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One-Pot Synthesis of 1*H*-Indazole-4,7-diols via Iodine(III)-Mediated [3+2] Cyclization in Water

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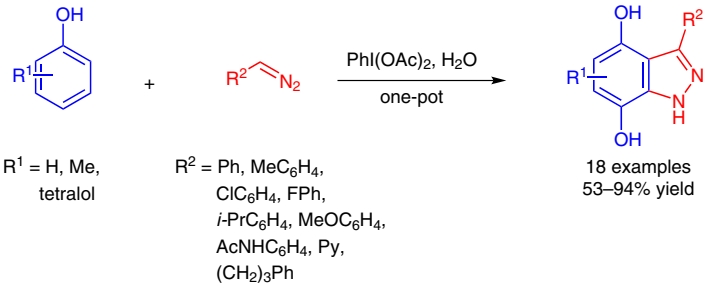

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Abstract An efficient route in one-pot to a new class of 1*H*-indazole-4,7-diols derivatives has been developed through [3+2] cycloadditive approach in water. The cycloaddition reaction was carried out via condensation of phenol and diazomethyl benzene intermediates by taking advantage of iodobenzene diacetate as an oxidant. Eighteen indazole derivatives were successfully prepared by the established method.

Key words synthesis, 1*H*-indazole-4,7-diols derivatives, one pot, water

Indazole is a very important heterocyclic scaffold with a wide range of biological activities including antifungal, β3-adrenergic receptor agonist, dopamine D2 receptor antagonist, 5-HT3 receptor antagonist, 5-HT2 and 5-HT4 receptor agonist, anti-inflammatory and anticancer activities.[1] In particular, the indazole derivatives due to their specific molecular shape and electrostatic distribution have been developed as useful drugs for anti-inflammatory, 5-HT3 receptor antagonist and anticancer action (Figure 1,A).[2–5] Lonidamine,[4] an anticancer drug developed by Aigelini Italy, was launched in 1988 for ovarian cancer patients, and pazopanib[6] is an angiogenesis inhibitor launched by GSK in 2009. Recently, as a tyrosine kinase inhibitor, axitinib[7] launched by Pfizer in 2012 was reported with anti-ovarian cancer activity. Niraparib,[8] a drug candidate developed by Tesaro, was on phase III research for ovarian and breast cancer. Indazoles and analogues are of great interest for biological and pharmaceutical research. Although indazoles are rare in nature, the natural products containing indazole nucleus exhibited fascinating biological activities. Nigellicine, nigellidine and nigeglanine isolated from the seeds of *Nigella sativa* were reported as potent anticancer agents (Figure 1,B).[9,10]

