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Homohalocyclization: Electrophilic Bromine-Induced Cyclizations of Cyclopropanes

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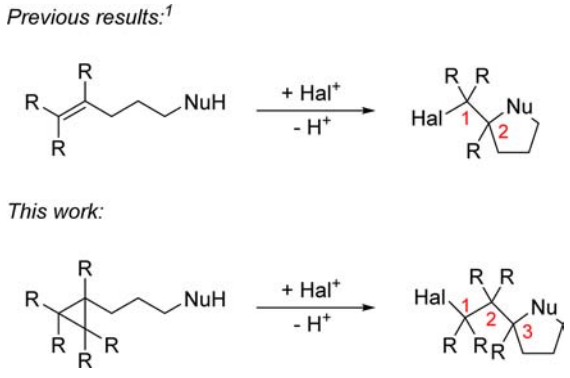
Supporting Information

ABSTRACT: An efficient method for the halocyclization of cyclopropanes has been developed. The cyclopropanes undergo a 1,3-addition reaction to form homohalocyclization products compared to conventional alkene halocyclizations. The reaction can be induced by various electrophilic halogenating agents including 1,3-dibromo-5,5-dimethylhydantoin and *N*-iodosuccinimide. In cyclopropane derivatives with a preexisting stereocenter, excellent induced diastereoselectivities can be observed.

The rapid generation of complex molecules from simple starting materials is a key goal of organic chemistry. Halocyclizations such as iodolactonization generate two stereocenters and a ring while introducing an additional functional group (the halogen) in a single transformation.[1,2] Therefore, this class of reactions is a powerful tool in organic synthesis. In general, halocyclizations are electrophilic additions to unsaturated C−C bonds such as alkenes, alkynes, or allenes. This means that the newly generated functional groups are placed vicinal (1,2) in the product (Scheme 1).

Scheme 1. Halocyclization of Alkenes and Cyclopropanes



During our investigations on asymmetric halocyclizations,[3] the question arose if halocyclizations are also possible using cyclopropanes as starting materials leading to 1,3-substituted products (Scheme 1). Due to the unusual bonding situation in the highly strained cyclopropanes, these compounds often show typical reactivity of unsaturated C−C bonds.[4] This is also true for the electrophilic addition of halogens and the 1,3-dibromination of cyclopropanes, which has been described previously.[5] However, in general only a few examples have been reported and very reactive halogenating agents such as the elemental halogens and related trihalogenids have been required for those reactions limiting the general applicability.[5,6] On the other hand cyclopropanes are important building blocks in synthetic and medicinal chemistry.[7] A range of methods for their preparation are known, including asymmetric variants.[8] Furthermore, due to the high ring strain, cyclopropanes can be easily transformed, for example by reduction or, in the case of donor−acceptor substituted cyclopropanes, by cycloadditions and a range of other transformations.[9] This includes the 1,3-dihalogenation of donor−acceptor substituted cyclopropanes, which is in many cases not taking place via an electrophilic halogenation mechanism.[10] In this manuscript we show that cyclopropanes can also undergo typical halocyclizations such as halolactonizations and halocycloetherifications. This transformation can proceed with very high diastereoselectivity and enable the rapid establishment of complex molecules by a simple cyclopropanation/halocyclization sequence placing the newly introduced groups in a 1,3-distance.

Initial experiments into halocyclization reactions of cyclopropanes were conducted using phenyl-substituted cyclopropane derivative **1a** (Table 1). Upon treatment with elemental bromine in dichloromethane, **1a** was converted among other products into the 5-*exo* cyclization product **2a** in moderate yield (41%) (Table 1, entry 1). Switching to 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) as a brominating agent, the yield was increased only marginally (Table 1, entry 2). However, by using *N*-bromosuccinimide (NBS) the yield could be increased significantly to 60% (Table 1, entry 3). The use of the very reactive brominating agent BDSB ($BrSEt_2 \cdot SbCl_5Br$), developed by Snyder et al.,[11] resulted in an excellent yield of 79% (Table 1, entry 4). Nearly the same yield of 76% was observed using 1,3-dibromo-5,5-dimethylhydantoin (1,3-DBDMH) (Table 1, entry 5). For further optimization this

