Tetrahedron Letters 50 (2009) 6661–6664

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 20 August 2009
Revised 11 September 2009
Accepted 13 September 2009
Available online 17 September 2009

Keywords:
Multicomponent reactions
Tandem reactions
Polycycles
Povarov reaction
Aza Diels–Alder reaction
Isoindoloquinoline system

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.

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 N_2-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 (^{1}H and ^{13}C), 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 (^{1}H, ^{13}C, 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 ^{1}H NMR.

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

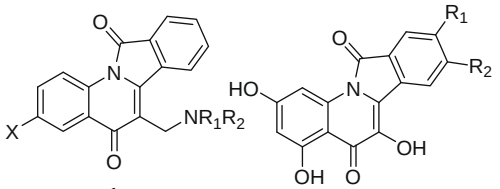

Figure 1. Bioactive isoindoloquinolines.

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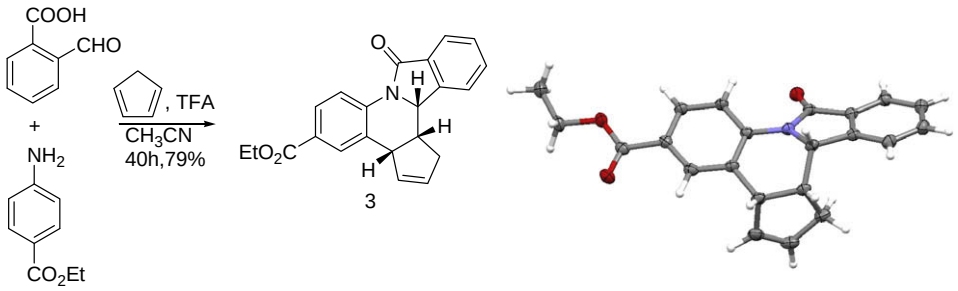
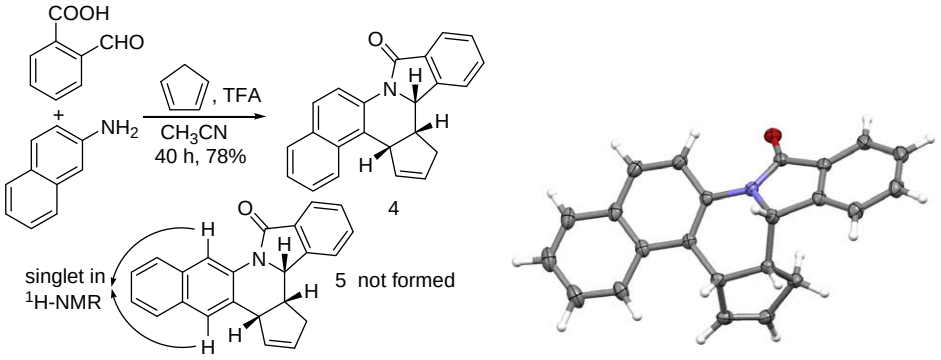
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2009.09.075



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



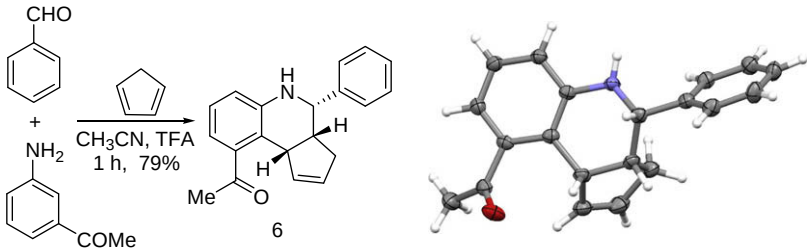
Scheme 2. Regioselective formation and X-ray structure of **4.**

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 Povarov[4]-cyclocondensation tandem reaction.