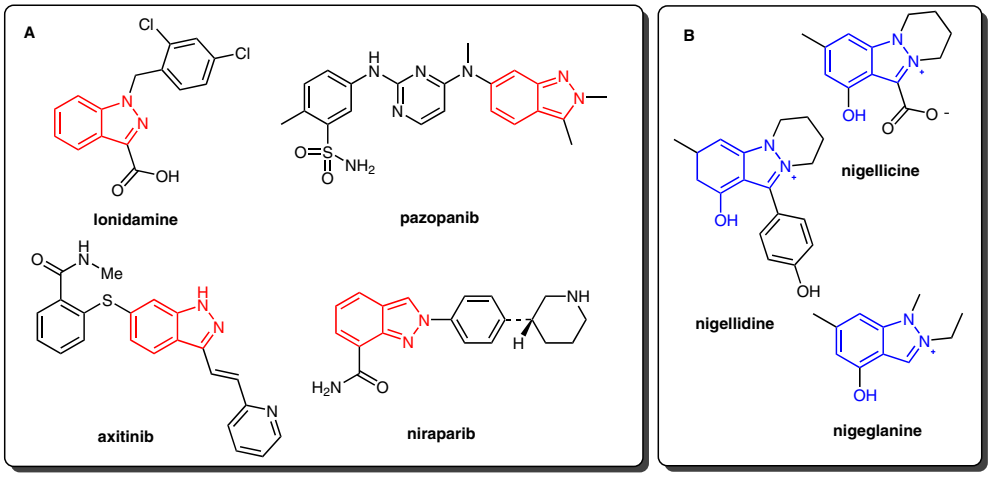


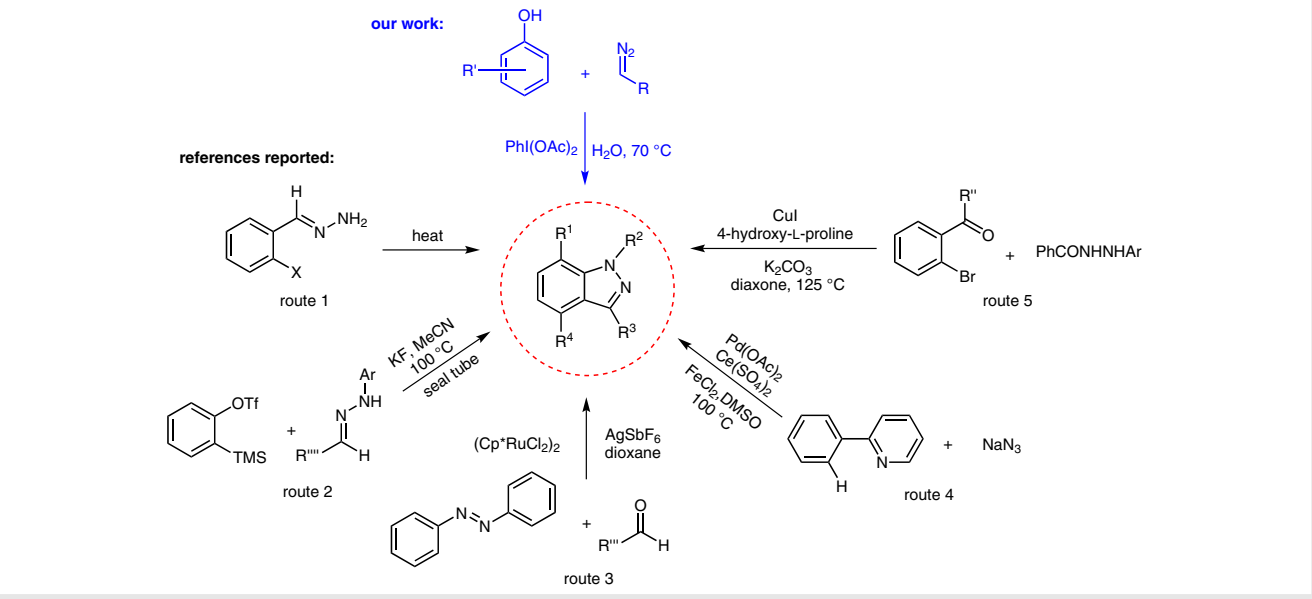
Figure 1 Indazole derivatives with bioactivities

Versatile synthetic methods have been reported for indazoles to accelerate their applications in the pharmaceutical industry.[11] Representative methods developed recently are depicted in Scheme 1.[12–18] Intramolecular cyclization (Scheme 1, route 1)[12] is mostly used for the construction of indazole fragments; however, it commonly involves three to four steps under harsh conditions as well as the use of dangerous reagents such as hydrazine. Recently, Larock reported[13–15] the synthesis of indazoles by the [3+2] cycloaddition with aryl hydrazones and arynes in situ (Scheme 1, route 2) under mild conditions, which was a concise protocol but still using toxic solvents such as acetonitrile. The Ellman group at Yale university reported[16] an attractive method for the synthesis of indazoles using $[RhCp^*Cl_2]_2$ as the effective catalyst which is a relatively expensive metal catalyst. Jiao and his co-workers at Peking university reported a method using C–H activation for preparing indazoles (Scheme 1, route 4).[18] Ma's group reported a new approach for the preparation of indazole derivatives using copper(I) salt as catalyst in 2012 (Scheme 1, route 5).[17] All routes for the construction of indazoles are very effective, but most of them require harsh conditions, metal catalysts, or toxic solvents, etc.

An one-pot synthesis of benzo[*d*]isoxazole-4,7-diols using iodine(III)-mediated [3+2] cyclization has been reported[19] in Liu's group. Iodobenzene diacetate [$PhI(OAc)_2$, DIB], one of the most important and commercially available representatives of aryliodine(III) carboxylates, is a mild oxidizing agent used for various selective oxidative transformations of complex molecules.[20] In this paper, a facile synthesis of 1*H*-indazole-4,7-diol via iodobenzene diacetate mediated [3+2] cycloaddition from phenol and diazomethyl benzene in water is reported. The approach described here is robust and avoids the use of dangerous and costly reagents, and water as the green solvent is more environment-friendly and safer.

