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Environmentally Benign Synthesis of Indeno[1,2-*b*]quinolines via an Intramolecular Povarov Reaction

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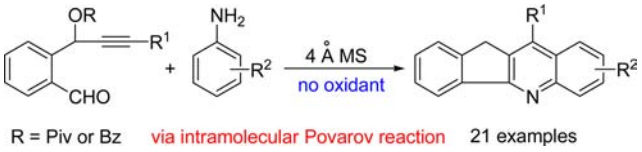
ABSTRACT



A new synthetic route to indeno[1,2-*b*]quinolines via reactions of *o*-propargylbenzaldehydes with *N*-aryl amines based on an intramolecular aza-Diels–Alder (Povarov) reaction has been developed. This method offers several advantages such as no requirement for an oxidant, high efficiency, and a wide reaction scope.

Quinoline ring systems occur widely in natural products, and many of them show interesting biological activities.[1] In particular, quinoline rings condensed with various heterocycles or carbocycles are of significant interest since they have been found to be potentially useful as anticancer agents by acting as DNA ligands.[2] For example, indenoquinoline **A** possesses cytotoxic properties with *in vivo* activity in colon 38 tumors.[2c] Indenoquinoline **B** exhibits cytotoxicities comparable to that of camptothecin against MCF-7 cells[2d] (Figure 1). Owing to their biological importance, much effort has been devoted to develop more efficient and convenient strategies for the synthesis of quinolines.[3] Classical methods, such as Skraup,[4a] Combes,[4b] Friedländer,[4c] Pfitzinger,[4d] and Doebner–von Miller[4e] reactions, are frequently employed. However, usually they do not allow the formation of quinolines with

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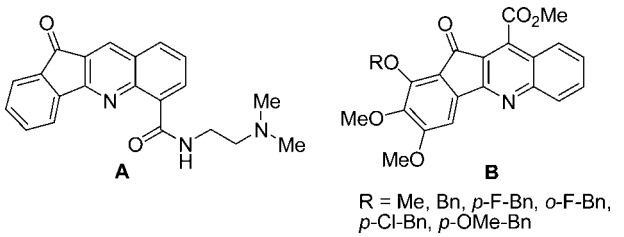
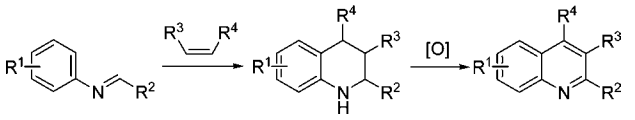


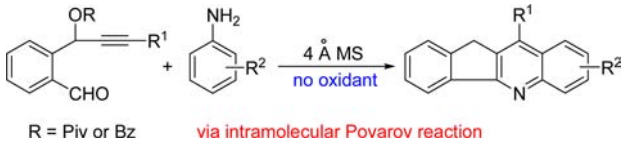
Figure 1. Biologically active indeno[1,2-*b*]quinolines.

wide diversity. Recently, the Povarov reaction,[5−7] an inverse electron-demand aza-Diels−Alder (IED-DA) reaction of *N*-aryl imines derived from aldehydes and anilines with electron-rich olefins, became one of the most efficient protocols for quinoline preparation (Scheme 1). Alkynes could also be used as dienophiles in a Povarov reaction, although it is much less common than that of alkenes.[7] To furnish the quinoline structure, further oxidation of the initial formed tetrahydro/dihydroquinoline under aerobic conditions or using an additional oxidant is often needed. The imine substrate is also known to act as an oxidant by accepting hydrogen in the presence of acid catalyst, and the corresponding reduction product, the amine, would be a byproduct.[6n,o,7f,7g,7i] The Povarov reaction usually requires a Lewis acid or protic acid such as $BF_3 \cdot Et_2O$, $SnCl_4$, lanthanide triflates, Tf_2NH, or *p*-trifluoroacetic acid to activate the imine substrates, with the reactions under catalyst-free conditions being quite rare. Nevertheless, the development of more simple and practical methods with wide diversity is highly desired. In this communication, we present a novel synthetic route to indeno[1,2-*b*]-quinolines via reaction of *o*-propargylbenzaldehydes with

Scheme 1. Synthesis of Quinolines through the Povarov Reaction



Scheme 2. Synthesis of Indeno[1,2-*b*]quinolines without the Use of Oxidant



N-aryl amines; it is based on the intramolecular Povarov reaction (Scheme 2).

