Synthesis of Azafluorenone Antimicrobial Agents

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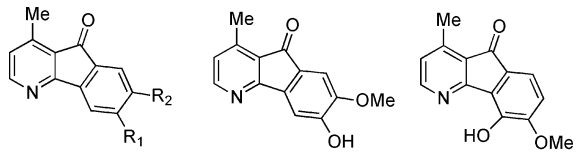
Received July 30, 2010

A flexible synthesis of the azafluorenone alkaloids **1**, **2**, **3**, and **4** is described.

The azafluorenones constitute a growing class of alkaloids.[1] Representative natural products of this class include compounds **1**−**5** as shown. Onychine (**1**) was active against *C. albicans* B311 with a MIC of 3.12 μg per milliliter.[2] In addition, compound **1** also exhibited antimicrobial activity against *S. aureus* NCTC 8530, *B. subtilis* IFO 3007, *Escherichia coli* IFO 3545, and *Saccharomyces cerevisiae* IFO 0203 in the range 50 to >100 μg per milliliter.[3] Polyfothine (**2**) shows DNA-damaging activity.[4] Isoursuline (**5**) exhibited antimalarial activity against *Plasmodium falciparum* at micromolar concentrations.[5] Both compounds **1** and **2** have been synthesized by Koyama using an acid-catalyzed rearrangement of the oxime *O*-allyl ether of an indanone.[6] Compound **1** has also been synthesized by way of intramolecular Friedel−Crafts reactions and organometallic coupling reactions.[7,8] Of particular note is the novel boronic acid coupling developed by Snieckus and co-workers.[9]



1: $R_1 = R_2 = H$
2: $R_1 = R_2 = OMe$
3: $R_1 = H$, $R_2 = OMe$

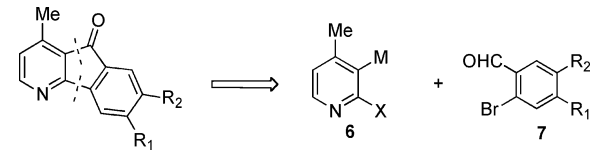
Our retrosynthetic analysis is depicted below in Scheme 1. The starting materials, substituted pyridines **6** and bromobenzaldehydes **7**, are either commercially available or are readily available in a few steps.

Initially, we envisioned a one-pot synthesis of the tricyclic skeleton **9** from 3-lithio-2-bromopyridine (**8**) and isovanillin, as shown in Scheme 2. Although the first step was successful, the intramolecular cyclization failed. Attempted cyclization of the corresponding benzophenone, prepared by Jones oxidation of the alcohol, also failed.

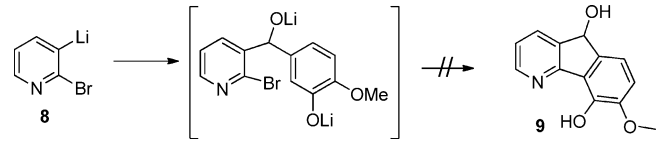
Interestingly, bromo ketone **10**, prepared in two steps from **8**, underwent an intramolecular Heck reaction to afford **11** in 40% yield, as shown in Scheme 3. This reaction was regioselective, providing only the isomer shown, as evidenced by the singlets for the para-hydrogens in the aromatic ring of **11**.

In order to develop a more general approach, the three-step synthesis illustrated in Scheme 4 was developed. It began with the reaction of an aldehyde with the anion derived by metal−halogen exchange between bromopyridine **12** and *n*-butyllithium.[10] This reaction afforded an unstable alcohol that was readily oxidized using manganese dioxide to generate ketone **13** in 86% yield over two steps, as shown in Scheme 4. An intramolecular Heck reaction[11] on bromo benzophenones **13a**−**13c** cleanly provided azafluorenones **1**, **2**, and **3** in 53%, 47%, and 50% yields, respectively.

