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A practical *one-pot* radical-ionic sequence for the preparation of epoxides: application to the synthesis of unnatural polyhydroxylated alkaloids

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ABSTRACT

An efficient *one-pot* sequence for the preparation of epoxides from α-iodoesters or α-iodonitriles and allylic alcohols is described. This sequence is based on the use of iodine atom transfer reaction onto allylic alcohols followed by a ring closing epoxidation reaction of the halohydrin intermediates. The feasibility of this sequence is showcased in the synthesis of the perhydroaza-azulene, an unnatural analog of castanospermine.

Introduction

Since their isolation, polyhydroxylated indolizidine alkaloids like (+)-castanospermine (**1**),[1] (−)-swainsonine (**2**),[2] and (+)-lentiginosine (**3**)[3] have attracted the attention of synthetic organic chemists due to their interesting structures and promising pharmaceutical applications.[4] In recent years, much effort has been made in order to synthesize stereochemically different and ring expanded analogs of the above-mentioned aza-sugars because in some cases, these analogs have shown increased glycosidase inhibitory and immunosuppressive activities.[5] In this regard, Dhavale and co-workers have successfully synthesized tetrahydroxylated perhydroaza-azulenes **4a** and **4b**[6] as well as a single seven-membered ring analog **5**[5b] (Fig. 1).

An efficient strategy for the preparation of pyrrolidines is through a 5-*exo-tet* cyclization of a primary or secondary amine onto an epoxide, which leads to the desired five-membered cyclic amine bearing a hydroxyl group with known stereochemistry.[6] In this Letter, we report an accessible *one-pot* sequence for the straightforward preparation of epoxides from either α-iodoesters or α-iodonitriles and allylic alcohols based on a free-radical atom-transfer reaction followed by a base-promoted cyclization. This sequence was applied to the synthesis of tetrahydroxylated perhydroaza-azulene **4a**.

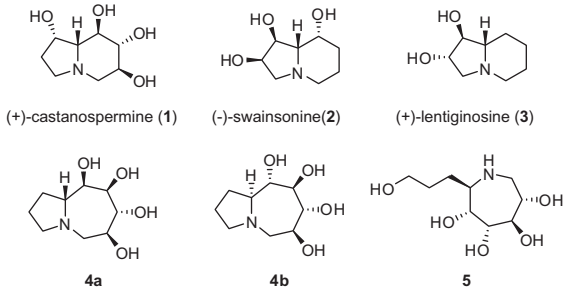
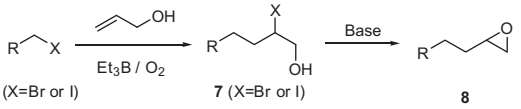


Figure 1. Natural and synthetic polyhydroxylated alkaloids.



Scheme 1. Radical-ionic strategy for the preparation of epoxides.

Results and discussion

Our strategy for the direct preparation of epoxides is depicted in scheme 1. We reasoned that a Kharash-type reaction[7] between an alkyl halide (**6**), serving as the radical precursor, and an allyl alcohol would afford adduct **7**, which upon treatment with a base, would furnish the desired epoxide **8**. The use of radical conditions for the first step, which are neutral and compatible with other

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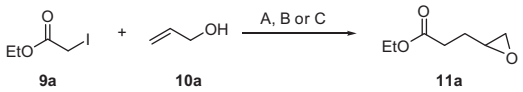
Table 1
Optimization of reaction conditions



9a **10a** **11a**

Conditions[a]	Initiator	Solvent(s)	Base	Yield (%)
A	Et_3B	$EtOH/H_2O$	K_2CO_3	49
B	Et_3B	CH_2Cl_2	DBU	78
C	Et_3B	(i)$EtOH/H_2O$ (ii) CH_2Cl_2	DBU	80

[a] Conditions A: Et_3B (1.0 M solution in THF), O_2 (trace), K_2CO_3 (2 equiv) in $EtOH/H_2O$ at rt. Conditions B: Et_3B (1.0 M solution in hexanes), O_2 (trace), CH_2Cl_2; then DBU (2 equiv). Conditions C: (i) Et_3B (1.0 M solution in THF), O_2 (trace), $EtOH/H_2O$ at rt. (ii) DBU, CH_2Cl_2.

reagents, would allow the use of an unprotected allylic alcohol and the second step—ionic cyclization—to be done in a *one-pot* manner.

