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A convenient synthesis of *ortho–ortho* disubstituted biphenyls containing an eight-membered lactam ring using radical chemistry

C. H. Wang *, S. Alluri, A. K. Ganguly

Department of Chemistry, Chemical Biology and Biomedical Engineering, Stevens Institute of Technology, Hoboken, NJ 07030, USA

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ABSTRACT

Compound **4** prepared from Isatin in two steps underwent an unusual radical-induced rearrangement reaction to yield **9** as the major product and **10** as the minor component. Compound **9** shows structural similarities to the antimitotic agent rhazinilam and the gamma secretase inhibitor LY411575. The scope of the reaction has been studied by changing the substitutions on the aromatic rings and the mechanism for the formation of **9** and **10** from **4** is suggested.

1. Introduction

There has been considerable interest[1] in the literature regarding the synthesis of *ortho–ortho* disubstituted biphenyls incorporating a median size (six- to nine-membered) lactam ring. Several of these compounds possess biological activities of interest, for example, rhazinilam[2,3] which shows antimitotic activity by inducing inhibition of polymerization and depolymerization of tubulin and LY 411575,[4] a gama secretase inhibitor for possible use in Alzheimer patients (Fig. 1). Other compounds possessing *ortho–ortho* disubstituted biphenyls and incorporating a carbocyclic ring[3a] are represented in the structures of the antimitotic agents colchicine and steganacin. Synthesis of these classes of compounds involve the assembly of the suitably *ortho–ortho* disubstituted biphenyls followed by the ring closure to form the median-sized ring.

2. Present work

In this Letter, we wish to disclose the synthesis of compound **9** and it's analogs using an unusual radical-induced rearrangement reaction. These compounds[5,6] are novel. They have certain similarities to the structures mentioned above. For example, they possess *ortho–ortho* disubstituted biphenyls containing an eight-membered lactam ring, however, in addition they have an extra nitrogen atom in the lactam ring.

The synthetic scheme for compound **9** is shown in Scheme 1. Thus, isatin **1** is treated with 2-bromo aniline **2** yielding the unstable imine **3** which without purification was treated with cinnamyl bromide, indium metal, and sodium iodide in dimethyl formamide to yield **4**. Compound **4** on heating in toluene solution with tributyl tin hydride and AIBN yielded **9** as the major compound[7] and **10** as a minor component.[8]

A plausible mechanism for the formation of **9** and **10** is also summarized in Scheme 1. The initial radical **5** adds to the aromatic ring of the oxindole moiety to yield **6** which then undergoes further rearrangement to form radicals **7** and **8**. Capture of hydrogen radical yields **9** from **7** and similarly **10** is obtained from **8**. It should be noted that in this reaction there was no evidence for the formation of **26**. Methylation of **10** yielded **11**.

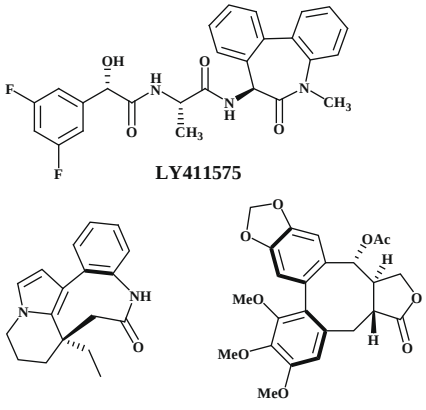

Figure 1.

* Corresponding author. Tel.: +1 201 216 8175; fax: +1 201 216 8240.
E-mail address: cwang0001@gmail.com (C.H. Wang).