During our studies of transition-metal-catalyzed transformations of propargyl carboxylates,[8] we occasionally found that the reaction of *o*-propargylbenzaldehyde **1a** with 2 equiv of aniline in DCE at 80 °C for 23 h afforded, unexpectedly, a ring-condensed product of indeno[1,2-*b*]-quinoline **2a** in 38% yield (Table 1, entry 1). The unique structural features and potential bioactivity of indenoquinolines prompted us to investigate this condensation reaction under various conditions. The results are summarized in Table 1. To our delight, in the presence of 4 Å molecular sieves (Alfa, 3−5 mm beads, 30 grains, ca. 1.5 g for 0.3 mmol scale) as a water-removing agent, 86% of **2a** was obtained in DCE at 80 °C for 8 h (entry 2). Using 1.0 equiv of aniline, the yield of **2a** was reduced to 69% (entry 3). Decreasing the amount of molecular sieves resulted in a slightly lower yield of **2a** (83%, entry 5, ca. 1.0 g 4 Å molecular sieves was used). The solvent effect was also examined. The reaction could proceed in toluene, where 79% of the desired product **2a** was obtained (entry 6). However, the use of EtOH gave only a complex reaction mixture (entry 7). In order to understand the effect of protecting groups, reactions were carried out with Bz (**1b**), Ac (**1c**), and CO_2Me (**1d**) protected substrates. The reaction proceeded smoothly in these cases, with the yields of **2a** ranging from 58% to 83% (entries 8−10).

With the optimized reaction conditions in hand, we next investigated the reaction scope of this methodology.

During this process, we found that when Piv-protected substrates were employed, in some cases, it was difficult to obtain the desired products with high purity. However, the use of Bz-protected substrates could circumvent the purification problem. Thus we also used Bz-protected

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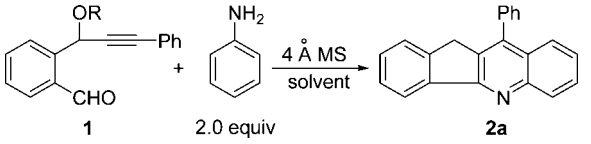
Table 1. Optimization Studies for the Formation of Indenoquinoline **2a**



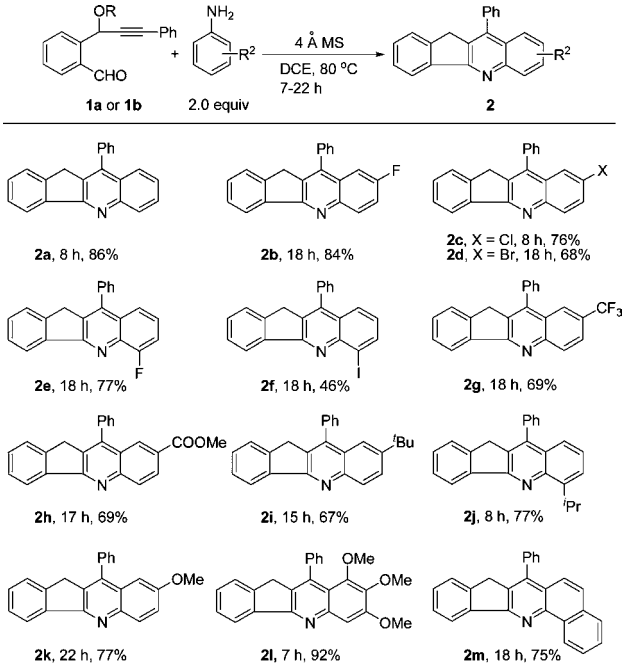
entry	R	MS (g)	solvent	temp (°C)	time (h)	yield (%)[a]
1	Piv (**1a**)	–	DCE	80	23	38
2	Piv (**1a**)	ca. 1.5	DCE	80	8	86
3[b]	Piv (**1a**)	ca. 1.5	DCE	80	9	69
4	Piv (**1a**)	ca. 1.5	DCE	50	9	82
5	Piv (**1a**)	ca. 1.0	DCE	80	6	83
6	Piv (**1a**)	ca. 1.5	toluene	80	4.5	79
7	Piv (**1a**)	ca. 1.5	EtOH	80	9.5	–[c]
8	Bz (**1b**)	ca. 1.5	DCE	80	7	83
9	Ac (**1c**)	ca. 1.5	DCE	80	7	68
10	COOMe (**1d**)	ca. 1.5	DCE	80	7	58

