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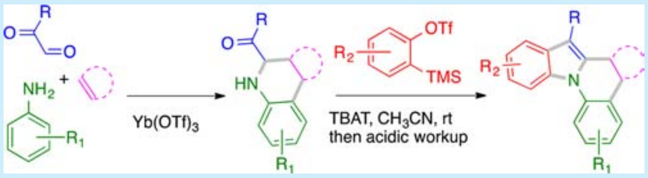
Three-Component Povarov Reaction–Heteroannulation with Arynes: Synthesis of 5,6-Dihydroindolo[1,2-*a*]quinolines

Ala Bunescu, Qian Wang, and Jieping Zhu*

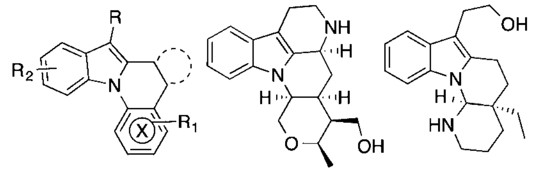
Laboratory of Synthesis and Natural Products, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne, Switzerland

S *Supporting Information*

ABSTRACT: A reaction of 2-acyl substituted tetrahydroquinolines, prepared by Lewis acid-catalyzed three-component reaction of α-oxo aldehydes, anilines, and dienophiles, with in situ generated arynes afforded 5,6-dihydroindolo[1,2-*a*]quinolines in good to excellent yields.



5,6-Dihydroindolo[1,2-*a*]quinolines **1** and its reduced or oxidized forms are structural units frequently found in bioactive natural products such as strychnohirsutine (**2**)[1] and goniomitine (**3**, Figure 1).[2,3] They also display interesting physical properties as semiconductors,[4] as dyes,[5] and as organic sensitizers for dye-sensitized solar cells.[6] Despite the development of a large number of synthetic methodologies for indoles,[7] methods allowing direct access to indolo[1,2-*a*]quinoline derivatives remained scarce.[8]

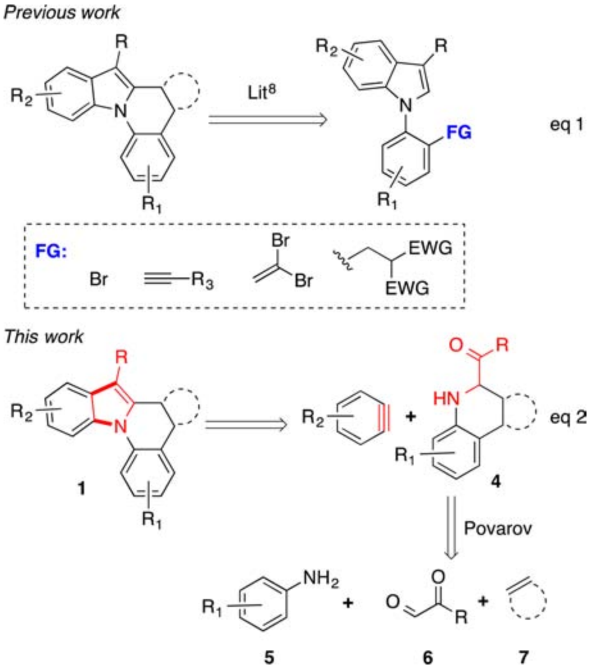


1 **2** Strychnohirsutine **3** Goniomitine

Figure 1. 5,6-Dihydroindolo[1,2-*a*]quinolines and related natural products.

