DIASTEREOSPECIFIC INTRAMOLECULAR CYCLOPROPANATION OF ENANTIOPURE 8-BROMO-3-PHENYLHEXAHYDROOXAZOLO-[3,2-a]PYRIDIN-5-ONES

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Abstract – A diastereospecific intramolecular cyclopropanation of (3R,8R,8aS)-8-bromo-3-phenylhexahydrooxazolo[3,2-a]pyridin-5-one 1 and (3R,8S,8aS)-8-bromo-3-phenylhexahydrooxazolo[3,2-a]pyridin-5-one 2 to generate the corresponding enantiopure 3-phenylhexahydro-5H-cyclopropa-[3,4]pyrrolo[2,1-b]oxazol-5-ones 3 and 4 in high yield is described.

The synthesis of chiral cyclopropanes remains a considerable challenge, especially due to the fact that cyclopropane rings are often found in a variety of natural products and biologically active compounds. Organic chemists have always been fascinated by the cyclopropane subunit which has played and continues to play a prominent role in organic chemistry. Its strained structure, interesting bonding characteristics and value as an internal mechanistic probe have attracted the attention of the physical organic community.1

Simmons-Smith cyclopropanation reaction is one of the most widely used reactions in the organic chemist’s arsenal for the conversion of olefins into cyclopropanes. This popularity is mainly due to the stereospecificity of the reaction with respect to the double bond geometry and its compatibility with a wide range of functional groups. The chemoselectivity of the reaction toward some olefins is excellent and very few side reactions are observed with functionalized substrates.2,3

Many of these reactions proceed in a cheletropic manner and several methods exist for converting alkenes to cyclopropane rings using carbene type reagents. As carbones themselves are highly reactive it is common for them to be used in a stabilized form, referred to as carbenoid. The metal carbenoid is electrophilic in nature and electron-rich alkenes usually react much faster than electron-poor alkenes. In
Simmons-Smith reaction the reactive carbenoid is iodomethylzinc, which is typically formed by a reaction between zinc-copper couple and diiodomethane. In addition, a groundbreaking procedure was introduced by Corey and Chaykovsky. They discovered that enones react with dimethylsulfoxonium methyldide to form cyclopropanes, a process known as Corey-Chaykovsky cyclopropanation. Using this reaction, Meyers et al. reported the diastereoselective synthesis of chiral bicyclic lactam in 80% yield by reaction of the dimethylsulfoxonium methyldide with an α,β-unsaturated bicyclic lactam derivative of (R)-(−)-2-phenylglycinol. Finally, starting from they synthesized the key precursor of the (−)-indolizomycin (Scheme 1).

![Scheme 1]

Now, considering that we recently published the synthesis of the (3R,8R,8aS)-8-bromo-3-phenylhexahydrooxazolo[3,2-a]pyridin-5-one 1 and (3R,8S,8aS)-8-bromo-3-phenylhexahydrooxazolo[3,2-a]-pyridin-5-one 2, we decided to investigate the conditions reaction to generate the carbanion at C-6 from these compounds to carry out the intramolecular nucleophilic attack on C-8 and to access to the 3-phenylhexahydro-5H-cyclopropa[3,4]pyrrolo[2,1-b]oxazol-5-ones 3 and 4 respectively.

In this way, we considered to utilize a strong base without nucleophilic capacity to prevent the opening of the oxazole function in the C-8aS position. Finally, we decided to use the lithium hexamethyldisilazide (LiHMDS) to generate stabilized required carbanion at C-6.

To a solution of LiHMDS (1 M, THF) at 0 °C under nitrogen atmosphere was added dropwise a solution of 1 in THF and the resulting mixture was stirred at for 2 hours. After, the reaction was treated with a brine, extracted with EtOAc and organic phase was dried over anhydrous Na2SO4. Finally, the solvent was removed and the solid obtained crystallized from hexane-dichloromethane affording 3 in 95% yield. This compound showed in 1H-NMR around 5.00 ppm a double signal $J = 1.4$ Hz that was assigned to H-6bS, an evident trans relationship between H-6aR.

Compound 2 in the same reaction conditions described above afforded 4 in 92% yield as a simple diastereoisomer after crystallization from hexane-dichloromethane. This compound showed close to 5.59 ppm a double signal $J = 5.0$ Hz an obvious cis relationship between H-6bS and H-6aS (Scheme 2).
Compounds 3 and 4 were recrystallized from hexane-dichloromethane and absolute configuration of each chiral center was assigned by X-ray diffraction analysis\(^{13}\) (Figure 1).