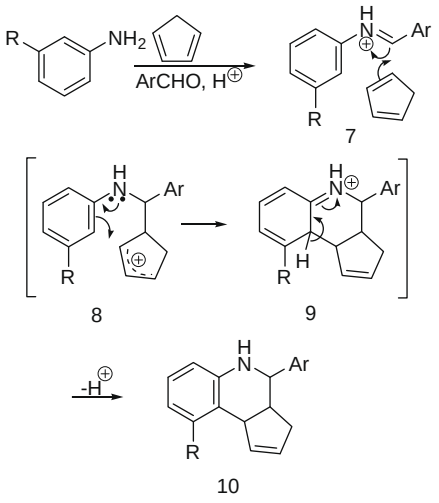
The tetrahydroquinoline obtained through Povarov type of this reaction can be viewed as being formed through either a concerted inverse electron demand hetero Diels–Alder reaction or via a stepwise process beginning from the addition of an olefin to an iminium ion forming carbocation as an intermediate 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.

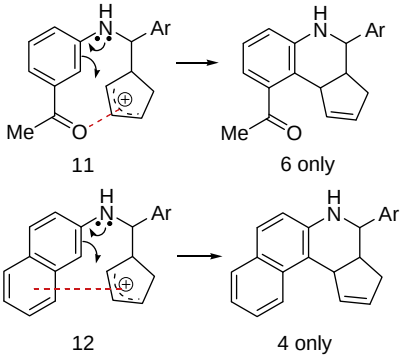
The only remaining possibility for the unique formation of **6** is the stepwise route through carbocation **11** illustrated in Scheme 5. Non-bonding pairs of electrons in Oxygen of the keto group theoretically can stabilize **11** and make it the predominant carbocation intermediate. In fact, in our 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**.



Scheme 4. Proposed role of substitution in the stepwise mechanism of Povarov reaction.

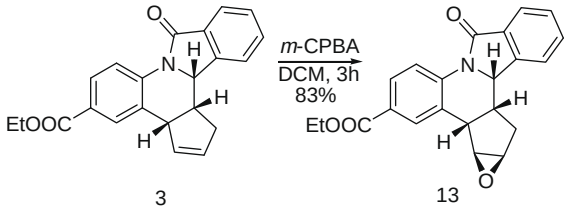


Scheme 5. Regioselectivity by stabilized carbocations.

may apply for product **4** by forming self-stabilized carbocation **12**. However, in this case there is actually no non-bonding pair(s) of the electron but only the electron-rich environment within naphthalene's second ring. This complete regioselectivity cannot be rationalized by a concerted cycloaddition mechanism. It should be noted that the complete diastereoselectivity in the construction of tetrahydroquinoline tricycles can be explained by the exclusive formation of Schiff base in its *E* form.

Pentacyclic compound **3** is a valuable scaffold in diversity oriented synthesis not only because it can be prepared in only one-pot, but also due to having several diversity sites. Moreover, it potentially contains an anchoring site needed for solid phase synthesis, that is, the carboxyl ester. One can imagine the potential diversification in both aromatic rings. Since we had already made the compound, we decided to explore some additional reactions on the double bond. Typical for alkenes, an addition reaction had to be designed. Chirality and the specific shape of **3** (see its X-ray in Scheme 1) enticed us to explore a stereoselective reaction. We decided to try epoxidation using *m*-CPBA on the double bond with desire to observe some stereoselectivity because of the difference between the two faces of **3**, that is, concave and convex faces. Epoxidation by *m*-CPBA smoothly proceeded in dichloromethane at room temperature (20 °C) and ended in 3 h (Scheme 6) resulting in **13**. Expecting some level of stereoselectivity, we observed only one compound. We believed that the epoxide ring is in β-position (as shown in Scheme 6).

The structure of compound **13** was determined by single-crystal X-ray diffraction (Fig. 2).[12]



Scheme 6. Stereoselective epoxidation of compound **3**.

