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The iodocyclization of unsaturated dihydroxysulfonamide derivatives. *N*- versus *O*-cyclization

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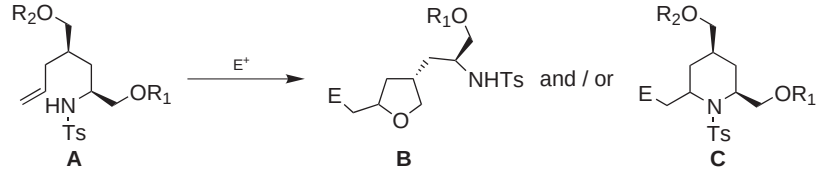
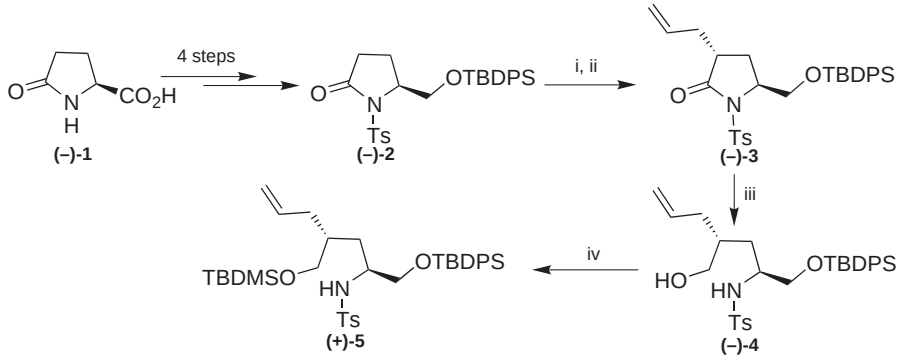
Abstract—Iodocyclization of unsaturated dihydroxysulfonamide derivatives can lead to substituted monocyclic or bicyclic compounds depending on the hydroxy protecting groups and the electrophilic reagent used.

Electrophilic cyclizations are an attractive method for the formation of substituted 5- and 6-membered saturated heterocyclic compounds.[1] Substituted tetrahydrofurans can be obtained from homoallylic alcohols[2] by 5-*endo*-*trig* cyclizations despite the apparent violation of Baldwin's rules,[3] as they are electrophile- rather than nucleophile-driven.[4] Electrophilic cyclizations of γ,δ-unsaturated alcohols as well as their corresponding ethers can lead to the stereoselective construction of substituted tetrahydrofurans.[5] The po-



Scheme 1.



Scheme 2. Preparation of compounds (−)-**4** and (+)-**5**. *Reagents and conditions*: i, LiHMDS, THF, −78°C; ii, allyl bromide, THF, −78°C → rt (89%); iii, $NaBH_4$, MeOH, rt (70%); iv, TBDMSCl, imidazole, CH_2Cl_2, 0°C → rt (78%).

Keywords: bicyclic heterocyclic compounds; cyclization; oxygen heterocycles; pyrrolidines; sulfonamides.

