Synthesis of Spirocyclic Compounds by a Ring-Expansion / Cationic Cyclization Cascade Reaction of Chlorosulfate Derivatives

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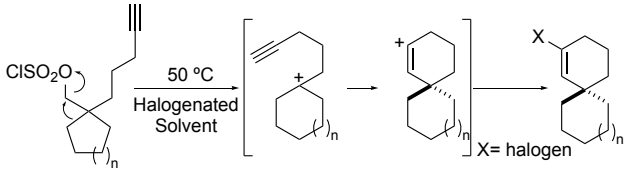
Supporting Information Placeholder



Elimination / Ring Expansion / Cationic Cyclization / Halide Trapping

ABSTRACT: A novel cascade reaction to prepare spirocarbocyclic compounds from chlorosulfate derivatives has been developed. The process involves an unusual thermal elimination of the chlorosulfate moiety, a ring-expansion reaction and a subsequent cationic cyclization reaction. Despite the relatively complex skeletal rearrangement, the reaction here described is featured by its operational simplicity, being just a thermal process that does not require of additional reagents, catalysts or additives.

Molecules containing a spirocyclic motif have been established as an important class of organic compounds. The tetrahedral nature of the spirocarbon atom confers these molecules well-defined three-dimensional spatial arrangements and so, many spirocyclic compounds specifically bind to enzymes and other biological receptors. Not surprisingly, many natural products,[1] drugs,[2] odorants,[3] and other biological active molecules contain in their structure a spirocarbocycle (some representative examples are shown in Figure 1).[4] Also, owing to the rigidity of spiranic carbocycles, compounds of this type are being widely used as ligands in asymmetric catalysis (i.e. SPINOL; see Figure 1).[5] From the synthetic point of view, the access to spirocarbocycles is a challenging task because creating the spiro quaternary carbon is usually a difficult synthetic transformation. All these features make spirocarbocycles attractive synthetic targets and substantial research in the field has been published.[6] However, the development of new approaches to synthesize spirocarbocycles is an area of undoubted interest.

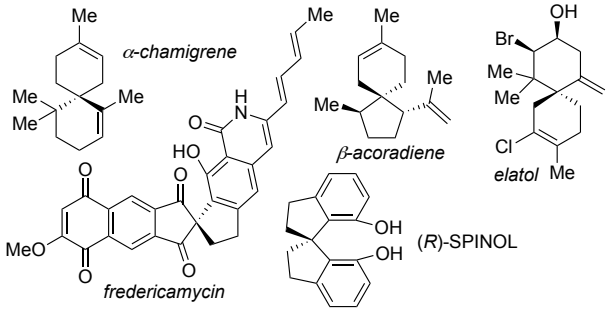
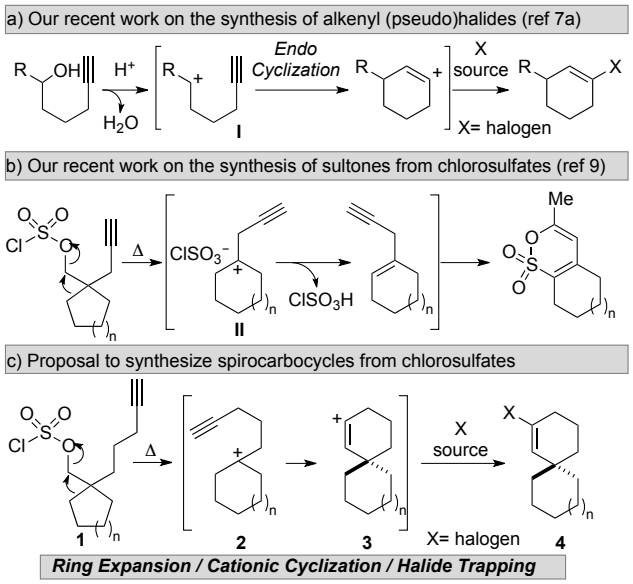


Figure 1. Interesting molecules containing a spirocarbocycle

On the other hand, we have recently reported the synthesis of cyclohexenyl halides through a cationic cyclization reaction of pentyn-5-ol derivatives (Scheme 1a).[7] This reaction proceeds through an acid promoted dehydration reaction to generate cationic species **I**. Intramolecular trapping of this cation by addition of the alkyne forms an alkenyl cation that in the presence of a halogen source generates the final cyclohexenyl halides.[8]

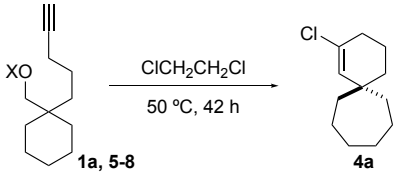
Scheme 1. Previous work and proposal



Also, we have recently reported an unusual reaction of alkyne-containing chlorosulfate derivatives to get sultones (Scheme 1b).[9] This thermal reaction proceeds through an initial ring-expansion process that renders an ionic pair **II**, which after an elimination reaction and subsequent addition of the in situ formed chlorosulfonic acid, forms the final sultone derivatives.