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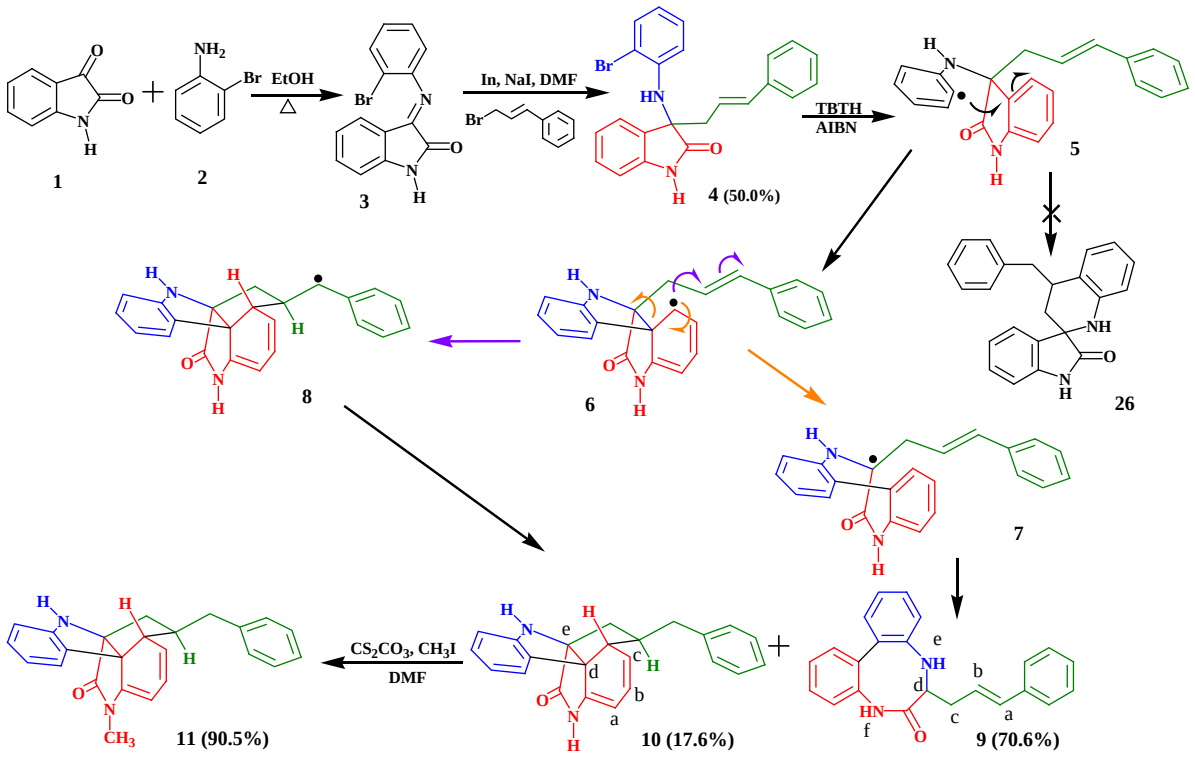
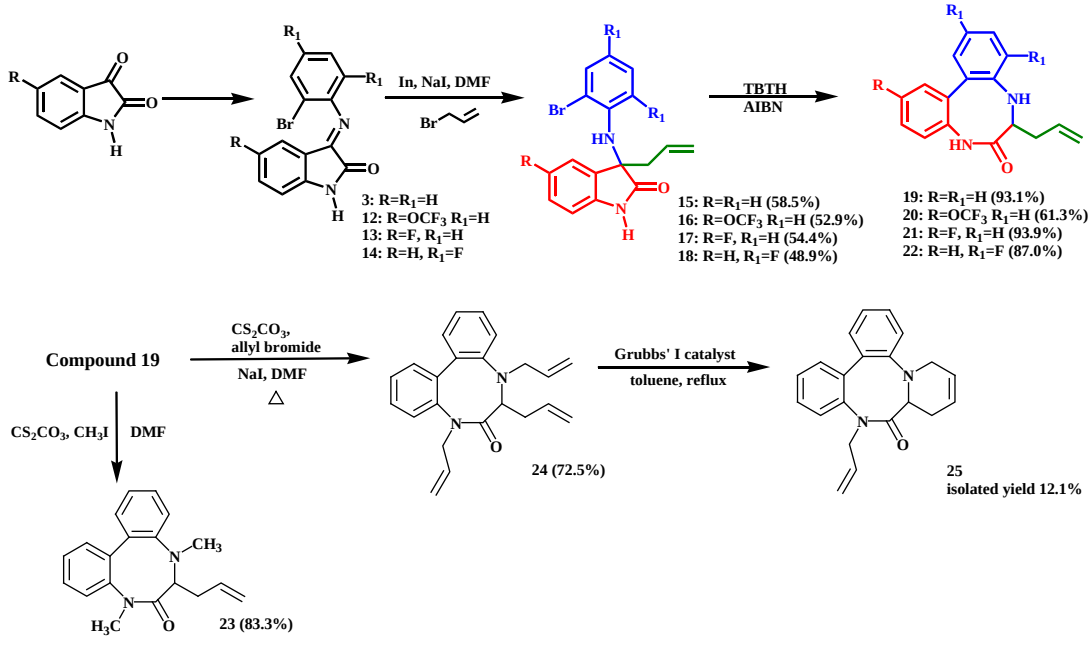


