



One-pot construction of isoindolo[2,1-*a*]quinoline system

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ABSTRACT

Polycyclic compounds bearing isoindolo[2,1-*a*]quinoline system were easily prepared stereo- and regioselectively, and in one-pot, in a tandem fashion containing Povarov's multicomponent and condensation reactions. Involving a stepwise route for the aza Diels–Alder reaction within the synthesis was suggested.

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1. Introduction

Isoindolo[2,1-*a*]quinolines possess an array of biological activities. For instance, 5,11-dioxosubstituted isoindolo[2,1-*a*]quinolines **1** (Fig. 1) show protective effects against N₂-induced hypoxia,¹ and trihydroxyisoindolo[2,1-*a*]quinolines **2** have inhibitory activities against human topoisomerase II and bacterial DNA-gyrase.² Isoindolo[2,1-*a*]quinoline system is attractive not only as a potential bioactive target but also as an interesting synthetic compound. However, not many synthetic methods for this system have been reported. Methodologies for the preparation of isoindolo[2,1-*a*]quinolines often involve several stages and are basically not satisfactory in either generality or yield.³ The main purpose of this work was the preparation of isoindolo[2,1-*a*]quinoline system directly from *N*-aryl compounds. This interest fortunately led us to the novel synthesis of cyclopenta[*c*]isoindolo[2,1-*a*]quinoline-11-one derivatives **3** (Scheme 1) using simple and commercially available starting materials in one-pot (tandem type). Consequently, it is considered as a multicomponent reaction. Besides synthesis, this report will also present the proposed mechanism, characterization of polycyclics, further reactions in the system, and future works.

2. Results and discussion

3-Ethyl-11-oxo-cyclopenta[*c*]isoindolo[2,1-*a*]quinoline carboxylate **3** (Scheme 1) was synthesized by a multicomponent reaction

using ethyl-4-aminobenzoate, 2-carboxybenzaldehyde, and cyclopentadiene as starting materials in acetonitrile and in the presence of trifluoroacetic acid (2 equiv). Only one product was observed by TLC. After purification, structural elucidation using 1D NMR (¹H and ¹³C), 2D NMR (COSY, HSQC), and finally X-ray crystallography was performed. Exploring the regioselectivity of this reaction was our next interest. In the next reaction, 2-aminonaphthalene as amine was used with the same reagents and conditions (Scheme 2). After the appearance of only one product by purification, complete data analysis was performed using mass spectra, 1D NMR (¹H, ¹³C, DEPT), 2D NMR (COSY, HSQC, HMBC), and finally X-ray crystallography. Distinguishing **4** and **5** was not problematic by the simple fact that the aromatic hydrogens in **5** should show **2** singlets but this was not observed in the ¹H NMR.

It seems reasonable if we assume that this tandem reaction contains: (a) Schiff base formation from nucleophilic attack of amine

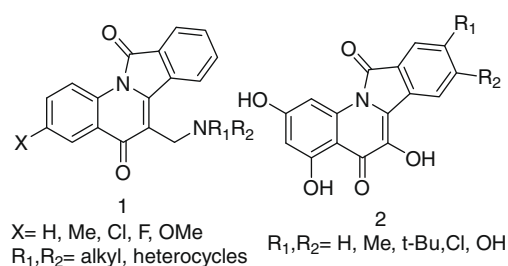
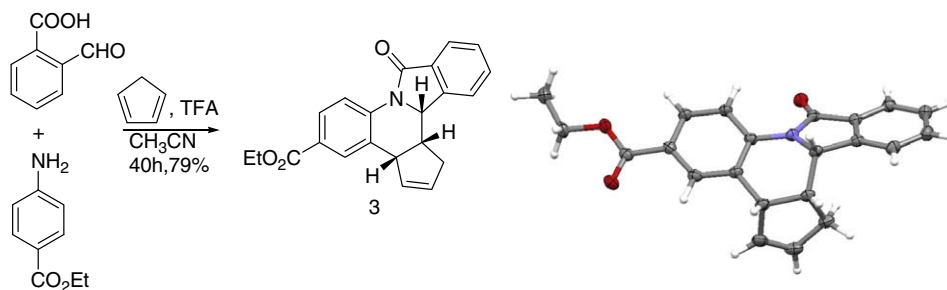