Taking into account all these precedent work, we conceived a new method to get spirocarbocycles from simple chlorosulfate derivatives based on a cascade ring expansion / cationic cyclization / halide trapping process (Scheme 1c). More precisely, we considered that chlorosulfate derivatives **1**, similar to those shown in Scheme 1b but containing a longer chain connecting the alkyne and the quaternary carbon, should evolve under thermal conditions to get cationic species **2** through a ring expansion reaction. Considering our work shown in Scheme 1a, this cation could be trapped by the alkyne to form alkenyl cation **3** that in the presence of a halogen source should render spirocarbocycles **4**. Details on the development of this cascade process and other related reactions aimed to the synthesis of spirocarbocycles are herein shown.

Table 1. Initial experiments



entry	starting mat.	X	yield (%)[a]
1	**1a**	$ClSO_2$	92
2	**5**	$MeSO_2$	-[b]
3	**6**	4-$MeC_6H_4SO_2$	-[b]
4	**7**	CF_3SO_2	-[c]
5[d]	**8**	H	-[c]

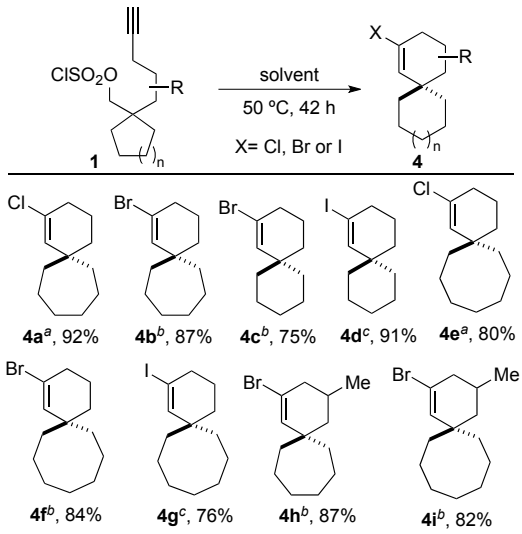
[a] Based on **1a**, **5**-**8**. [b] Starting material recovered. [c] Complex mixture of unidentified products. [d] Reaction performed in the presence of 1 equivalent of HBF_4·Et_2O.

In our initial experiment, chlorosulfate derivative **1a** was used as a model substrate to explore the viability of the proposed strategy (Table 1, entry 1). Thus, taking into account our previous research,[7,9] we simply heated this compound at 50 ºC in 1,2-dichloroethane as solvent and source of chloride. Gratifyingly, we observed the clean formation of the desired [5.6] spirocarbocycle **4a** in very high yield (92%). Considering that in this reaction the chlorosulfate group formally acted as a leaving group, we thought that other leaving groups could also be appropriate in this transformation. Thus, in order to determine if this new reaction was specific of chlorosulfates or it could be performed with related reagents, we did some additional experiments. Thus, we tried the reaction with starting materials such as mesylate (**5**), tosylate (**6**) and triflate (**7**) derivatives (Table 1, entries 2-4). Despite containing excellent leaving groups, low reactivity and/or formation of complex mixtures was observed when they were reacted under identical conditions to those previously applied for chlorosulfate **1a**. We also considered the possibility of getting our desired product **4a** from alcohol **8** (Table 1, entry 5). From this starting material, we thought that formation of the initial cation **II** (see Scheme 1b) could be promoted by an acid. However, when this alcohol **8** was reacted with one equivalent of tetrafluoroboric acid (HBF_4) in 1,2-dichloroethane we observed the formation of complex mixtures of products where the desired [5.6] spirocarbocycle **4a** could not be identified. All these experiments showed that the proposed strategy to get spirocarbocycles was viable but only when chlorosulfate derivatives were used as starting materials.[10] The absence of reactivity, under our reaction conditions, of the mesylate and tosylate derivatives could be associated to their poorer leaving group ability (OMs < OTs <OSO_2Cl < OTf). On the other hand, the triflate derivative seems to be too reactive.[11]

At this point, it should be noted that most of the known reactivity of chlorosulfates is limited to formal substitutions of the chlorine atom by nucleophiles.[12] Consequently, the above commented reaction supposes a new application of chlorosulfate derivatives in organic synthesis. It should also be noted that the new reaction here described does not require any reagent or additive, being just a thermal process. This makes this reaction different from our previous work on the synthesis of alkenyl halides where an acid was required to promote the reaction.[7a]

