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SHORT COMMUNICATION

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A Tandem Strategy for the Synthesis of 1*H*-Benzo[*g*]indazoles and Naphtho[2,1-*d*]isoxazoles from *o*-Alkynylarene Chalcones

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o-Alkynylarene chalcones when treated with hydrazines and hydroxylamine in the presence of iodine gave 1*H*-benzo[*g*]indazoles and naphtho[2,1-*d*]isoxazoles, respectively. The transformations involve tandem oxidative cyclocondensation/electrophilic hydroarylation. The methodology was applied to quinoline-based chalcones, which also afforded the corresponding quinoline-fused benzindazole and benzisoxazole.

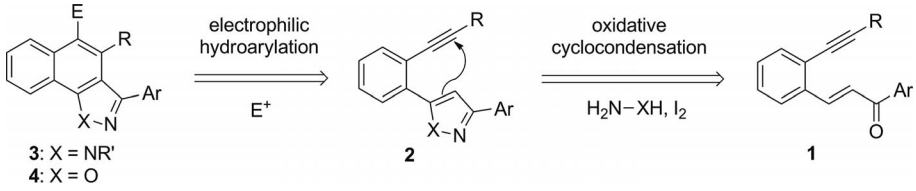
Introduction

Indazole and benzisoxazole cores are found in a large number of biologically active compounds,[1] including the drugs/drug candidates granisetron,[2] adjudin,[3] gamendazole,[4] zonisamide,[5] risperidone,[6] and paliperidone.[7] Thus, it is not surprising that numerous methods have been reported for the synthesis of these scaffolds.[8] In contrast, only a limited number of reports are available for the synthesis of their benzo-fused derivatives, viz., benzindazoles and naphthisoxazoles.[9] This prompted us to develop a generalized synthetic method for these two classes of heterocycles.

o-Alkynylarene chalcones **1** are versatile synthons, and their synthetic potentials have been exploited for the construction of certain carbo- and heterocyclic frameworks.[10] We envisaged that chalcones **1** could be converted into benzo[*g*]indazoles (**3**) and naphtho[2,1-*d*]isoxazoles (**4**) in two steps, as retrosynthetically proposed in Scheme 1. Accordingly, heterocycles **3** and **4** could be obtained from intramolecular electrophilic hydroarylation of intermediate alkynylarenes **2** having pyrazole and isoxazole moieties in the *ortho* position. This kind of hydroarylation is well known in the realm of alkynylarenes and can be achieved by using iodine reagents,[11] Brønsted acids,[12] or transition-metal compounds.[13] Alkynylarenes **2** could in turn be prepared by oxidative cyclocondensation of chalcones **1** with hydrazine or hydroxylamine. Reagents such as 2,2-diphenyl-1-picrylhydrazyl (DPPH),[14] air/DMSO,[15] iodine,[16] and sulfur[17] are known to effect this type of oxidative cyclocondensation. It would be possible to couple both steps in a tandem (or one-pot) manner if the proper choices of reagent and reaction conditions are made.

Results and Discussion

Starting chalcones **1** with various substitution patterns were prepared from the appropriate *o*-alkynylarene carboxaldehydes and acetophenones by standard procedures. Iodine was chosen as the reagent for carrying out the first oxidative cyclocondensation step, because it is also capable of bringing about the next hydroarylation step, and hence, the one-pot synthesis of the target heterocycles would be possible. Thus, an equimolar mixture of chalcone **1a** and phenyl hydrazine was heated under reflux in the presence of iodine (1.2 equiv.) in AcOH. Astonishingly, instead of expected alkynylarene **2a**, the final product, benzindazole



Scheme 1. Retrosynthetic route to 1*H*-benzo[*g*]indazoles and naphtho[2,1-*d*]isoxazoles.

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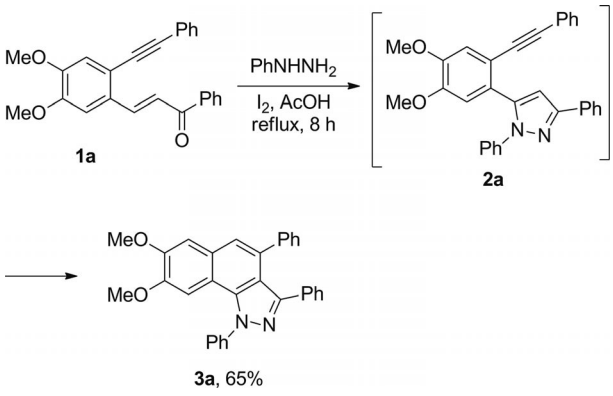
3a (E = H), was directly isolated in 65% yield after column chromatography (Scheme 2). This implied that intermediate alkynylarene **2a** formed in the first step underwent further electrophilic hydroarylation caused by AcOH (also by the co-product HI) to give benzindazole **3a**. Thus, both oxidative cyclocondensation and electrophilic hydroarylation had taken place in a tandem manner to give the final product.