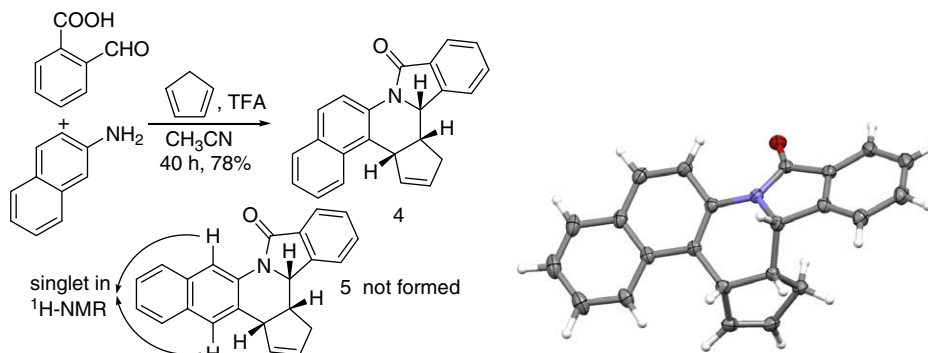
Figure 1. Bioactive isoindoloquinolines.

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Scheme 1. One-pot synthesis of pentacycle (isoindoloquinoline) **3** and its X-ray structure.



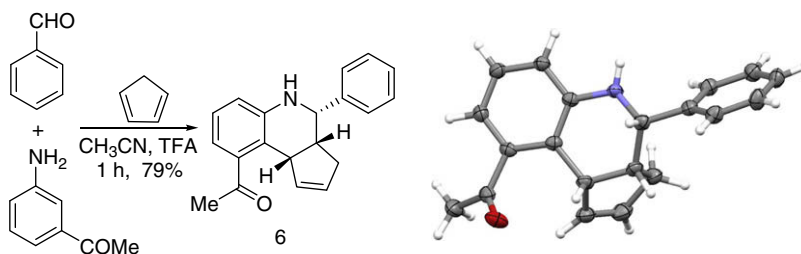
Scheme 2. Regioselective formation and X-ray structure of **4**.

to more reactive carbonyl function of 2-carboxybenzaldehyde, that is, aldehyde, (b) reaction of Schiff base with cyclopentadiene, and (c) intramolecular condensation (dehydration) of the generated secondary amine (located at tetrahydroquinoline core) to *o*-carboxylic acid function (formation of a γ -lactam ring), resulting in the construction of a whole polycyclic system. This mechanism, however, may simply be explained by a Povarov⁴-cyclocondensation tandem reaction.

The tetrahydroquinoline obtained through Povarov type of this reaction can be viewed as being formed through either a concerted inverse electron demand hetero Diels–Alder reaction or via a stepwise process beginning from the addition of an olefin to an iminium ion forming carbocation as an intermediate followed by an intramolecular electrophilic aromatic substitution (Friedel–Crafts) reaction to generate tetrahydroquinoline. Despite the initial proposed mechanism by Povarov and few groups in favor of the cycloaddition route,^{5–7} many other chemists found the stepwise route more complying with their observed results.^{8,9} Both mechanisms, however, can appropriately explain the regio- and/or stereoselectivity nature of the reaction.^{10,11} Almost all of the reported works on the mechanism of this reaction have emphasized their approach on the olefin and/or the aza-butadiene fragment but rarely on the aromatic ring. Our approach to the mechanism of the Povarov reaction and further synthesis of complex polycyclics considers the role of the aromatic substitutions.

For better understanding of stereo- and regioselectivity of the Povarov reaction, we performed this reaction with benzaldehyde, 3'-aminoacetophenone, cyclopentadiene as dienophile, and trifluoroacetic acid (1 equiv) in acetonitrile (Scheme 3). Tetrahydroquinoline tricyclic compound **6** generated only in one of its diastereomeric form. This compound was fully characterized by mass, 1D and 2D NMR, and finally X-ray crystallography. Therefore, tetrahydroquinoline **6** was afforded not only stereoselectively but also regioselectively. A more detailed stepwise mechanism for a better explanation is presented in Scheme 4. Intermediate **8** was initially generated from Schiff base **7** and cyclopentadiene. The electron demanding allylic carbocation **8** is stabilized by the neighboring group R on the aromatic ring affording **9** which after re-aromatization generates the product **10**. Carbocation **8** should not be a predominant intermediate unless by assistance from R. Otherwise, less crowded allylic carbocation would generate the product. Concerted [4+2] cycloaddition route would afford a mixture of regio-isomeric products due to free *N*-Ar bond rotation prior to addition.

The only remaining possibility for the unique formation of **6** is the stepwise route through carbocation **11** illustrated in Scheme 5. Non-bonding pairs of electrons in Oxygen of the keto group theoretically can stabilize **11** and make it the predominant carbocation intermediate. In fact, in our performed reaction, **11** must be the only generated carbocation. Electron-rich neighboring group orients in close proximity with allylic carbocation. The similar approach



Scheme 3. Regioselective formation and X-ray structure of **6**.

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