The diastereospecificity observed in this process could explain as follows. Treatment of 1 or 2 with LiHMDS generates the stabilized carbanion at C-6, and only the transition state that has the bromide atom at C-8 in a pseudo equatorial disposition and with the collinearity required can carry out the diastereospecific intramolecular substitution reaction (Scheme 3).
In conclusion, we have described a diastereospecific intramolecular cyclopropanation of 1 and 2 that allowed us to synthesize 3 and 4 in 95% and 92% yield respectively. This is the first report that full spectral data and X-ray of these compounds are described. We are currently investigating the potential of these structures as starting material in asymmetric synthesis of natural products.

**EXPERIMENTAL**

All moisture-sensitive reaction were performed using syringe-septum cap techniques under nitrogen atmosphere and all glassware was dried in an oven at 80 °C for 2 h prior to use. Melting point was measured with a hot stage melting point apparatus (uncorrected). Optical rotations were measured with a Perkin-Elmer 341 polarimeter, using a 1 dm cell with a total volume of 1 mL and are referenced to the D-line of sodium. The $^1$H-NMR and $^{13}$C-NMR spectra were recorded at 500 MHz and 125 MHz respectively using a Bruker Avance III Spectrometer. Chemical shifts are reported in δ (ppm). Mass spectra (EI, 70 eV) were measured by a JEOL Station JMS-700 instrument. X-Ray diffraction analysis was performed on a diffractometer Agilent Gemini Atlas.


To a solution of LiHMDS (1.0 mL, 1.5 equiv, 1 M in THF) at 0 °C under nitrogen atmosphere was added dropwise a solution of 1 (200 mg, 0.68 mmol, in 12 mL THF anh) and the resulting mixture was stirred at 0 °C for 2 h. Then the reaction was concentrated, brine was added (3 mL) and extracted with EtOAc (3 x 20 mL). The organic phase dried over anhydrous Na$_2$SO$_4$, filtered, and the solvent removed in vacuo. Compound 3 was obtained in 95%. Reaction of 2 under the same conditions described above afforded 4 in 92% yield.
(3R,5aS,6aR,6bS)-3-Phenylhexahydro-5H-cyclopropa[3,4]pyrrolo[2,1-b]oxazol-5-one 3: solid, mp 99-100 °C, [α]D20 -140.6 (c 1.0, CH2Cl2). 1H-NMR (500 MHz, CDCl3) δ 1.18 (td, J = 4.6, 3.4 Hz, 1H-7), 1.33 (td, J = 8.4, 4.9 Hz, 1H-7), 2.07 (m, 1H-5a), 2.44 (ddd, J = 8.5, 5.4, 1.4 Hz, 1H-6aR), 3.77 (dd, J = 8.7, 7.5 Hz, 1H-2), 4.57 (dd, J = 8.2, 8.7 Hz, 1H-2), 4.99 (d, J = 1.4 Hz, 1H-6bS), 5.09 (t, J = 7.5, 8.2 Hz, 1H-3), 7.17-7.34 (m, 5H-ArH). 13C-NMR (125 MHz, CDCl3) δ 14.6, 20.2, 22.7, 57.7, 74.0, 92.5, 125.8, 127.5, 128.7, 140.0, 181.9. MS (EI): calc. for C13H13NO2 ([M+H]+) 215; found: 215.

(3R,5aR,6aS,6bS)-3-Phenylhexahydro-5H-cyclopropa[3,4]pyrrolo[2,1-b]oxazol-5-one 4: mp 109-110 °C, [α]D20 -158.9 (c 1.0, CH2Cl2). 1H-NMR (500 MHz, CDCl3) δ 1.13 (m, 2H-7), 2.06 (m, 1H-6aS), 2.20 (dd, J = 4.2, 5.6 Hz, 1H-5a), 3.90 (dd, J = 7.4, 8.8 Hz, 1H-2), 4.64 (dd, J = 7.6, 8.8 Hz, 1H-2), 4.74 (dd, J = 7.4, 7.6 Hz, 1H-3), 5.59 (d, J = 5.0 Hz, 1H-6bS), 7.24-7.35 (m, 5H-ArH). 13C-NMR (125 MHz, CDCl3) δ 9.7, 13.6, 24.9, 57.1, 77.1, 91.6, 125.7, 127.5, 128.8, 139.4, 176.8. MS (EI): calc. for C13H13NO2 ([M+H]+) 215; found: 215.

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REFERENCES


13. CCDC-964322 (for 3), CCDC-964323 (for 4). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.