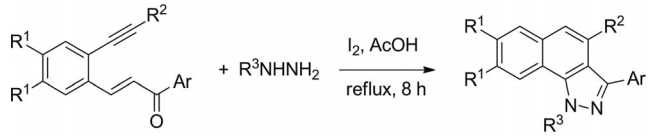
Scheme 2. Formation of benzindazole **3a** by tandem oxidative cyclocondensation/electrophilic hydroarylation.

No iodine-incorporated benzindazole (E = I) could be observed, even when up to 10 equiv. of iodine were used in the reaction (obviously, H^+ wins over I^+ as the electrophile). When other iodinating agents such as NIS and PhI-$(OAc)_2$ were used, the first step itself was problematic, and the corresponding nonaromatized cyclocondensation product (pyrazoline) was obtained instead of **2a**. When MeOH (or EtOH) was used as the solvent, final product **3a** was obtained in about 40% yield. The formation of **3a** in the absence of AcOH indicates that the second hydroarylation step is triggered by the HI co-product that was formed during the first oxidative cyclocondensation step. Other solvents such as DMF, MeCN, 1,2-dichloroethane (DCE), and dichloromethane (DCM) did not give any trace amounts of **3a**. Thus, we stuck to the original conditions in spite of the moderate yield and set out to investigate the scope of the reaction.

Other *o*-alkynylarene chalcones **1b**–**d** bearing OMe and Br substituents at different positions all reacted smoothly with phenyl/4-bromophenyl hydrazines under the prevailing conditions to afford corresponding benzo[*g*]indazoles **3b**–**f** in yields ranging from 60 to 73% (Table 1, entries 2–6). However, chalcone **1e** having a NO_2 substituent on the Ar ring did not provide expected benzindazole **3g** (Table 1, entry 7; the reaction stopped at the initial hydrazone stage). Chalcone **1f**, which bears no substituent on the aryl rings, also afforded corresponding benzindazole **3h** in 68% yield (Table 1, entry 8). Chalcone **1g**, which has an alkyl-yne unit, was also tested; however, corresponding benzindazole **3i** could not be obtained in pure form, as it decomposed readily (Table 1, entry 9). Chalcone **1a** was also treated with hydrazine hydrate to furnish benzindazole **3j** in 67% yield (Table 1, entry 10). The products were all characterized by various spectroscopic techniques, and for product **3h**, the structure was unequivocally confirmed by single-crystal X-ray analysis (Figure 1).

To support the involvement of tandem oxidative cyclocondensation/electrophilic hydroarylation reactions in the methodology, we performed the following experiments (Scheme 3). Intermediate (*o*-alkynylaryl)pyrazole **2e** was synthesized separately by subjecting chalcone **1d** to cyclocondensation with phenylhydrazine and then oxidizing the resulting pyrazoline by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). When **2e** was heated under reflux in AcOH for 2 h, benzindazole **3e** was produced in 68% yield, whereas upon treatment with iodine in DCM at room temperature for 8 h, it afforded iodobenzindazole **5** in 85% yield. These reactions clearly demonstrate that **2e** was indeed formed as an intermediate in the course of the synthesis.

Table 1. Synthesis of benzo[*g*]indazoles **3a**–**j**.



