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Regio- and stereoselective synthesis of spiro-pyrrolidine/pyrrolizidine/thiazolidine-grafted macrocycles through intramolecular 1,3-dipolar cycloaddition reaction

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ABSTRACT

Regioselective synthesis of spiropyrrolidine-grafted 11-membered macrocycle was accomplished through an intramolecular [3+2] cycloaddition of azomethine ylides. The key precursor alkenyl diketone (**4a–b**) was obtained from simple starting materials. The dipole generated from isatin tethered to *O*-alkyl enone (**4a–b**) was reacted intramolecularly to yield the spiropyrrolidine-grafted macrocycles (**6a–b**). The structures of the cycloadducts were assigned by 2D NMR and confirmed by single crystal analysis.

Spiroheterocycles are very much prevalent as basic skeleton in many natural products possessing diverse biological activities.[1] Specifically, spirooxindole derivatives are present in various alkaloids,[2] and exhibit anticancer,[3] antimalarial,[4] antimicrobial,[5] antitubercular,[6] and anti-HIV[7] properties. They also act as potential inhibitors against AChE and MDM2[8,9] and show cytotoxicity against the P388 cell (IC_{50} = 24 μg/ml).[10] They find application as progesterone receptor modulators.[11]

In recent years, macrocyclic compounds are known to have a variety of application in the field of chemistry, biology, material science, and nanotechnology.[12] Precisely, the nitrogen containing macrocycles presents a unique structural feature that allows the molecules to function as receptors in supra molecular chemistry. These molecules are used as anion and cation receptors in the molecular recognition process.[13] Over a period of years, receptors that are selective toward the recognition process were also synthesized.[14] In particular, the macrocycles containing crown ether and salen units are found to possess good molecular recognition properties.[15] The heterocycle bound peptidomimetic macrocycles have better pharmacokinetic properties than its peptide analogs.[16] Overall, these macrocycles or macrolides that represent heterocycle bound natural products, which has good applications in medicine[17] and supramolecular chemistry has created a considerable amount of interest in synthetic organic chemistry.

Methods available in the literature for the construction of these macrocycles involve either complex processes or lengthy protocols.[18] Hence, there arises a need to develop a simpler method for the construction of complex macrocycles of synthetic and biological importance. 1,3-Dipolar cycloaddition (1,3-DC) reaction is an elegant and efficient methodology for regio- and stereoselective synthesis of structurally complex five-membered heterocycles.[19] These heterocycles, often constitute the core structure of numerous alkaloids and pharmacologically active compounds.

In continuation of our research in 1,3-DC reaction of azomethine ylides,[20] herein we report, the synthesis of spiropyrrolidine-grafted macrocycles via an intramolecular [3+2] cycloaddition reaction of azomethine ylides. The synthetic plan for the construction of spiropyrrolidine-grafted macrocycle (**6a–b**) is shown in Scheme 1.

Initially, the required monobromo alkenes (**2a–b**) were prepared from salicylaldehyde by two different routes to get good yields of the products. For the preparation of *O*-alkyl enenone **2a**, we first prepared the enone by aldol condensation of salicylaldehyde with *p*-bromoacetophenone. The enone was subsequently reacted with 1,4-dibromobutane to give O-alkylated benzylidene acetophenone **2a** (Scheme 2).

For the preparation of *O*-alkyl alkenyl ester, we first mono alkylated salicylaldehyde with dibromobutane which followed Wittig olefination of aldehyde to give the alkenyl ester (**2b**) as given below (Scheme 3).

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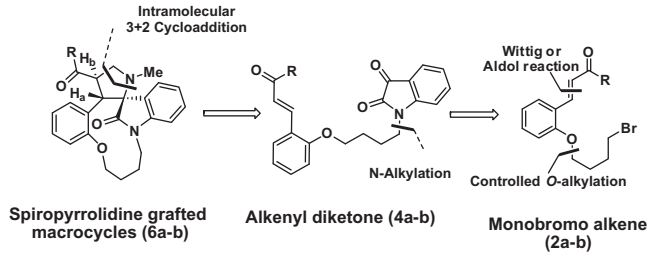
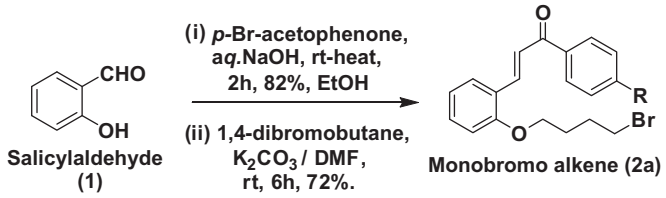
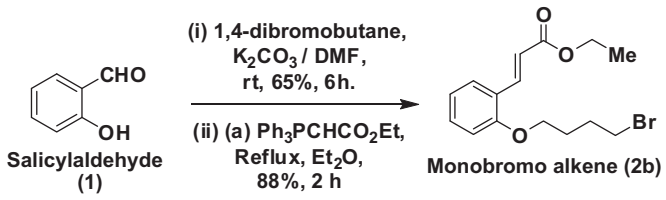


Scheme 1. Synthetic plan for spiropyrrolidine-grafted macrocycles (**6a**–**b**).



Scheme 2. Synthesis of monobromo alkene (**2a**).



Scheme 3. Synthesis of monobromo alkene (**2b**).