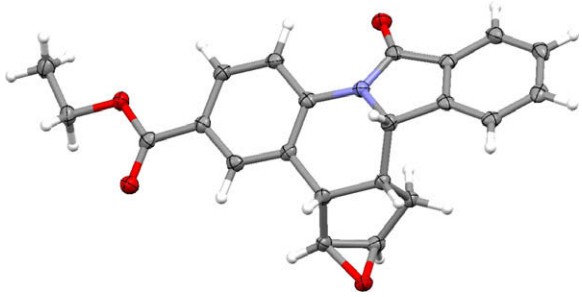
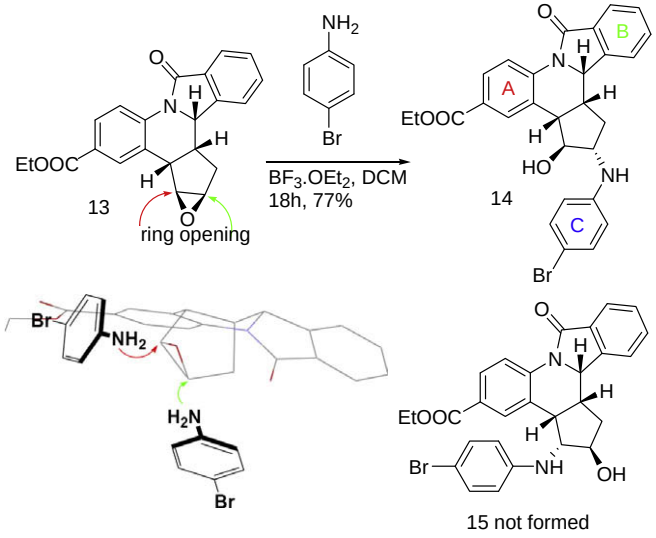


Figure 2. X-ray structure of compound **13**.

Since epoxide-opening reaction provides at least two diversity sites, any nucleophile capable of the reaction can be considered. For the ring opening, we decided to use *p*-bromoaniline; a good nucleophile having a symmetrical structure (easier for NMR assignment) which provides an additional secondary amine for diversification purpose. However, we did not know about the regioselectivity of the reaction. By looking at the structure of epoxide **13**, specially its X-ray structure (Fig. 2 and Scheme 7), it seems that there is a difference for α-nucleophilic attack between two sides of the epoxide ring. On the other hand, the size of the nucleophile also plays an important role in the regioselectivity.

As illustrated in Scheme 7, nucleophilic attack from the right side of the epoxide (green arrow) would give **14** and from the left (red arrow) provide its regioisomer (**15**). Interestingly, only one single compound appeared as the product confirming the complete regioselectivity was achieved. Compound **14** has some interesting features: (a) it has five stereogenic centers, (b) it has several diversity sites: (i) initial diversification may come from aromatic rings **A**



Scheme 7. Regioselective epoxide opening on compound **13**.

and/or **B**, (ii) nucleophile itself is a choice, in this situation **C** ring with bromine, (c) it generated further reaction possibilities; in this case hydroxyl, bromine, and secondary amine, and (d) it has a potential anchoring site for solid phase exploration, that is, carboxy-ester group which can easily be modified to become active in the loading process. In addition, the reaction was performed in only three stages and it proceeded with complete stereo- and regioselectivity.

In summary application of the well-known Povarov's multicomponent reaction to *o*-carboxybenzaldehyde followed by a condensation reaction in the same pot (a tandem reaction) leads to the stereo- and regioselective formation of polycyclic compounds containing isoindolo-[2,1-*a*]quinoline segment. For the purpose of diversity oriented synthesis, library designation has already been performed. The solid phase synthesis and any successful results on library generation will be submitted for publication once they are available.

Acknowledgments

This work was supported by the NRC Genomics and Health Initiative. S.K. thanks the University of Ottawa for financial support/scholarship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.075.

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12. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 729775, 729776, 729777, and 729778. Copies of the data can be obtained, free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; or e-mail: deposit@ccdc.cam.ac.uk].