Most of the recently reported syntheses of **1** involved the elaboration of appropriately functionalized *N*-arylindoles (eq 1, Scheme 1). In connection with our interests in indole[9] and indole alkaloid synthesis,[10] we recently reported a synthesis of *N*-aryl-2,3-disubstituted indoles via a formal [2 + 3] cycloaddition reaction between benzyne[11] and *N*-aryl-α-amino ketones with a wide application scope.[12,13] This novel heteroannulation reaction proceeds via formation of N1–C7a/C3–C4a bonds that offered an alternative bond-disconnection perspective in a more complex indole-containing polyheterocyclic setting. Indeed by applying this reaction as a key indolization step, the 5,6-dihydroindolo[1,2-*a*]quinoline (**1**) could be disconnected to benzyne and 2-acetyl tetrahydroquinoline **4**, the latter being readily accessible via three-component Povarov reaction (eq 2, Scheme 1). This strategy, allowing the construction of **1** in two steps from simple starting materials, is completely different from previous described ones and has an advantage being easily amenable to introduce the molecular diversity. Indeed, it has been amply demonstrated for the past two decades that the sequence of multicomponent reaction/postfunctionalization is particularly powerful for the construction of heterocyclic compound libraries.[14,15] Herein we report a straightforward synthesis of 5,6-dihydroindolo[1,2-*a*]quinolines from anilines **5**, glyoxal derivatives **6**, dienes **7**, and 2-(trimethylsilyl)phenyl triflates **8** as benzyne precursors.

Scheme 1. Synthetic Routes to 5,6-Dihydroindolo[1,2-*a*]quinolines



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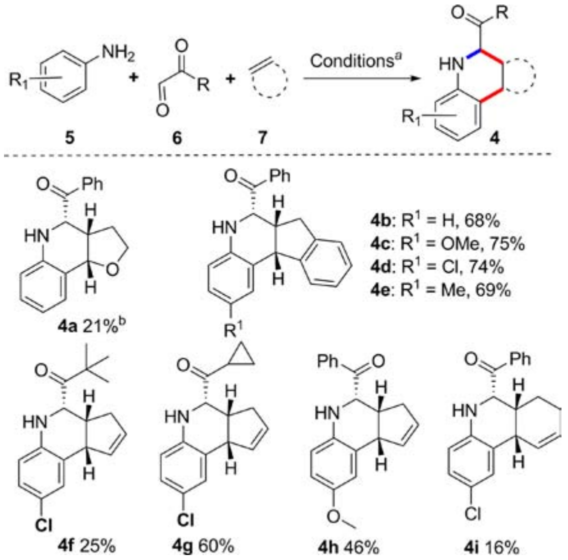
Many different conditions have been developed for performing the Povarov reaction,[16,17] including the enantioselective version.[18] There were nevertheless few reports dealing with the use of α-oxo aldehydes as one of the reaction partners.[18e,19,20] After several unsuccessful trials, the conditions developed by Kobayashi [Yb(OTf)$_3$ (0.1 equiv), MgSO$_4$ (6.5 equiv), MeCN, 0 °C][19] were found to be the most general. Using slightly modified literature procedures, the diversely substituted 2-acyl-tetrahydroisoquinolines **4** synthesized is depicted in Scheme 2.

Scheme 2. Synthesis of 2-Acyl-tetrahydroquinoline 4 by Three-Component Povarov Reaction



^{a}Conditions: Yb(OTf)$_3$ (0.1 equiv), MgSO$_4$ (6.5 equiv), MeCN, 0 °C then rt. ^{b}BF$_3$·OEt$_2$ (0.05 equiv), MgSO$_4$ (1.0 equiv), CH$_2$Cl$_2$, 0 °C then rt.

The all *cis* stereochemistry of these cycloadducts was based on the spectroscopic data that were in accord with the literature precedents.[19,20] The yield of **4** referred to the crystalline product obtained by direct crystallization of the crude product. Therefore, the actual yield might be higher than what was indicated in the scheme.