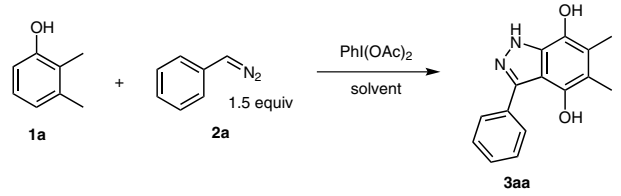
2,3-Dimethylphenol (**1a**) and diazomethyl benzene (**2a**) prepared according the literature[21] were chosen as the reactants, and mixtures of acetonitrile and water were initially selected as solvents to investigate the proposed [3+2] cycloaddition reaction (Table 1). The amount of iodobenzene diacetate was determined as two equivalents based on the mechanism of the reaction proposed in Scheme 2.[15] Unfortunately, acetonitrile mixed with water as solvents (Table 1, entries 1–3) did not generate any anticipated new products no matter what solvent ratio was employed. However, only water as solvent supplied the desirable product **3aa** in a moderate yield of 66% (Table 1, entry 4). We screened reaction times from 6–10 hours under aqueous conditions at room temperature (Table 1, entries 4–6), but no significant effect was observed. By raising the reaction temperature to 70 °C (Table 1 entry 8), the yields of **3aa** were obviously increased to 82%. Considering the solubility of different reactants, we screened the reaction solutions under the mixtures of water with THF, DMF or DMSO (Table 1, entries 10–12). By using water mixed with THF (Table 1, entry 12), **3aa** was obtained in the yield of 85%. Meanwhile, it was found that the yields of **3aa** achieved 91% and 92%, respectively, with the addition of 1% (v/v) trifluoroacetic acid (Table 1, entries 9 and 13), while the use of base, such as triethylamine, obtained the opposed effect (Table 1, entry 14).

Once we obtained the optimal one-pot approach for the iodine(III)-mediated [3+2] cyclization reaction, versatile indazole derivatives were successfully synthesized according to the following procedure.[22] Compound **1a** (1.0 mmol) in



Scheme 1 Synthetic methods of indazole derivatives

Table 1 Screening Studies for Optimal Conditions

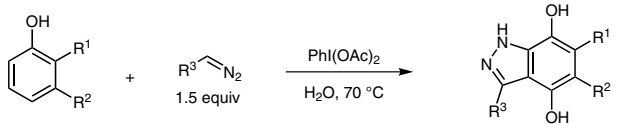


Entry	Solvent	Temp (°C)	Time (h)	Additive	Yield (%)[a]
1	MeCN–H_2O (2:1)	25	6		none
2	MeCN–H_2O (10:1)	25	6		none
3	MeCN–H_2O (1:10)	25	6		none
4	H_2O	25	6		66
5	H_2O	25	8		69
6	H_2O	25	10		68
7	H_2O	50	8		75
8	H_2O	70	8		82
9	H_2O	70	8	1% TFA	91
10	H_2O–DMF (10:1)	70	8		71
11	H_2O–DMSO (10:1)	70	8		61
12	H_2O–THF (10:1)	70	8		85
13	H_2O–THF (10:1)	70	8	1% TFA	92
14	H_2O–THF (10:1)	70	8	1% Et_3N	72

[a] Yield after column chromatography.

12 mL of water with 1% v/v trifluoroacetic acid was first treated with DIB (2.0 mmol) for 2 h at r.t. to form benzoquinone, and then 1.5 mmol of **2a** was added at room temperature. The reaction was continued for eight hours at 70 °C, and the desired product **3aa** was obtained after the addition of 2.0 mmol of $Na_2S_2O_3$ in 8 mL of water for overnight at room temperature (Table 1, entry 9). Afterwards, the scope of this reaction was systematically investigated on the basis of our previous report. It was determined that our protocol was suitable for versatile diazomethyl benzene substrates (Table 2), and the corresponding products were obtained in good to excellent yields. It was found that the substituents of diazomethyl benzene contributed positive effects to the yields of products (Table 2, entries 2–10). Alkyl and alkoxyl substitutions contributed to the high yields up to 93% (Table 2, entries 2–4). Single or multiple chloro or fluoro substitutions slightly or significantly decreased the yields (Table 2, entries 5–7), while other electron-donating groups, such as acetamido, presented a good yield (Table 2, entry 8). Meanwhile, heteroaromatic diazomethyl such as 4-pyridyl yielded the anticipated compound in good yield (Table 2, entry 9), as did the alkyl example (Table 2, entry 10). Phenol variabilities were next studied (Table 2, entries 11–18), and it was found that less alkyl substitution clearly resulted in low yields. In spite of the different structures of diazo employed, tetrahydronaphthol (**1b**) was found to give good to excellent yields of anticipated products (Table 2, entries 11–16). When there was only one substituent at the 2- or 3-position of phenol, two isomers of the 5- and 6-substituted indazoles were simultaneously produced (Table 2, entry 18).