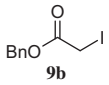
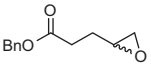
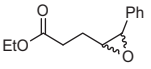
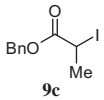
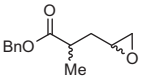
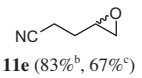
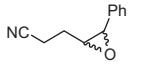
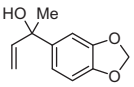
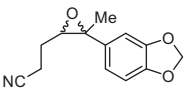
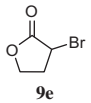
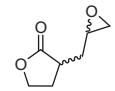
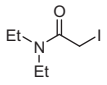
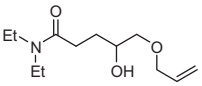
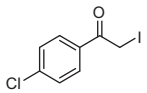
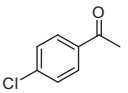
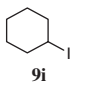
Table 1 shows the optimization of reaction conditions for this transformation. We initially chose ethyl iodoacetate and allyl alcohol as model substrates. In the first attempt (conditions A), both the radical initiator and the base were added since the beginning of the reaction in an aqueous medium, leading to the isolation of the desired product (**11a**), albeit in low yield (49%). Furthermore, using dichloromethane as the solvent and DBU as the base (when the radical reaction was completed), enhanced the yield to 80% (conditions B). Finally, aqueous conditions for the radical step were used again, but adding DBU as the base after switching the solvent to CH_2Cl_2, affording epoxide **11a** in 78% yield (conditions C).

Next, the scope of the procedure was studied for other substrates (Table 2). Good yields were observed for primary stabilized electrophilic radicals such as α-iodoesters **9a**–**b** (entries 1–3) and α-iodonitriles (**9d**, entries 5–7). In the case of substituted allylic alcohols (**10b** and **10c**), nearly equimolar mixtures of *cis*:*trans* isomers were observed in lower yields (entries 3, 6, and 7). The sequence also worked with a secondary electrophilic radical (**9c**, entry 4) and for a bromolactone (**9e**, entry 8), albeit in modest yields (30%). It is worth noting that for the latter substrate, the radical step only succeeded in ethanol–H_2O, which is in agreement with that reported by Fujimoto and co-workers, who proposed that bromine atom transfer is better achieved in solvents with a high dielectric constant.[8] When *N*,*N*′-diethyliodoacetamide **9f** was employed as a radical precursor (entry 9), the expected epoxide was surprisingly not observed, but compound **11j**, which is presumably formed by opening of the initially formed epoxide by allyl alcohol. For α-iodoacetophenone **9g** (entry 10), only the reduced product **11j** was observed, probably due to the formation of the boron enolate prior to the radical addition.[9] On the other hand, nucleophilic radicals **9h** and **9i** failed to carry on the radical reaction (entries 11 and 12), which was somehow expected due to unfavorable polar effects.[10]

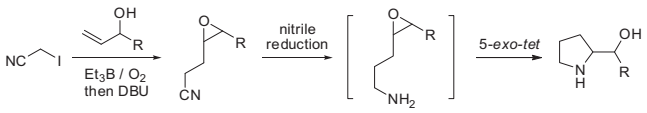
The success of this sequential reaction when α-iodonitriles were used encouraged us to prepare 2-hydroxypirrolidines via a 5-*exo*-*tet* cyclization of 1-amino-5,6-epoxide. Typically, the route for obtaining the mentioned epoxides involves a Claisen–Johnson rearrangement of an allylic alcohol, followed by epoxidation, ester reduction, transformation of the resulting alcohol into a leaving group, substitution by the azide, and reduction of the latter to produce the primary amine which carries on the desired 5-*exo*-*tet* cyclization.[6] By using our protocol, the cyclization precursor would be obtained in only 2 steps (*one pot*) from the corresponding allylic alcohol (Scheme 2).

Based on the above-mentioned strategy for the preparation of 2-hydroxypyrrolidines we proceeded to apply it to the synthesis of perhydroaza-azulenes **4a** and **4b**. As shown in scheme 3, the original route described by Dhavale and co-workers (path A) involves a 5 step linear sequence to prepare azide **13** from allylic alcohol **14**. The azide is then reduced and cyclized into the advanced intermediate **12**. In our strategy, we planned to elaborate epoxy nitrile **15**

Table 2
Different precursors and alcohols

Entry	Precursor	Alcohol	Product (Yield%)
1	**9a**	**10a**	**11a** (49[a], 78[b], 80[c])
2	 **9b**	**10a**	 **11b** (79%[b], 61%[c])
3	**9a**	 **10b**[d]	 **11c** (77%, 42%[c])
4	 **9c**	**10a**	 **11d** (15%[b], 30%[c])
5	 **9d**	**10a**	 **11e** (83%[b], 67%[c])
6	**9d**	 **10b**	 **11f** (71%[b], 58%[c])
7	**9d**	 **10c**	 **11g** (47%[b], 49%[c])
8	 **9e**	**10a**	 **11h** (0%[b], 30%[c])
9	 **9f**	**10a**	 **11i** (45%[b])
10	 **9g**	**10a**	 **11j**[b,c,e]
11	 **9h**	**10a**	S.M.[b,c,f]
12	 **9i**	**10a**	S.M.[b,c,f]

[a] Conditions A were used.
[b] Conditions B were used.
[c] Conditions C were used.
[d] Compounds **10b**–**d** were prepared by reaction of the corresponding aldehyde with vinylmagnesium bromide according to known procedures.
[e] Only 4-chloroacetophenone (reduced product) was detected after complete consumption of the starting material and addition of 0.3 equiv of Et_3B.
[f] Only starting material was recovered after several hours of reaction.



Scheme 2. Planned route for the synthesis of 2-hydroxypirrolidines.