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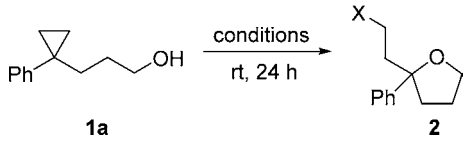
Table 1. Halocyclization of Cyclopropanol 1a: Optimization of Reaction Conditions



1a 2

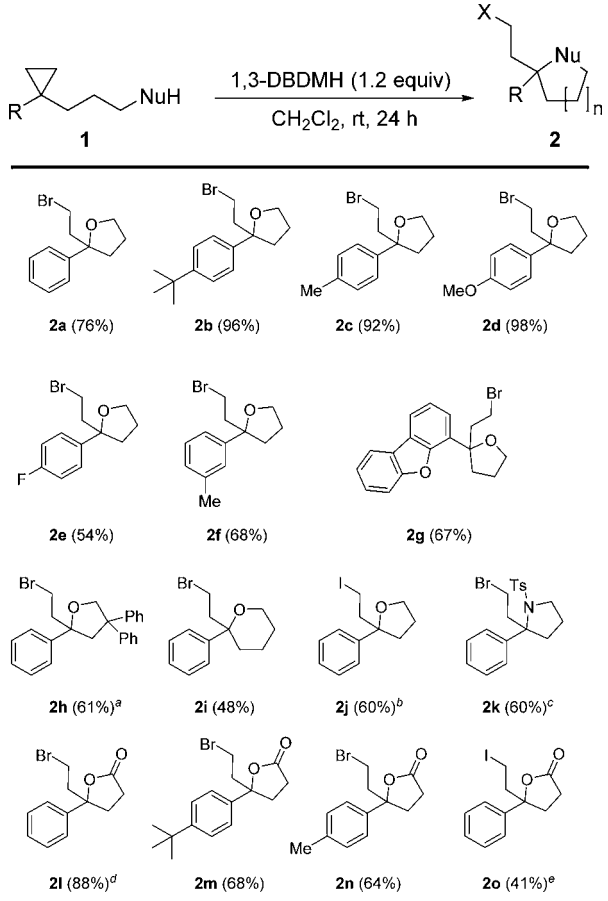
entry	reagent (1.2 equiv)	solvent	yield [%]
1	Br_2	CH_2Cl_2	41
2	TBCO	CH_2Cl_2	47
3	NBS	CH_2Cl_2	60
4	$BrSEt_2^+ \cdot SbCl_5Br^-$	CH_2Cl_2	79
5	1,3-DBDMH	CH_2Cl_2	76
6	1,3-DBDMH	THF	39
7	1,3-DBDMH	CH_3CN	49
8	1,3-DBDMH	toluene	14
9	1,3-DBDMH[a]	CH_2Cl_2	69
10	NIS	CH_2Cl_2	8
11	$BnMe_3N^+ \cdot ICl_2^-$	CH_2Cl_2	18
12	ICl	CH_2Cl_2	52

[a]0.6 equiv of 1,3-dibromo-5,5-dimethylhydantoin (1,3-DBDMH).

reagent was chosen due to its low acquisition costs and simpler handling. Attempts to increase the yield by using different solvents led to no improvement, and yields in less (toluene) and more polar solvents (THF, MeCN) were lower than in dichloromethane (13−69%) (Table 1, entries 6−8). The yield of product **2a** was good (69%) but no longer excellent if only 0.6 equiv of 1,3-DBDMH were used (Table 1, entry 9). This shows that both bromine atoms of 1,3-DBDMH do react, but better yields are obtained if only the more reactive bromine is required. The use of iodinating agents such as NIS or iododichloride salts to induce iodocyclizations was also possible; however, the reactions took much longer, and the yield of iodocyclization product **2k** after 24 h was low (Table 1, entries 10, 11). Only with the very reactive iodine monochloride high conversion was observed after 24 h and the iodocyclization product **2k** could be isolated in 52% yield (Table 1, entry 12).