With these tetrahydroisoquinolines **4** in hand, the heteroannulation between **4** and benzynes was investigated. Applying our previously developed conditions [CsF (3.0 equiv), Cs$_2$CO$_3$ (2.0 equiv), 18-C-6 (1.1 equiv), isopropionitrile/dichloroethane (1/4), rt, then MeOH/CH$_2$Cl$_2$/AcOH (1/1/1), silica gel at 40 °C], the reaction of **4a** with 2-(trimethylsilyl)phenyl triflate (**8a**)[20] afforded indeed the desired compound **1a**, albeit in low yield (16%). The major product was *N*-aryl tetrahydroisoquinoline **9a**. It is reasonable to assume that formation of both products went through intermediate **10a**. While intramolecular nucleophilic addition followed by dehydration (pathway a) would produce **1a**, an intramolecular proton transfer (pathway b) of intermediate **10a** could account for the formation of **9a** (Scheme 3).[21]

To improve the yield of desired 5,6-dihydroindolo[1,2-*a*]quinoline **1a**, a brief survey of reaction conditions was carried out varying the fluoride sources (CsF, TBAT), the solvents, the temperature, and the reaction time. Some representative results are presented in Table 1. The optimum conditions for the above heteroannulation consisted of performing the reaction in acetonitrile (*c* 0.10 M) at room temperature in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT). Under these conditions, the desired product was isolated, after acidic treatment, in 57% yield.

Scheme 3. Synthesis of 5,6-Dihydroindolo[1,2-*a*]quinolines

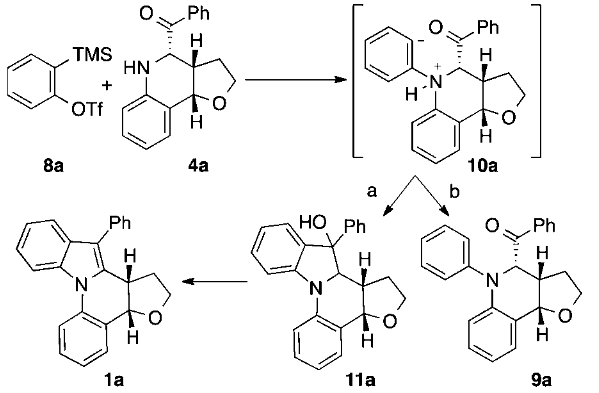


Table 1. Heteroannulation between 8a and 4a, Survey of Reaction Conditions^{a,b}

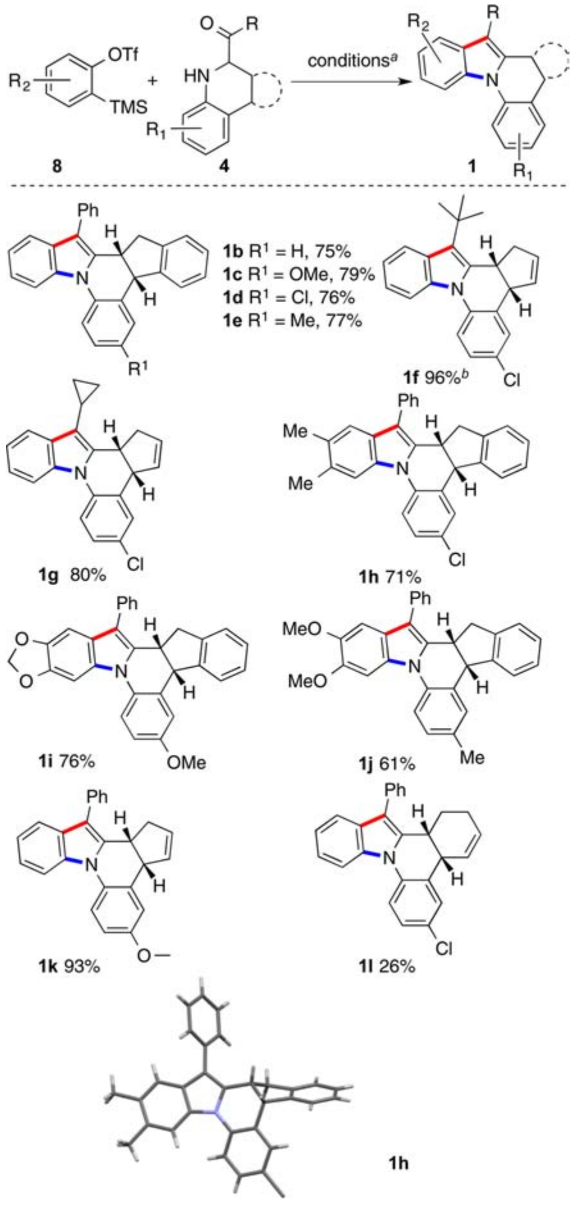
entry	additives	solvent, *t* (°C)	ratio **11a**/**9a**	yield of **1a**^{f}
1	CsF,18-C-6,^{c} Cs$_2$CO$_3$^{d}	*i*-PrCN/DCE (1/4),^{e} rt	0.5	16
2	CsF	CH$_3$CN, 65 °C	1.5	(46)^g
3	CsF	CH$_3$CH$_2$CN, 65 °C	1.2	(22)
4	TBAT	THF, 65 °C	0.5	(30)
5	CsF	CH$_3$CN, rt	2.2	52 (73)
6	TBAT	CH$_3$CN, rt	2.7	57 (77)