[a] 0.3 mmol scale. Isolated yields. [b] 1.0 equiv of $PhNH_2$ was used. [c] Complex reaction mixture was observed.

o-propargylbenzaldehydes as substrates in some cases to examine the reaction scope. As shown in Schemes 3 and 4, a wide variety of diversely substituted *o*-propargylbenzaldehydes and *N*-aryl amines were suitable for this reaction, furnishing the desired indeno[1,2-*b*]quinolines in generally good-to-high yields. We first examined the scope of *N*-aryl amine substrates (Scheme 3). The results indicated that both electron-poor and -rich aryl substituents were tolerated well, and the electronic nature on *N*-aryl rings did not have a strong influence on this reaction. For example, *p*-F, *p*-Cl, *p*-Br, *p*-CF_3, and *p*-CO_2Me substituted anilines afforded the corresponding products **2b**–**2d** and **2g**–**2h** in 68–84% yields. *p*-^{t}Bu and *p*-MeO-substituted anilines provided the corresponding **2i** and **2k** also in good yields of 67% and 77%, respectively. *Ortho*-substituted *N*-aryl amines such as 2-fluorobenzenamine or 2-isopropylbenzenamine afforded **2e** or **2j** in the same yield of 77%. However, the use of 2-iodobenzenamine resulted in only a 46% yield of **2f**. *Meta*-substituted anilines, such as 3,4,5-trimethoxybenzenamine underwent the reaction well with **1a** to afford **2l** in a high yield of 92%. When naphthalen-1-amine was used, a pentacyclic compound **2m** was obtained in 75% yield. Next, we examined the substituent effect (R^1) on the alkyne terminus (Scheme 4). Substrates with weak electron-withdrawing groups such as *p*-Cl on the aryl ring afforded **2n** in 76% yield, whereas with strong-electron-withdrawing groups, such as *p*-CF_3 or *p*-CO_2Et, the formation of **2o** and **2p** occurred in lower yields of 60% and 51%, respectively. The electron-rich *p*-MeO-substituted

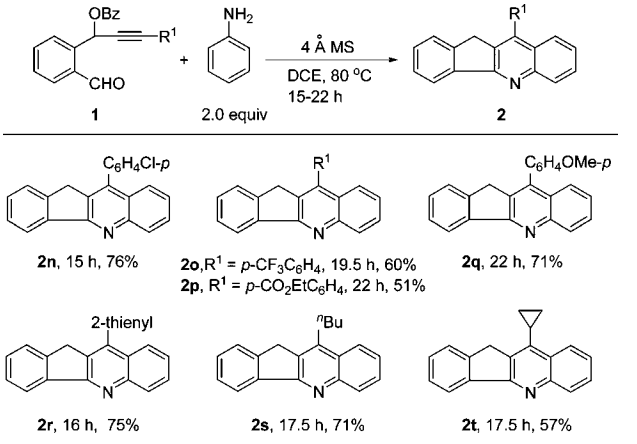
(9) (a) Reference 2h. (b) Malecki, N.; Carato, P.; Rigo, B.; Goossens, J.; Houssin, R.; Baillyc, C.; Hénicharta, J. *Bioorg. Med. Chem.* **2004**, *12*, 641. (c) Waldmann, H.; Karunakar, G. V.; Kumar, K. *Org. Lett.* **2008**, *10*, 2159. (d) Mohammadi, A. A.; Azizian, J.; Hadadzahmatkesh, A.; Asghariganjeh, M. R. *Heterocycles* **2008**, *75*, 947. (e) Yang, D.; Jiang, K.; Li, J.; Xu, F. *Tetrahedron* **2007**, *63*, 7654.

Scheme 3. Scope of *N*-Aryl Amines[a]



[a] Isolated yields. Substrate **1a** was used for **2a**, **2c**, **2i**, **2j**, and **2l**. Substrate **1b** was used for **2b**, **2d**–**h**, **2k**, and **2m**.

Scheme 4. Scope of *o*-Propargylbenzaldehydes[a]

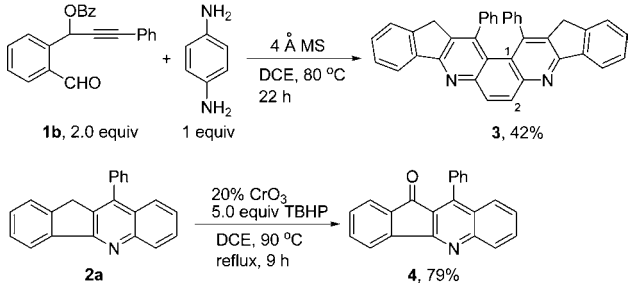


[a] Isolated yields.