With the optimized reaction conditions in hand the scope of the reaction was investigated (Scheme 2). Starting materials bearing alkyl groups in the *para*-position on the aryl group led to excellent yields [**2b** (96%), **2c** (92%)]. Substrate **1d** with an even more electron-donating methoxy group was converted to the product **2d** in an even better yield (98%). With an electron-withdrawing fluorine substituent in the *para*-position the bromocyclization product **2e** was produced in lower yield (54%). Substituents in the *meta*- or *ortho*-position were well tolerated including bulky substrate **1g**, bearing a benzofurane substituent. In both cases the cyclization products **2f** and **2g** could be obtained in good yield (68% and 67%, respectively). Furthermore, the linker between the cyclopropane and the hydroxyl group can contain substituents such as two phenyl groups (**2h**, 64%) or an additional CH_2 group to give pyran derivative **2i** via a 6-*exo* cyclization (48%). As mentioned before, the corresponding iodocyclizations are slower than the bromocyclizations. Nevertheless, under slightly optimized conditions (trifluoroethanol, 72 h) the iodocyclization product **2j** was obtained in respectable yield (60%) using *N*-iodosuccinimide as an iodinating agent. Finally, the reaction was not limited to cycloetherifications and the hydroxyl group can be replaced by other nucleophilic groups such as carboxyl

Scheme 2. Scope of Haloetherification, Halolactonization, and Haloamination



[a]NBS (1.1 equiv) instead of 1,3-DBDMH in F_3CCH_2OH/CH_2Cl_2 1:1. [b]NIS (1.2 equiv) instead of 1,3-DBDMH, reaction time 72 h, F_3CCH_2OH instead of CH_2Cl_2. [c]F_3CCH_2OH instead of CH_2Cl_2. [d]1,3-DBDMH (1.7 equiv), reaction time 77 h. [e]*N*-Iodopyrrolidin-2-one (1.2 equiv) instead of 1,3-DBDMH, reaction time 72 h, addition of 2 mL of F_3CCH_2OH.

groups or tosyl amides. For example, compound **1k** carrying a tosylamide instead of a hydroxyl group could be cyclized to the tosylated pyrrolidine **2k** in good yield (60%) under the standard conditions. Bromolactonizations of the cyclopropane derivatives **1l**, **1m**, and **1n** proceeded equally well and delivered the γ-lactones **2l**, **2m**, and **2n** in good to very good yields. Again, the corresponding iodolactonization was slower and required adjusted reaction conditions to give lactone **2o** in moderate yield (41%).

The similarity in reactivity of cyclopropanes to alkenes suggests a mechanism related to conventional alkene halocyclizations. For alkene halocyclizations, it is usually assumed that a cyclic, three-membered halonium ion, a haliranium ion, is formed as an intermediate explaining the stereospecific *anti*-addition.[12] However, whereas cyclic halonium ions with a ring size of three and five are well-known, examples with a four-membered ring, haletanium ions, have only been observed in special cases or implicated as reaction intermediates based on stereochemical grounds.[13] This leads to the question if the intermediate of the current transformations is either a rare cyclic, four-membered bromonium ion, brometanium ion **A**, or a benzylic carbocation **B** (Scheme 3). For the dibromination of different cyclopropanes the reaction

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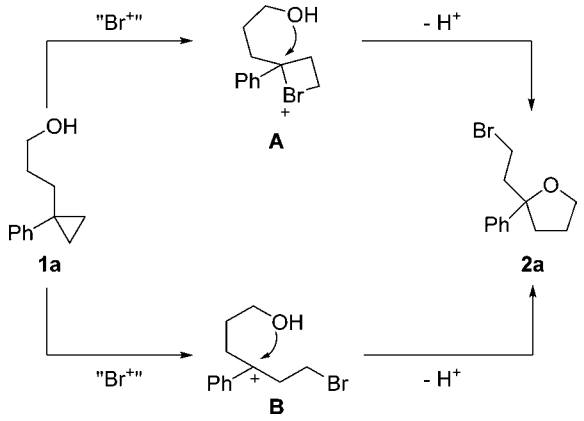
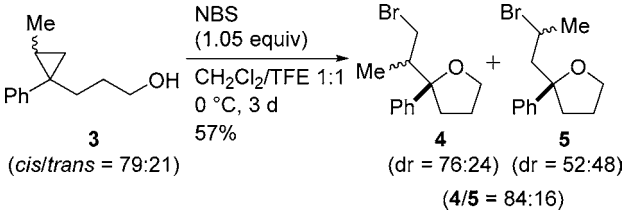
Scheme 3. Possible Mechanism of the Bromocyclization of Cyclopropanols



via a cyclic halonium ion as well as a carbocation has been suggested.[5] In our case, the higher yields obtained with starting materials containing electron-rich aryl groups could point to a benzylic carbocation **B** as an intermediate; however, brometanium ion **A** would probably also be stabilized by an electron-donating group. Nevertheless it should be possible to distinguish between these scenarios based on the stereochemistry of the cyclizations as the involvement of **A** should lead to a stereospecific reaction whereas **B** should not.