Table 2 Synthesis of 3-Substituted 1*H*-indazole-4,7-diols

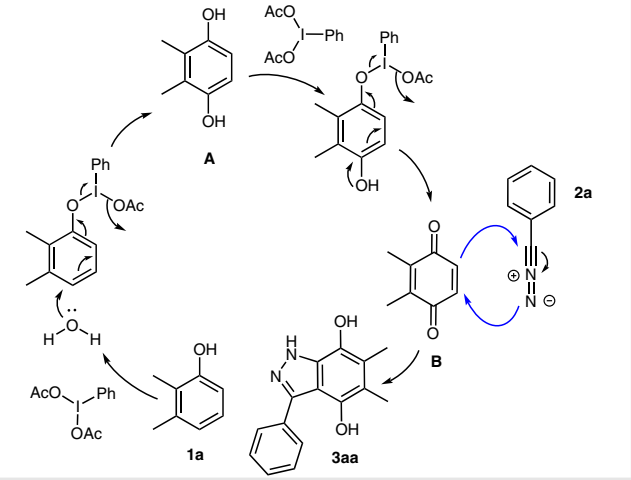


Entry	**1** R^1, R^2	**2** R^3	Product **3**	Yield (%)[a]
1	**1a** Me, Me	**2a** Ph	**3aa**	91
2	**1a**	**2b** 4-MeC_6H_4	**3ab**	89
3	**1a**	**2c** 4-*i*-PrC_6H_4	**3ac**	93
4	**1a**	**2d** 4-$MeOC_6H_4$	**3ad**	92
5	**1a**	**2e** 3-ClC_6H_4	**3ae**	77
6	**1a**	**2f** 2,5-$Cl_2C_6H_3$	**3af**	79
7	**1a**	**2g** 4-FC_6H_4	**3ag**	64
8	**1a**	**2h** 4-$AcNHC_6H_4$	**3ah**	81
9	**1a**	**2i** 4-Py	**3ai**	79
10	**1a**	**2j** $(CH_2)_3Ph$	**3aj**	90
11	**1b** -$(CH_2)_4$-	**2a**	**3ba**	94
12	**1b**	**2c**	**3bc**	89
13	**1b**	**2d**	**3bd**	91
14	**1b**	**2e**	**3be**	85
15	**1b**	**2f**	**3bf**	81
16	**1b**	**2i**	**3bi**	82
17	**1c** H, H	**2a**	**3ca**	53
18	**1d** Me, H	**2a**	**3da**	67

[a] Yield after column chromatography.

Our proposed mechanism for the construction of indazoles through [3+2] cycloaddition is depicted in Scheme 2. Water, as a nucleophile, first attacked **1a**, and then aided by 1.0 equivalents DIB to afford dihydroxybenzene **A**. It is believed that alcohol solvents such as methanol will induce the ether linkage on **A**. Subsequently, an excess amount of DIB (1.0 equiv) was continuously added for oxidation of phenolic hydroxyl groups, and benzoquinone **B** was achieved in water. Ultimately, a [3+2] cycloaddition between **2a** and **B** successfully occurred to afford anticipated product **3aa**.

In summary, we presented an efficient and environment-friendly method for the synthesis of 1*H*-indazole-4,7-diols by iodine(III)-mediated [3+2] cycloaddition in water. Versatile indazole derivatives were synthesized in moder-



Scheme 2 Proposed mechanism of one-pot synthesis of 1*H*-indazole-4,7-diols

ate to excellent yields by phenol and diazomethyl benzene condensation in one pot. Further investigations to increase the scope of this methodology and its applications are under way in our research group.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560596.

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(22) **Procedure of Preparing Compound 3ab**

DIB (644 mg, 2.0 mmol) was added to a solution of compound **1a** (112 mg, 1.0 mmol) in TFA (12 mL) and H_2O (1%, v/v). After the mixture was stirred for 2 h at r.t., compound **2b** (198 mg, 1.5 mmol) was added. The resulting solution was stirred for another 8 h at 70 °C. After the addition of $Na_2S_2O_3$ (2.0 mmol) in H_2O (8 mL), the mixture was poured into brine (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine (2 × 50 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by silica gel (MeOH–CH_2Cl_2, 1:100) to obtain the product **3ab** (238 mg, 89% yield). ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.49 (s, 1 H, OH), 7.80 (d, *J* = 8.2 Hz, 2 H, ArH), 7.29 (d, *J* = 8.0 Hz, 2 H, ArH), 2.42 (s, 3 H, $ArCH_3$), 2.36 (s, 6 H, $ArCH_3$). ^{13}C NMR (126 MHz, acetone-d_6): δ = 170.94, 151.29, 145.24, 140.56, 130.94, 130.42, 130.32, 130.14, 129.32, 125.57, 21.84, 21.46. HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{17}N_2O_2$ [M + H]$^+$: 269.1285; found: 269.1284.