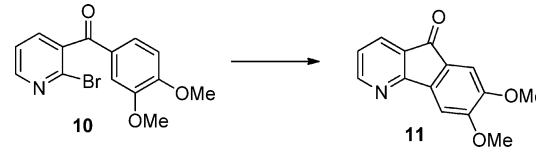
Scheme 1. Retrosynthetic Analysis



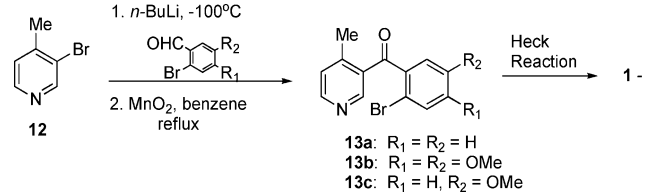
Scheme 2. First Approach to Azafluorenone Skeleton



Scheme 3. Model System Results

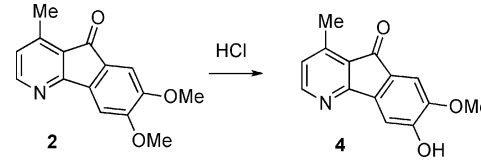


Scheme 4. General Synthesis of Azafluorenones



13a: $R_1 = R_2 = H$
13b: $R_1 = R_2 = OMe$
13c: $R_1 = H$, $R_2 = OMe$

Scheme 5. Synthesis of **4** from **2**



Natural product **4** was isolated from the stem barks of *Oncodostigma monosperma*.[12] This compound can be readily prepared from azafluorenone **2** using hydrochloric acid, as illustrated in Scheme 5.[13]

In conclusion, the synthesis of four azafluorenones has been achieved in three steps in good overall yields. Our synthesis of azafluorenones **1** and **2** is strategically distinct from previous syntheses. Our synthetic approach to azafluorenones is flexible and will permit the synthesis of a variety of analogues for additional antibacterial testing.

Experimental Section

General Experimental Procedures. Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Bromobenzaldehydes were made on the basis of literature

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10.1021/np100536a
Published on Web 10/21/2010

procedures without further modification. Tetrahydrofuran was distilled from sodium and benzophenone. All experiments were performed under an argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or a Varian 400 MHz instrument. Coupling constants (*J*) are reported in Hz with abbreviations s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Standard grade silica gel (60 Å, 32−63 μm) was used for flash column chromatography.

General Procedure for the Synthesis of 1−3. To a solution of 3-bromo-4-methylpyridine (**12**) (1 equiv) in THF (0.05 M) was added *n*-BuLi (1 equiv) at −100 °C. The mixture was stirred at this temperature for 10 min followed by the addition of bromobenzaldehyde (1 equiv) as a solution in THF. The reaction was warmed to 78 °C for 2 h and then stirred at rt for 8 h. The reaction was quenched with water and extracted with EtOAc. The organic phase was then washed with brine and dried over $MgSO_4$, followed by filtration and concentration in vacuo.

To the unpurified alcohol was added activated MnO_2 (5 equiv) in 50 mL of benzene. The solution was heated to reflux with a Dean−Stark trap for 18 h. The MnO_2 was filtered, and the solution was concentrated in vacuo. The residue was purified with silica gel flash chromatography (3:1−1:2 hexanes−EtOAc).

A solution of bromo-keto pyridine (1 equiv), TBAC (1.5 equiv), $Pd(OAc)_2$ (0.1 equiv), and base (1.5 equiv) in DMF (0.05 M) was heated and stirred until completion (TLC). After the reaction was complete, the solution was extracted with diethyl ether and washed with water, followed by brine, and dried over $MgSO_4$. The organic phase was filtered and concentrated in vacuo. The residue was purified with silica gel flash chromatography (1:1−1:3 hexanes−EtOAc) to afford **1**−**3**.

Characterization Data ^{1}H and ^{13}C NMR for 10, 11, 13a, 13b, 13c, and 3. Further details of the preparation and characterization and the ^{1}H and ^{13}C NMR data for compounds **10**, **11**, **13a**, **13b**, **13c**, and **3** are provided in the Supporting Information.

Acknowledgment. We thank the Department of Chemistry at Iowa State University for partial support of this work.

Supporting Information Available: Experimental procedures and characterization data; ^{1}H and ^{13}C NMR for **10**, **11**, **13a**, **13b**, **13c**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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NP100536A