Entry	Chalcone	R^1	R^2	Ar	R^3	Product, yield [%][a]
1	**1a**	MeO	Ph	Ph	Ph	**3a**, 65
2	**1b**	MeO	4-$MeOC_6H_4$	Ph	Ph	**3b**, 60
3	**1c**	MeO	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Ph	**3c**, 73
4	**1c**	MeO	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-BrC_6H_4[b]	**3d**, 61
5	**1d**	MeO	4-$MeOC_6H_4$	4-BrC_6H_4	Ph	**3e**, 64
6	**1d**	MeO	4-$MeOC_6H_4$	4-BrC_6H_4	4-BrC_6H_4[b]	**3f**, 60
7	**1e**	MeO	4-$MeOC_6H_4$	4-$O_2NC_6H_4$	Ph	**3g**, n.r.[c]
8	**1f**	H	Ph	Ph	Ph	**3**h, 68
9	**1g**	MeO	*n*Bu	Ph	Ph	**3i**, –[d]
10	**1a**	MeO	Ph	Ph	H[e]	**3j**, 67

[a] Isolated yield. [b] Used as its hydrochloride salt (NaOAc was also included to neutralize the salt). [c] No reaction. [d] Product **3i** could not be obtained in pure form. [e] Used as its hydrate.

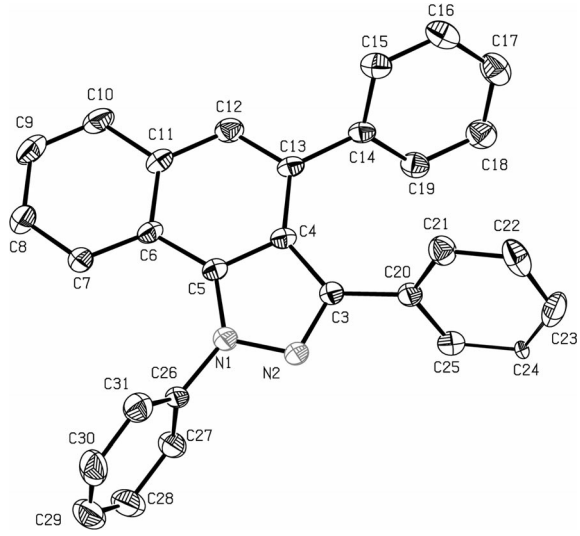
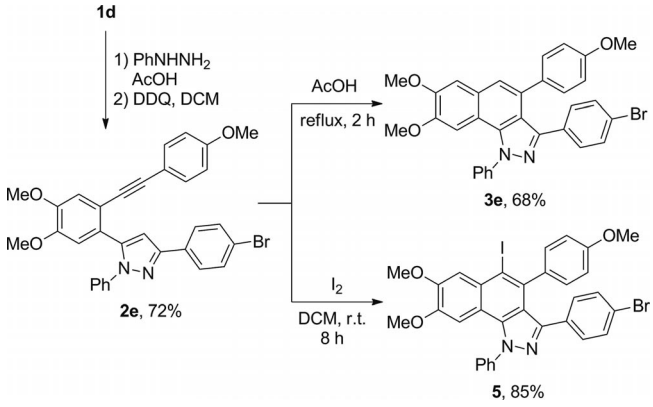


Figure 1. ORTEP plot of the crystal structure of **3h**.

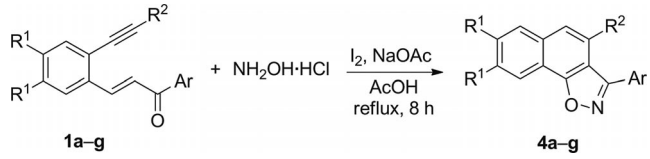


Scheme 3. Synthesis of intermediate **2e** and its reactions.

Next, we turned our attention to the synthesis of analogous naphtho[2,1-*d*]isoxazoles from *o*-alkynylarene chalcones. When chalcones **1a**–**d** were heated under reflux with hydroxylamine in the presence of iodine in AcOH (NaOAc was included to neutralize the hydroxylamine hydrochloride), respective naphthisoxazoles **4a**–**d** were isolated in 52–59% yields (Table 2, entries 1–4). Chalcone **1e** having a NO_2 substituent on the Ar ring did not afford naphthisoxazole **4e** (Table 2, entry 5). We were not able to isolate naphthisoxazole **4f** in pure form from the reaction of unsubstituted chalcone **1f** (Table 2, entry 6). Chalcone **1g** having an alkyl-yne unit furnished respective naphthisoxazole **4g** in 59% yield (Table 2, entry 7). The yields of the naphthisoxazoles produced are generally lower by about 10% relative to those of the benzindazoles.

Finally, we extended our methodology to quinoline-based chalcone **6**. When treated with phenylhydrazine and hydroxylamine, chalcone **6** also smoothly underwent the tandem oxidative cyclocondensation/electrophilic hydroarylation sequence to give quinoline-fused benzindazole **7** and benzisoxazole **8** in 58 and 55% yield, respectively (Scheme 4).