^{a}All reactions were carried out under Ar using **4a** (1.0 equiv), **8a** (1.5 equiv), CsF (3.0 equiv) or TBAT (1.5 equiv), solvent (*c* = 0.10 M). ^{b}The crude product was treated with MeOH/CH$_2$Cl$_2$/AcOH (1/1/1), silica gel, 40 °C. ^{c}1.1 equiv of 18-C-6. ^{d}2.0 equiv of Cs$_2$CO$_3$. ^{e}Solvent (*c* = 0.14 M). ^{f}Isolated yield. ^{g}In parentheses, NMR yield using CH$_2$Br$_2$ as an internal standard determined before acidic treatment.

The scope of the reaction was next examined using optimized conditions. The results are summarized in Scheme 4. Functionalized silyl aryl triflates were prepared following literature procedure.[22,23] As it is seen, the reaction tolerated a variety of functional groups and is insensitive to the electronic properties of the aromatic ring. Steric hindrance around the secondary amines is also well tolerated as reaction of **4f** having a pivaloyl group at C-2 position with **8a** afforded **1f** in excellent yield. In general, tetrahydroquinolines having a fused indene, cyclopetene rings (**4b**−**4h**) are better substrates than that having a fused furan ring (**4a**), furnishing the desired 5,6-dihydroindolo[1,2-*a*]quinoline derivatives (**1b**−**1k**) in good to excellent yields. However, reaction of **4i** having a cyclohexene unit with **8a** produced indoloquinoline **1l** in a low yield (26%). The structure of 5,6-dihydroindolo[1,2-*a*]quinolines **1h** was determined unambiguously by X-ray crystallographic analysis (Scheme 4).

In summary, we have developed a two-step synthesis of 5,6-dihydroindolo[1,2-*a*]quinolines **1** from simple starting materials. It features (a) a Lewis acid-catalyzed three-component Povarov reaction of α-oxo aldehydes, anilines and dienes; (b) a heteroannulation reaction between the Povarov adducts and benzynes. Five chemical bonds were created in this operationally simple two-step sequence. Since both indoles and quinolines are important core structures for pharmaceuticals,

Scheme 4. Scope of Benzannulation of Tetrahydroquinolines 4 with Arynes to 5,6-Dihydroindolo[1,2-*a*]quinolines 1



[a] All reactions were carried out under argon atmosphere using tetrahydroquinolines **4** (1.0 equiv), benzyne precursors **8** (1.4 equiv), TBAT (1.5 equiv), CH_3CN (*c* 0.10 M) at rt for 12−14 h; the crude reaction mixture was subsequently treated with MeOH/CH_2Cl_2/AcOH (1/1/1), silica gel at 40 °C. [b] The crude reaction mixture was treated with TFA, CH_2Cl_2, silica gel, rt.

we expected that a rapid synthesis of a hybrid structure could find application in medicinal chemistry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, product characterization data, ^1H and ^{13}C NMR spectra for new compounds, X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jieping.zhu@epfl.ch.

Notes

The authors declare no competing financial interest.

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