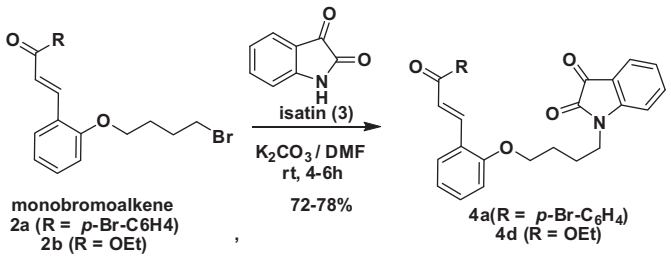
The O-alkylated monobromo alkenes **2a–b** were then coupled with isatin to give *N*-alkyl isatin *O*-alkyl enone derivatives **4a–b** in excellent yields as shown below (Scheme 4).

The structures of **4a–b** were confirmed on the basis of spectroscopic data. The geometry of the olefinic double bond was found to be *E* as evidenced by ^{1}H NMR spectra where one of the olefinic protons of **4a** appeared as a doublet at δ 8.13 (J = 15.9 Hz). In the ^{13}C NMR spectrum of **4a**, the carbonyl carbon's peaks resonated at 187.7, 157.2, and 155.4 ppm and the remaining carbons exhibited peaks at their corresponding ppm values. Similarly, in the ^{1}H NMR spectrum of **4b**, signals for the protons appeared at the expected δ values.

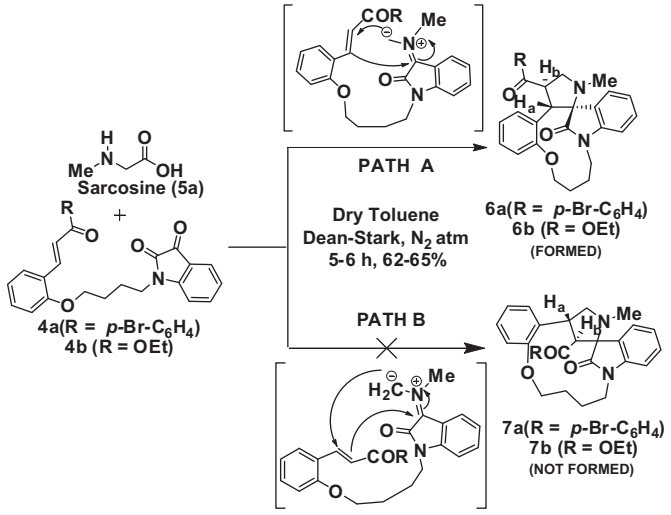
The macrocyclic precursor thus prepared is poised to undergo intramolecular cycloaddition reaction. Thus alkyl enenones tethered to isatin (**4a–b)** when refluxed with sarcosine in toluene under Dean–Stark reaction condition; generated azomethine ylide via decaroboxylative condensation which underwent neat intramolecular [3+2] cycloaddition reaction with the enone regioselectively to give eleven-membered macrocyclic spiropyrrolidines **6a–b** in moderate yields (Scheme 5).

The structures and the regiochemistry of the cycloadducts **6a–b** were unambiguously established by their spectroscopic data. [21a]

The ^{1}H NMR spectrum of **6a** exhibited one singlet at δ 2.10 corresponding to the *N*-methyl group. The benzylic proton H_a showed a doublet at δ 5.45 (d, J = 10.8 Hz). The coupling constants suggested a *trans* fusion at the ring junction. A multiplet in the region δ 4.26–4.35 was observed for H_b proton. This clearly proved the regio- and stereoselectivity of the cycloaddition reaction. If the other possible regioisomer **7a** had formed, then the benzylic H_b proton would have shown a doublet instead of a multiplet.



Scheme 4. Synthesis of alkyl enenones (**4a**-**b**).



Scheme 5. Synthesis of spiropyrrolidine-grafted macrocycles (**6a**–**b**).

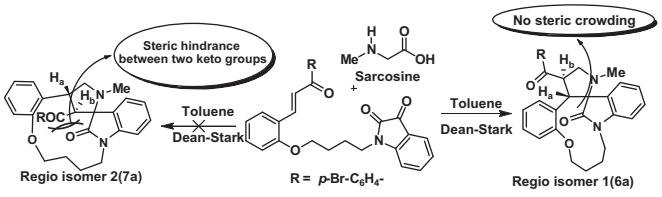
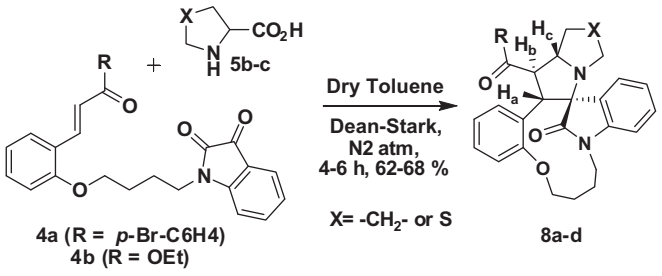


Figure 1. Regioselectivity of intramolecular 1,3-DC reaction.



Scheme 6. Synthesis of spiropyrrolizidine-grafted macrocycles (**8a**–**d**).

The presence of *N*-methyl and *N*-methylene carbons was confirmed by two signals at 34.8 and 57.4 ppm, respectively, in the ^{13}C NMR and DEPT 135 spectrum of **6a**. The *O*-methylene carbon exhibited a peak at 68.6 ppm and the spiroquaternary carbon showed a peak at 76.5 ppm. The oxindole carbonyl carbon was seen at 177.0 ppm. The carbonyl carbon exhibited a peak at 197.5 ppm. The rest of the carbons of **6a** exhibited peaks at their