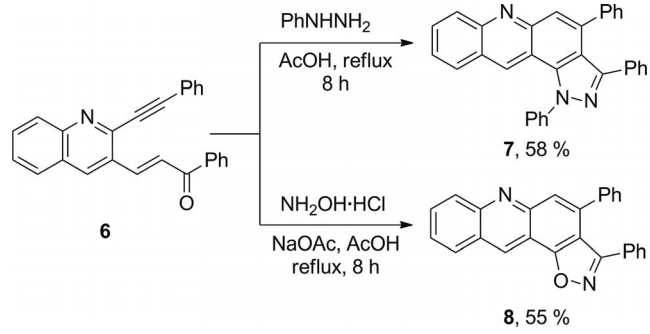
Table 2. Synthesis of naphthisoxazoles **4a**–**g**.



1a–g **4a–g**

Entry	Chalcone	R^1	R^2	Ar	Product, yield [%][a]
1	**1a**	MeO	Ph	Ph	**4a**, 54
2	**1b**	MeO	4-$MeOC_6H_4$	Ph	**4b**, 52
3	**1c**	MeO	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**4c**, 57
4	**1d**	MeO	4-$MeOC_6H_4$	4-BrC_6H_4	**4d**, 59
5	**1e**	MeO	4-$MeOC_6H_4$	4-$O_2NC_6H_4$	**4e**, n.r.[b]
6	**1f**	H	Ph	Ph	**4f**, –[c]
7	**1g**	MeO	*n*Bu	Ph	**4g**, 59

[a] Isolated yield. [b] No reaction. [c] Product **4f** could not be isolated in pure form.



Scheme 4. Synthesis of quinoline-fused benzindazole **7** and benzisoxazole **8**.

Conclusions

We have developed an iodine-mediated tandem method for the facile synthesis of 1*H*-benzo[*g*]indazoles and naphtho[2,1-*d*]isoxazoles from *o*-alkynylarene chalcones. When treated with arylhydrazine/hydrazine/hydroxylamine, these chalcones underwent oxidative cyclocondensation to yield *o*-alkynylarylpyrazoles/oxazoles as intermediates, which underwent electrophilic hydroarylation to afford the benzindazoles and naphthisoxazoles. The methodology could be extended to the synthesis of hybrid heterocycles such as quinoline-fused benzindazoles and benzisoxazoles. Work is in progress to explore other possibilities of this methodology.

Experimental Section

General Procedure for the Synthesis of 1*H*-Benzo[*g*]indazoles and Naphtho[2,1-*d*]isoxazoles: To a solution of *o*-alkynylarene chalcone (0.25 mmol) in acetic acid (3 mL) was added iodine (0.3 mmol) and phenylhydrazine, *p*-bromophenylhydrazine hydrochloride, hydrazine hydrate, or hydroxylamine hydrochloride (0.3 mmol) [when *p*-bromophenylhydrazine hydrochloride or hydroxylamine hydrochloride was used, NaOAc (0.3 mmol) was also included to neutralize the hydrochloride salt]. The reaction mixture was heated under reflux for 8 h, then cooled to room temperature, diluted with water,

neutralized with aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with saturated $Na_2S_2O_3$ solution, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; EtOAc/hexane, 1:9) to afford the pure compound.

7,8-Dimethoxy-1,3,4-triphenyl-1*H*-benzo[*g*]indazole (3a): Yield 65%, light-yellow solid, m.p. 185–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.0 Hz, 2 H),7.64 (t, J = 7.6 Hz, 2 H), 7.59–7.57 (m, 1 H), 7.43 (s, 1 H), 7.29 (s, 1 H), 7.25–7.02 (m, 10 H), 6.95 (s, 1 H), 4.00 (s, 3 H), 3.52 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 148.5, 147.7, 141.8, 139.6, 137.8, 133.7, 133.1, 129.6, 129.4, 129.1, 128.7, 128.2, 127.5, 127.3, 127.0, 126.7, 122.9, 116.9, 114.4, 108.2, 102.8, 55.9, 55.3 ppm. HRMS (ESI): calcd. for $[C_{31}H_{24}N_2O_2 + H]^+$ 457.1911; found 457.1916.

CCDC-911852 (for **3h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra of all compounds.

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