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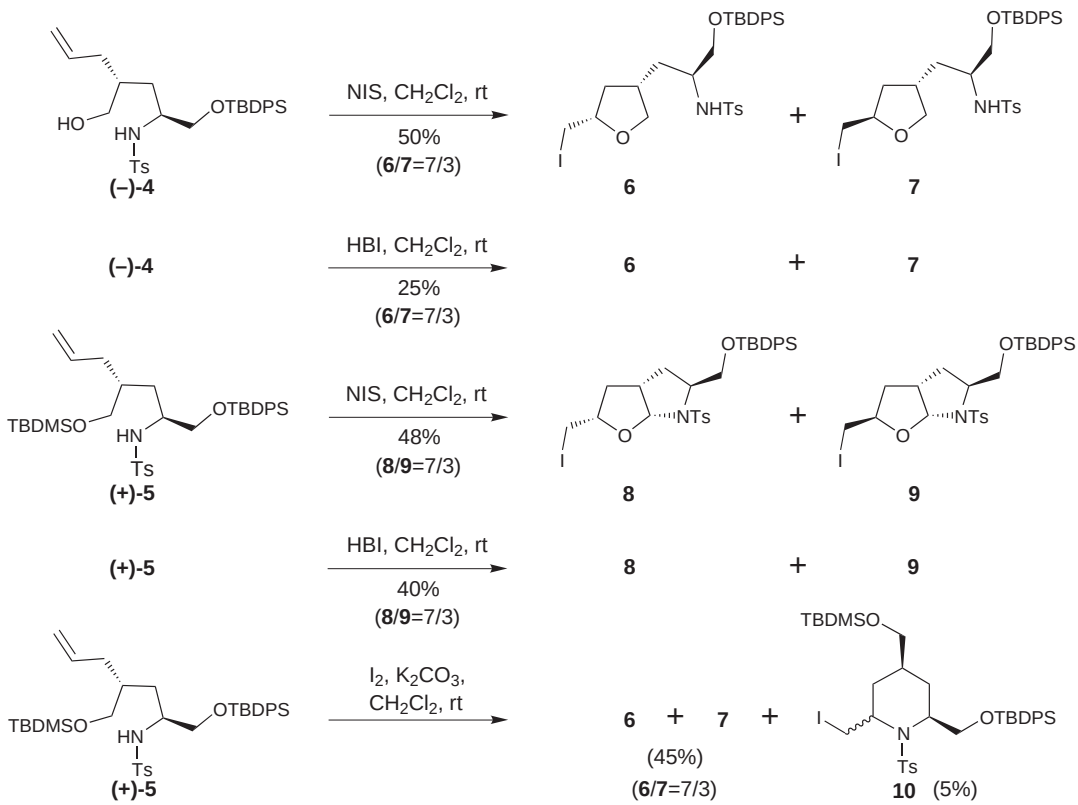
tential of these electrophilic cyclizations was also used to build substituted pyrrolidines[6,7] and piperidines,[8] respectively, from homoallylic tosylamides or δ,ε-unsaturated amines.

Here, we would like to report our preliminary studies on the iodocyclization of dihydroxysulfonamide derivatives of type **A**, which can lead either to substituted tetrahydrofurans **B** and/or substituted piperidines **C** (Scheme 1).

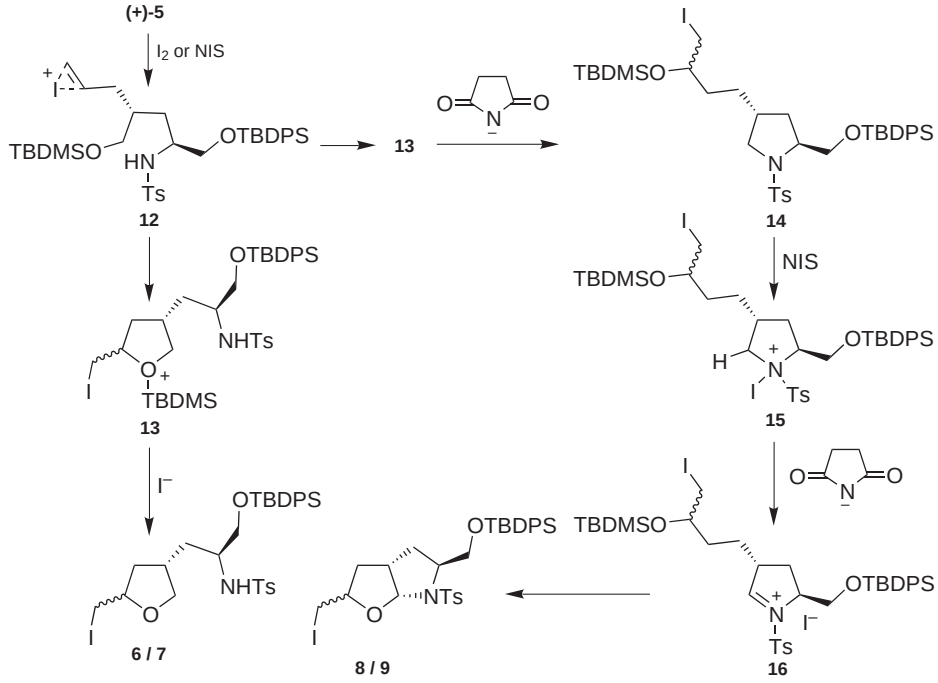
The required substrates (−)-**4** and (+)-**5** were efficiently obtained, as outlined in Scheme 2, from L-pyroglutamic acid. L-Pyroglutamic acid (−)-**1** was transformed to the *N*-tosyl lactam (−)-**2** in four steps, following a described procedure.[9] After alkylation of (−)-**2** with allyl bromide (LiHMDS, THF, −78°C, de>96%, 89% yield), the *N*-tosyllactam (−)-**3** was reduced to the monoprotected diol (−)-**4** by $NaBH_4$ (MeOH, rt, 70% yield). Compound (−)-**4** was converted to (+)-**5** by treatment with TBDMSCl (imidazole, CH_2Cl_2, 78% yield).

