A New Ring-Forming Methodology for the Synthesis of Conformationally Constrained Bioactive Molecules

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(Received December 12, 2000; CL-001115)

A new, general, one pot method for introducing carbocyclic rings alpha to a nitrile moiety is described. Treatment of readily available arylacetonitriles with potassium bis(trimethylsilyl)-amide and subsequent alkylation with α,ω-dibromo or dichloro-alkanes in tetrahydrofuran under anhydrous conditions at 0 °C produces cycloalkyl adducts in good yields and short reaction times.

The biological activity and stability of bioactive molecules are frequently enhanced when such molecules are subjected to conformational constraint.[1] Previously, we and others, have published[2,3] the synthesis of molecules of biological interest bearing conformationally constrained side chains. In the course of our program directed towards the synthesis of conformationally constrained (–)-Δ^8-tetrahydrocannabinol and melatonin analogs, we were faced with the problem of introducing cyclopropane, cyclobutane, cyclopentane and cyclohexane rings at the α-position of nitriles of type **1** and **2** (Figure 1).

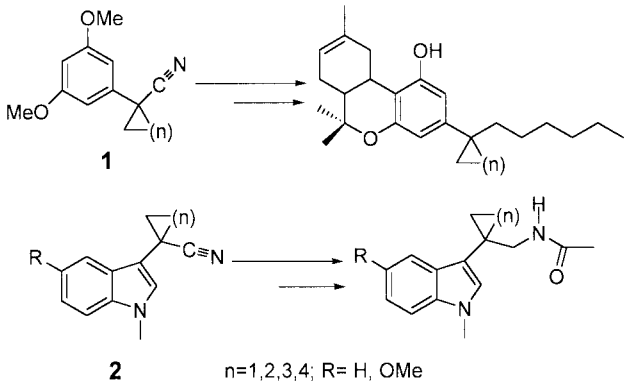
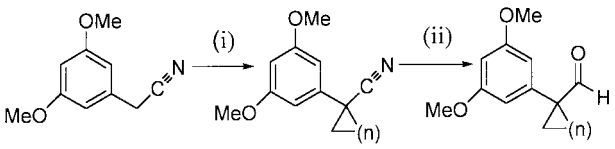


Figure 1.

This has motivated us to develop a general method for substituting activated aryl methylenes with cycloalkyl groups of varying ring size. Cyclobisalkylation reactions are especially valuable when the resulting rings bear functional groups that can be further elaborated to target molecules. In the specific case of α,α-cycloalkylaldehyde synthesis, several methods have been reported including alkylation of enolates derived from aldehydes with α,ω-dihaloalkanes. However, this approach usually leads to complex mixtures often without the formation of the desired cycloalkane carboxaldehydes.[4] Masked forms of aldehydes have, therefore, been utilized in order to achieve these transformations.

A typical example of this approach is the cyclobisalkylation of activated oxazine derivatives, which upon reduction and subsequent hydrolysis give the desired α,α-cyclobisalkylated aldehydes.[5] More recently, the construction of cycloalkyl rings at the α-position of aldehydes by cyclization of ω-haloaldimines was described. This method involves alkylation of the corresponding aldimines with α,ω-dihaloalkanes followed by treatment with LDA to give α,α-cyclobisalkyl aldimines which are then hydrolyzed to the α,α-cycloalkylaldehydes.[4] However, all of these literature methods are generally not very efficient and give relatively low yields.

We now report a new, general, one pot method for the construction of carbocyclic rings alpha to the nitrile moiety which serves as a masked aldehyde. As shown in Scheme 1, our approach is simple, highly efficient and also suitable for the preparation of strained rings. After considerable experimentation we found that when readily available 3,5-dimethoxyphenylacetonitrile in dry tetrahydrofuran (0.1 M), was deprotonated with potassium bis(trimethylsilyl)amide (3 equiv) at 0 °C under an argon atmosphere and subsequently alkylated at the same temperature with α,ω-dibromo or dichloroalkanes (1.1 equiv) the cycloalkyl adducts **3–6** were formed in 58–94% yield. The reaction is simple to carry out and is usually complete in 20–25 min.



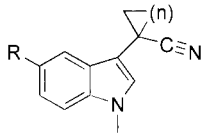
3: n= 1 58%[9] **7:** n= 1 89%
4: n= 2 64% **8:** n= 2 88%
5: n= 3 88% **9:** n= 3 87%
6: n= 4 94% **10:** n= 4 89%

Scheme 1. Reagents and conditions: (i) reaction conditions as described in text; (ii) DIBAL-H, CH_2Cl_2, –78 °C; then sodium potassium tartrate.

In order to explore the versatility of our method we applied it to the construction of the 3-indolylcycloalkane analogs **11–18** (Table 1), which, like their phenolic counterparts, **3–6**, were obtained in good yields. Table 1 includes examples of carbocyclic rings synthesized according to the above method and

illustrates the efficiency and generality of this reaction. Three through six membered analogs were readily formed and even in the case of the cyclopropane and cyclobutane derivatives, **11,12,15,16** the yields recorded were high. This method is comparable or superior to other 3- and 4-membered ring forming procedures (e.g., LDA and α,ω-dihalides and NaH in diethyl ether–DMSO with α,ω-dihalides).[6] Compounds bearing the cyclopropane[7] or cyclobutane[8] moieties can be of considerable biological value and serve as interesting targets in synthetic organic chemistry. Thus, they function to conformationally constrain amino acid analogs and provide mechanistic probes for the determination of reaction pathways. In this regard, development of new methods of cycloalkylation presents a challenging area for current research.

Table 1. Examples of carbocyclic rings synthesized according to the described method



Entry	Com. No	R	n	Yield/%
1	**11**	H	1	40[a]
2	**12**	H	2	58
3	**13**	H	3	49
4	**14**	H	4	50
5	**15**	OMe	1	42[a]
6	**16**	OMe	2	56
7	**17**	OMe	3	66
8	**18**	OMe	4	65

[a]See ref 10.

The ready availability of compounds with restricted conformations through carbocyclic annelation should give biologically active molecules of value in medicinal chemistry. Efforts to provide such systems are in progress in our laboratories.

References and Notes

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9 Use of potassium bis(trimethylsilyl)amide (5 equiv) and 1,2-dichloroethane (3 equiv) was found to be more effective (68% yield).
10 Use of potassium bis(trimethylsilyl)amide (5 equiv) and 1,2-dichloroethane (3 equiv) was found to be more effective (62% yield).