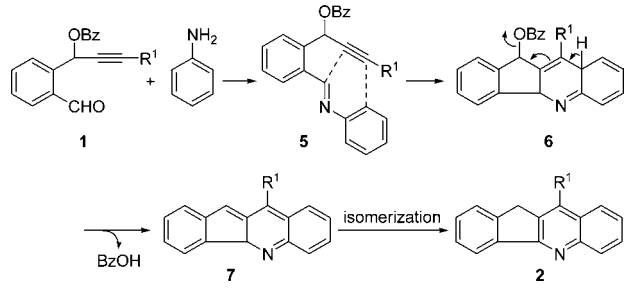
aryl alkyne provided **2q** in 71% yield. The results indicated that the electronic nature of the aryl rings on the alkyne terminus has a strong influence on this reaction. The 2-thienyl group was also compatible with this reaction, leading to **2r** in 75% yield. In addition, alkyl-substituted alkynes were also well accommodated. For example, an ^{n}Bu- or cyclopropyl-substituted alkynes afforded **2s** and **2t** in 71% and 57% yields, respectively. Most of the above indenoquinoline products are fluorescent, which could find utility also in organic materials synthesis. It should

(10) See Supporting Information.

Scheme 5. Formation of Polycyclic Compound and Further Transformation



Scheme 6. Possible Reaction Mechanism



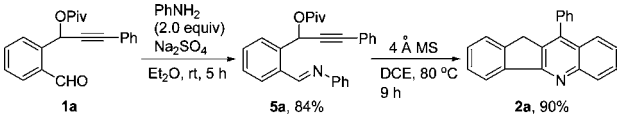
be noted that although indeno[1,2-*b*]quinolines can be prepared by the Pfitzinger reaction between an appropriate isatin and 1-indanone[2c,e–g] or a Friedländer reaction between a 2-aminobenzaldehyde or 2-aminoaryl ketone and 1-indanone,[9] the availability of the substrates employed in these methods can be quite limited, which restricts the structural elaboration of the indeno[1,2-*b*]quinolines, especially, on the quinoline ring moiety. The structures of **2h**, **2l**, and **2m** were unambiguously determined by X-ray crystallography.[10]

Interestingly, when benzene-1,4-diamine was employed, a hepta-fused-heterocyclic compound **3** was obtained in 42% yield as the major product, in which the second ring closure occurred at the C-1 position of the *N*-phenyl ring, but not at the C-2 position (Scheme 5). The structure of **3** was also confirmed by X-ray crystallography.[10] The regioselectivity in this case can be rationalized by invoking π-stacking of the aromatic groups during the second ring-closing process, leading to indenoquinoline **3** with two phenyl groups on the same side. To demonstrate the synthetic utility of indenoquinoline **2**, compound **2a** was subjected to the oxidation conditions.[11] It was found that the indeno[1,2-*b*]quinolin-11-one **4** was formed smoothly via oxidation of the bridged CH_2 group.

We proposed the following reaction mechanism for this reaction (Scheme 6). First, an imine **5** is formed via condensation of aldehyde **1** with aniline. Then an aza-Diels–Alder reaction (Povarov reaction) of the aza-diene moiety with the alkyne occurs to give a cyclized intermediate **6**. Subsequently, elimination of the OBz group[12] followed by double bond isomerization furnishes the final indenoquinoline **2**. In these reactions, no oxidant is required, since aromatization can be achieved by elimination of a leaving group and isomerization.

To understand the mechanism, the imine intermediate **5a** was isolated in 84% yield under controlled reaction conditions. **5a** cyclized under similar reaction conditions to afford **2a** in 90% yield (Scheme 7). These results supported our proposed mechanism.

Scheme 7. Control Experiments



In summary, we have successfully developed a facile synthetic strategy for indeno[1,2-*b*]quinolines based on an intramolecular Povarov reaction. Our reactions proceeded efficiently in the absence of oxidants. Aromatization was achieved by elimination of a leaving group and isomerization. A wide variety of substituents could be incorporated, which allows for a convenient structural modification of simple indenoquinolines. Further studies to extend the scope of the synthetic utility involving an intermolecular Povarov reaction are in progress in our laboratory.

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Supporting Information Available. Experimental details, spectroscopic characterization of all new compounds, and X-ray crystallography of compounds **2h**, **2l**, **2m**, and **3** are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.