To investigate this question for the present case, methyl-substituted cyclopropane derivative **3** was prepared. Unfortunately, it proved to be very difficult to prepare or isolate **3** as a single diastereoisomer and only a mixture of ***cis*-3** and ***trans*-3** (79:21) could be obtained. Upon treatment with electrophilic brominating agents such as 1,3-DBDMH or NBS cyclopropane **3** underwent bromocyclization. Depending on the reaction conditions a product mixture was obtained containing two different, regioisomeric cyclization products, each consisting of two diastereoisomers. Additionally, aromatic bromination of the cyclization products was observed. However, under optimized conditions (NBS in CH_2Cl_2/TFE 1/1 at 0 °C) aromatic bromination could be almost completely suppressed and the bromcyclization product **4**, which is formed by bromination at the least hindered cyclopropane carbon, was formed as the major regioisomer (Scheme 4). The diastereo-

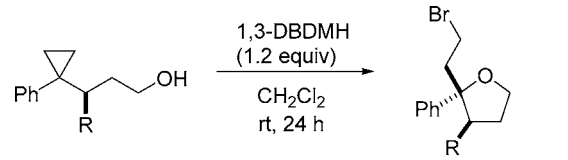
Scheme 4. Bromocyclization of a Trisubstituted Cyclopropane



meric ratio (76:24 dr) was only slightly lower than in the starting material. This effect was much more pronounced for the minor regioisomer **5**, resulting from bromination at the more hindered cyclopropane carbon, which was formed in 52:48 dr, indicating a nonstereospecific reaction. Based on these initial experiments we suggest a reaction via the benzylic, tertiary cation **B**. The observed diastereoselectivity is probably induced by the preexisting stereocenter during the cyclization onto the benzylic carbocation **B**. Nevertheless, it is clear that further, more extended studies on the mechanism are necessary.

If the reaction is indeed taking place via the benzylic carbocation **B**, this offers the possibility to control the relative configuration by a substituent in the α-position to the cyclopropane. In alkene halocyclization a substituent in this position leads to very high diastereoselectivities.[14] Furthermore, for benzylic carbocations, Bach has also shown that very high diastereocontrol can be obtained by substituents in this position.[15] To test this hypothesis α-substituted cyclopropane derivatives **6a–c** were prepared (Scheme 5). Upon treatment

Scheme 5. Highly Diastereoselective Bromocyclization of α-Substituted Cyclopropanes 7a–c



6a, R = Ph
6b, R = Me
6c, R = Et

7a (63%, dr = 91:9)
7b (50%, dr = 95:5)
7c (55%, dr = 84:16)

with 1,3-DBDMH under standard conditions phenyl-substituted **6a** underwent clean cyclization to the trisubstituted tetrahydrofuran **7a** in good yield (63%) and with excellent diastereoselectivity (91:9 dr). The relative configuration of the main product was established using NOESY experiments. The substituent R is placed *cis* to the 2-bromoethyl group, which is in agreement with an addition of the hydroxyl group to the benzylic carbocation via a conformation with a minimized allylic-1,3-strain.[16] With alkyl substituents in the α-position, similar high diastereoselectivites were observed. The methyl- and ethyl-substituted tetrahydrofurans **7b** and **7c** could be obtained in moderate yield and diastereoselectivities of 95:5 and 84:16 dr, respectively (Scheme 5).

In summary we have demonstrated that cyclopropane derivatives can undergo halocyclizations in very much the same way as alkenes, alkynes, and allenes. However, instead of vicinal addition products, 1,3-addition products are obtained. This means the combination of a cyclopropanation, which could be a highly enantioselective metal-catalyzed variant, followed by halocyclization leads to the formation of homohalocyclization products with two new, neighboring stereocenters. This two-step sequence is ideally suited for the rapid generation of complex molecules from simple alkenes as starting materials. Reagent-controlled asymmetric versions of these reactions are currently under development in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for the preparation of all starting materials and products including full spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01315.

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Notes

The authors declare no competing financial interest.

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