.51, 128.79, 128.99, 129.10, 129.45, 129.47, 130.27, 130.41, 137.87, 149.63, 155.14, 155.31, 158.54, 158.71, 161.25, 161.39, 164.60, 164.74; Mass (70 eV) *m/z* (rel. intensity) 63 (15), 76 (21), 128 (11), 152 (10), 306 (M^+, 100).
Compound **3c**: 74%; white solid, mp 108–109 °C; IR (KBr) 3055, 1597, 1504 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 7.08–7.47 (m, 11H), 7.70 (dt, J = 8.4 and 0.9 Hz, 1H), 7.79 (dt, J = 8.7 and 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$+1 drop of CF_3COOD) δ 20.36, 114.55, 119.87, 120.02, 122.58, 123.80, 125.24, 128.39, 128.59, 128.65, 128.67, 128.79, 136.54, 137.12, 138.80, 144.89; FAB Mass 285 (M^++1).
Compound **3d**: 74%; white solid, mp 125–126 °C; IR (KBr) 3059, 1608, 1504 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H), 6.89 (d, J = 9.0 Hz, 2H), 7.06–7.12 (m, 1H), 7.23–7.46 (m, 8H), 7.67 (dt, J = 8.7 and 0.9 Hz, 1H), 7.78 (dt, J = 8.7 and 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.39, 114.42, 117.81, 120.75, 121.74, 122.28, 122.33, 126.13, 127.07, 128.27, 129.09, 131.07, 135.49, 140.47, 149.09, 159.73; FAB Mass 301 (M^++1).
Compound **3e**: 80%; white solid, mp 121–122 °C; IR (KBr) 3059, 1597, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.32 (s, 3H), 6.83 (d, J = 8.1 Hz, 1H), 7.02–7.10 (m, 2H), 7.21–7.46 (m, 8H), 7.57 (dt, J = 8.4 and 0.9 Hz, 1H), 7.79 (dt, J = 8.7 and 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 54.72, 111.41, 141.30, 148.87, 156.62, 117.60, 119.03, 120.65, 120.79, 121.90, 122.49, 124.47, 126.65, 127.62, 128.51, 130.55, 131.57, 132.43; FAB Mass 301 (M^++1).
Compound **3f**: 20%; white solid, mp 109–110 °C; IR (KBr) 3059, 2978, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (s, 9H), 6.93–6.99 (m, 1H), 7.16 (dt, J = 8.4 and 0.9 Hz, 1H), 7.23–7.29 (m, 1H), 7.39–7.51 (m, 5H), 7.72 (dt, J = 8.7 and 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 31.54, 63.02, 117.00, 120.12, 121.04, 124.15, 125.84, 128.16, 128.75, 131.06, 132.87, 135.29, 145.97; FAB Mass 251 (M^++1).
Compound **3f′**: 57%; white solid, mp 111–112 °C; IR (KBr) 3178, 1620, 1342 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19–7.25 (m, 1H), 7.34–7.56 (m, 5H), 7.98–8.05 (m, 3H), 11.03 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 110.14, 120.97, 121.12, 121.36, 126.79, 127.67, 128.16, 128.90, 133.54, 141.67, 145.76.
Compound **3g**: 69%; oil; IR (KBr) 2954, 2927, 1597, 1504 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 7.2 Hz, 3H), 1.21–1.28 (m, 4H), 1.62–1.69 (m, 2H), 3.03 (t, J = 7.5 Hz, 2H), 7.04–7.10 (m, 1H), 7.28–7.34 (m, 1H), 7.48–7.55 (m, 5H), 7.67 (dt, J = 8.4 and 0.9 Hz, 1H), 7.71 (dt, J = 8.7 and 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.81, 22.14, 25.23, 29.05, 31.41, 117.56, 120.21, 120.85, 121.02, 126.16, 126.60, 128.85, 129.13, 136.91, 140.07, 148.57; FAB Mass 265 (M^++1).
Compound **4**: 58%; white solid, mp 155–156 °C; IR (KBr) 3421, 1504, 1369 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.11 (s, 3H), 1.49–1.57 (m, 1H), 1.74 (d, J = 4.8 Hz, OH, 1H, D_2O exchangeable), 1.96–2.07 (m, 1H), 2.66–2.78 (m, 1H), 2.85–2.93 (m, 1H), 4.17 (d, J = 4.8 Hz, 1H, converted into singlet with D_2O treatment), 7.22–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 20.30, 23.93, 25.99, 30.38, 35.27, 70.50, 119.53, 125.18, 127.18, 128.44, 128.66, 128.97, 129.78, 130.15, 140.34, 141.48, 149.28; FAB Mass 319 (M^++1).
Compound **5**: 61%; white solid, mp 107–108 °C; IR (KBr) 3433, 1604, 1504 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.23 (s, 2H), 6.04–6.05 (m, 1H), 6.27–6.29 (m, 1H), 7.15–7.27 (m, 3H), 7.34–7.39 (m, 3H), 7.97 (d, J = 7.8 Hz, 1H), 8.04 (d, J = 7.8 Hz, 1H), 8.11 (br s, 1H, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) δ 31.23, 106.55, 110.55, 110.80, 119.04, 119.49, 119.59, 120.15, 120.34, 123.52, 123.65, 125.76, 126.29, 138.54, 139.52, 141.65, 153.36.
Selected spectroscopic data of starting materials **2g** and **2h** are as follows.
Compound **2g**: 47%; oil; ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 6.9 Hz, 3H), 1.17–1.26 (m, 4H), 1.41–1.48 (m, 2H), 1.75–1.87 (m, 4H), 2.51 (t, J = 6.0 Hz, 2H), 2.60 (t, J = 7.8 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 7.29–7.45 (m,

5H); ^{13}C NMR ($CDCl_3$) δ 13.77, 20.72, 22.08, 23.33, 23.38, 23.43, 24.67, 28.05, 31.32, 114.75, 125.21, 127.16, 128.81, 139.21, 140.37, 149.48.

Compound **2h**: 45%; oil; ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 6H), 1.67 (t, J = 6.6 Hz, 2H), 2.38 (s, 2H), 2.82 (t, J = 6.6 Hz, 2H), 7.15–7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 20.55, 28.16, 30.42, 35.46, 36.24, 116.77, 124.88, 126.68, 127.84, 128.50, 128.83, 129.38, 130.96, 138.92, 140.53, 149.41.

8. For the mechanism of carbazole synthesis, see: Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 119–206.