Scheme 1.



Scheme 2.

To explore the scope of the above reaction, we have converted the Schiff's bases **3**, **12, 13,** and **14** to their corresponding *C*-allyl adducts **15** to **18** using allyl bromide, sodium iodide, and indium metal in dimethyl formamide. Heating in toluene solution, these adducts with tributyltin hydride in the presence of AIBN yielded compounds **19** to **22,** thus establishing that a variety of aromatic substitutions are well tolerated in the reaction disclosed in the present Letter (see Scheme 2). Methylation of compound **19** yielded **23**.

As compounds such as **19** are obtained in three easy steps starting with commercially available starting materials, we investigated its conversion to another novel heterocycle **25**. Thus compound **19** was converted to the diallyl derivative **24**, which was submitted to ring-closing metathesis in the presence of Grubbs' I catalyst to yield **25**. Although compound **25** could be isolated in pure condition, it underwent slow decomposition on standing at room temperature. Obviously **25** could be further functionalized to impart drug like properties.

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5. The purity of the compounds was established using various chromatographic techniques. NMR and high resolution mass spectra of all the compounds described in this letter were consistent with the assigned structures. Assignments were further confirmed using 2D NMR and NOE experiments.
6. Excepting compounds **10**, **11**, **16**, **20**, **24,** and **25**, all the other compounds described in this Letter were crystalline. Crystals were obtained from dichloromethane and hexane. The melting points of compounds **4**, **9**, **15**, **17**, **18**, **19**, **21**, **22,** and **23** were 163–165, 195–197, 180–182, 160–162, 187–189, 179–181, 191–193, 156–158, and 101–103 °C, respectively. Yields are indicated in parentheses.
7. The ^{1}H NMR spectrum of compound **9** showed the presence of two vinyl hydrogens at δ 6.4 (d, J = 15.8 Hz, 1H, H-a) and δ 6.1 (td, J = 15.8 Hz, J = 7.0 Hz, 1H, H-b), a CH_2 group at δ 2.7–2.5 (m, 2H, H-c), and a CH group at δ 4.4 (td, J = 9.3 Hz, J = 7.1 Hz, 1H, H-d). The amine proton H-e appeared at δ 3.9 (d, J = 9.3 Hz, 1H) and the amide hydrogen H-f showed a singlet at δ 8.0.
8. The ^{1}H NMR spectra of compound **10** showed three vinyl hydrogens representing the diene system at δ 5.5 (d, J = 5.3 Hz, 1H, H-a), δ 6.1 (dd, J = 9.4 Hz, J = 5.3 Hz, 1H, H-b), and δ 5.7 (dd, J = 9.4 Hz, J = 5.5 Hz, 1H, H-c). In the ^{13}CNMR spectrum, the two quaternary carbons appeared at δ 60.1 (C-d) and δ 78.0 (C-e).