Next, we explored the scope of the reaction on different substrates (Scheme 2). In order to get spirocarbocycles substituted with different halogen atoms, the reactions were performed with different halogenated solvents (1,2-dichloroethane, dibromomethane or methyl iodide). Thus, considering that these solvents also served as source of halide,[7a,13] several spirocyclic compounds containing an alkenyl chloride, bromide or iodide were obtained in high yield. As shown, [5.5], [5.6], and [5.7] spirocarbocycles were easily obtained. However, regarding the new carbocycle containing the alkenyl halide moiety, we were not able to extend the method to the synthesis of other cycles different from a six-membered ring.[7]

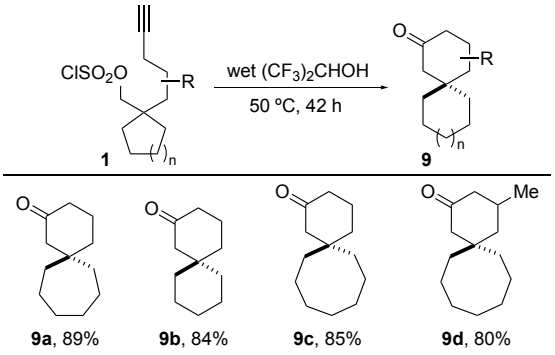
Scheme 2. Synthesis of alkenyl halide-containing spirocarbocycles **4**.



[a] Solvent = 1,2-dichloroethane. [b] Solvent = dibromomethane. [c] Solvent = iodomethane; reactions performed in a sealed tube.

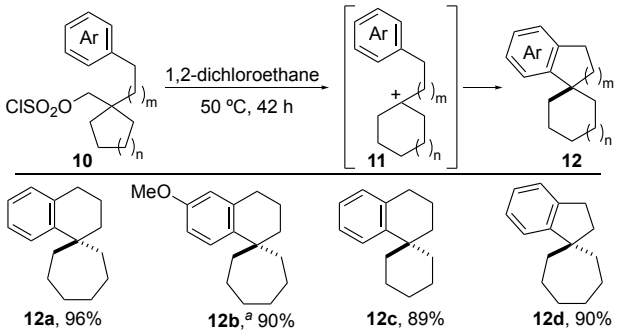
Interestingly, this method could be adapted to get spirocyclic compounds containing a ketone functionality (Scheme 3). Thus, when the solvent of the reaction was changed from a halogenated one to wet hexafluoro-2-propanol,[7b] ketones **9** were isolated in high yields. These products are supposed to be formed when the cation **3**, generated after the ring expansion / cyclization cascade process (see Scheme 1c), is trapped by a molecule of water to form an enol intermediate that tautomerizes to deliver the corresponding ketones **9**.

Scheme 3. Synthesis of ketone derived spirocarbocycles **9**.



Finally, we demonstrated that the originally proposed cascade sequence to get spirocarbocycles (see Scheme 1c) could be tuned by introducing other nucleophiles, different from an alkyne, and able to trap the in situ formed cation similar to **2**. More precisely, we considered that chlorosulfates **10**, containing an aromatic ring, could be precursors of cations **11** that after a Friedel-Crafts-type cyclization should deliver a new type of spirocarbocycles **12** (Scheme 4). In fact, when chlorosulfate derivatives **10** were heated at 50 °C in 1,2-dichloroethatne for 42 hours, we observed the clean formation of the new [4.5], [5.5] or [5.6] spirocarbocycles **12** in very high yield.

Scheme 4. Synthesis of aromatic fused spirocarbocycles **12.**



[a] Obtained as 4:1 mixture of 6'-methoxy / 8'-methoxy derivatives.

In conclusion, a new method to synthesize spirocarbocycles is described. More precisely, we have found that simple chlorosulfate derivatives may be easily transformed into spirocarbocycles through a cascade reaction that includes a ring expansion process and a cationic cyclization. This intricate rearrangement simply occurs by heating a solution of the starting material in an appropriate solvent without the need of any additional reagent or catalyst. The simplicity of the starting materials and procedure makes this reaction a useful alternative strategy to synthesize spirocarbocycles containing additional functionalities for subsequent transformations. Considering the limited reported applications of chlorosulfates, the work here presented further expands the utility of these molecules in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

Supporting Information.
Experimental details and characterization data for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(10) Evolution of chlorosulfate **1** to the corresponding cation (ionic pair) **2** is believed to occur through a cascade process that implies an initial [2,3]-sigmatropic rearrangement of the chlorosulfate group and a simultaneous [1,2]-alkyl shift. For a computational study on this atypical formal *type I dyotropic rearrangement*, see reference 9.

(11) We suspect that trace amounts of triflic acid are formed from triflate derivative **7** under the reaction conditions. This strong acid could promote the undesired decomposition and/or polymerization reactions of the starting material and/or products.

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