Initially, we examined iodocyclization of hydroxysulfonamide (−)-**4** by using *N*-iodosuccinimide (NIS, 3 equiv.) in dry CH_2Cl_2 at room temperature. This first attempt led to the rapid formation of two inseparable diastereomers **6** and **7** in 50% yield, in a ratio of 7:3. When the electrophile bis(*sym*-collidine)iodine(I) hexafluorophosphate (HBI)[10] was used, **6** and **7** were obtained with the same ratio (7:3) but with lower yield (25%). The treatment of the protected unsaturated dihydroxysulfonamide (+)-**5** with NIS (3 equiv., CH_2Cl_2, rt) or HBI (3 equiv., CH_2Cl_2, rt) produced two separable bicyclic compounds **8** and **9** (ratio 7:3) in similar yields (NIS, yield: 48%; HBI, yield: 40%). The relative stereochemistry in **8** and **9** was determined by NOE experiments. Modification of the conditions, in the electrophilic treatment of (+)-**5**, by replacing NIS by I_2 in the presence of K_2CO_3 led to a mixture of the two diastereomers **6** and **7** in 45% yield in a 7:3 ratio. We have to point out that under these conditions a trace of piperidine **10** was observed (∼ 5%) (Scheme 3).

The same diastereomeric ratio **6**/**7** (obtained from the iodocyclization of (+)-**5** or (−)-**4**) and **8**/**9** (obtained from (+)-**5**) led us to speculate that the major isomer **6** should have a 2,4-*cis* relative stereochemistry. Depending on the source of electrophile, (+)-**5** can be transformed into monocyclic compounds **6**/**7** or bicyclic compounds **8**/**9**. According to these results, it seems that the treatment of (+)-**5** with I_2 led to the iodonium intermediate **12**, which can be attacked by a silyl ether to produce intermediate **13** and I^-. The desilylation of intermediate **13** by I^-, liberated in the reaction media, produced the observed tetrahydrofurans **6**/**7**. When the same protected dihydroxysulfonamide derivative (+)-**5** was treated with NIS, the same intermediate **12** was formed and the succinimide anion was liberated. This succinimide anion is not nucleophilic enough to transform **13** into **6**/**7** by desilylation. However, the tosylamide group is able to attack intramolecularly the C-5 of intermediate **13** to produce the substituted *N*-tosylpyrrolidine **14**. As an excess of NIS is present in the reaction media, the *N*-tosylpyrrolidine **14** can react



Scheme 3. Iodocyclizations.



Scheme 4. Formation of **6**/**7** and **8**/**9**.

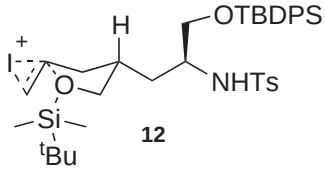


Figure 1. Possible chair-like transition state.

with an excess of electrophile[11] to form intermediate **15**, which can be transformed to the tosyliminium **16** by β-elimination of HI in the presence of succinimide anion. This iminium can then be attacked intramolecularly by the silyl ether group to produce the observed bicyclic compounds **8**/**9**, after desilylation by I^- (Scheme 4).

The diastereoselectivity observed in this iodocyclization is readily rationalized in terms of a preference for a chair-like transition state **12** with a pseudoequatorial [$CH_2CH(NHTs)(CH_2OTBDPS)$] group (Fig. 1).

Iodocyclization of unsaturated protected dihydroxysulfonamide derivatives are regio-, chemo- and stereoselective and lead to substituted tetrahydrofurans or bicyclic α-aminoethers depending on the reaction conditions.

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