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

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01101 Read Online

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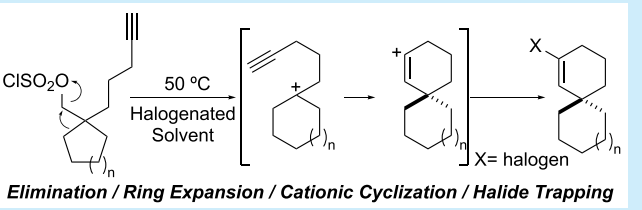
ABSTRACT: A novel cascade reaction to prepare spirocarbocyclic compounds from chlorosulfate derivatives has been developed. The process involves an unusual thermal elimination of the chlorosulfate moiety, a ring-expansion reaction, and a subsequent cationic cyclization reaction. Despite the relatively complex skeletal rearrangement, the reaction described here is featured by its operational simplicity, being just a thermal process that does not require 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 3D 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

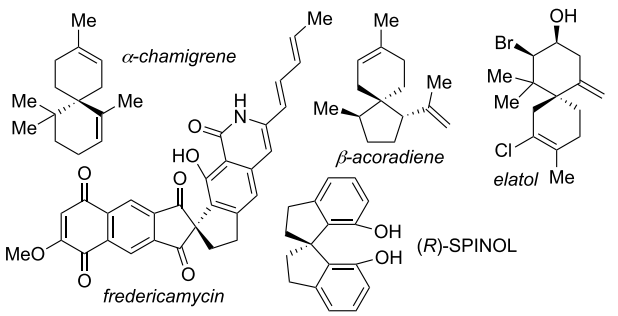
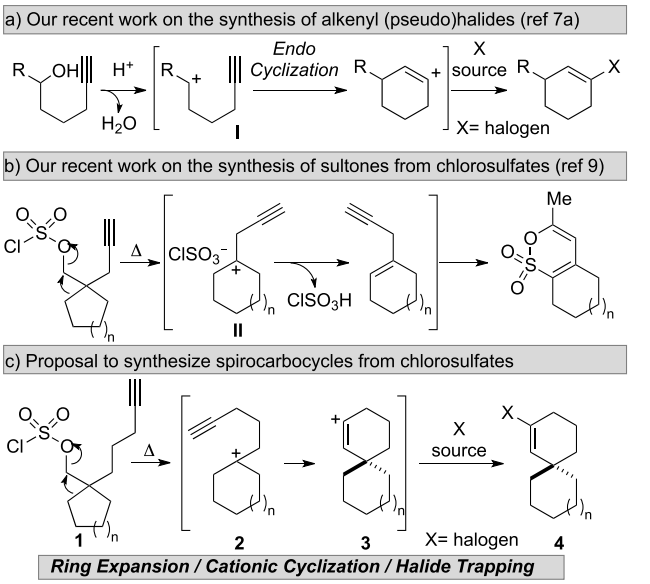


Figure 1. Interesting molecules containing a spirocarbocycle.

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, access to spirocarbocycles is a challenging task because creating the spiro quaternary carbon is usually a difficult synthetic transformation. All of 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.

On the contrary 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

Scheme 1. Previous Work and Proposal



through an acid-promoted dehydration reaction to generate cationic species **I**. Intramolecular trapping of this cation by the addition of the alkyne forms an alkenyl cation that in the presence of a halogen source generates the final cyclohexenyl halides.[8]

Received: March 26, 2020

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 the subsequent addition of the in-situ-formed chlorosulfonic acid forms the final sultone derivatives.

Taking into account all of this 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**, which, in the presence of a halogen source, should render spirocarbocycles **4**. Details of the development of this cascade process and other related reactions aimed to the synthesis of spirocarbocycles are shown herein.

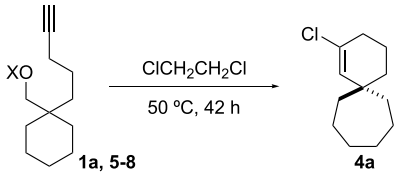
In our initial experiment, chlorosulfate derivative **1a** was used as a model substrate to explore the viability of the proposed strategy (Table 1, entry 1). Thus, taking into account our previous research,[7,9] we simply heated this compound to 50 °C in 1,2-dichloroethane as the solvent and the source 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, to determine if this new reaction was specific to chlorosulfates or if it could be performed with related reagents, we did some additional experiments. 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 the 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 the 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 of 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 with their poorer leaving group ability (OMs < OTs < OSO_2Cl < OTf). On the contrary, the triflate derivative seemed 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 previously described reaction supposes a new application of chlorosulfate derivatives in organic synthesis. It should also be noted that the new reaction described here does not require any reagent or additive and is 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). 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 a 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]

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

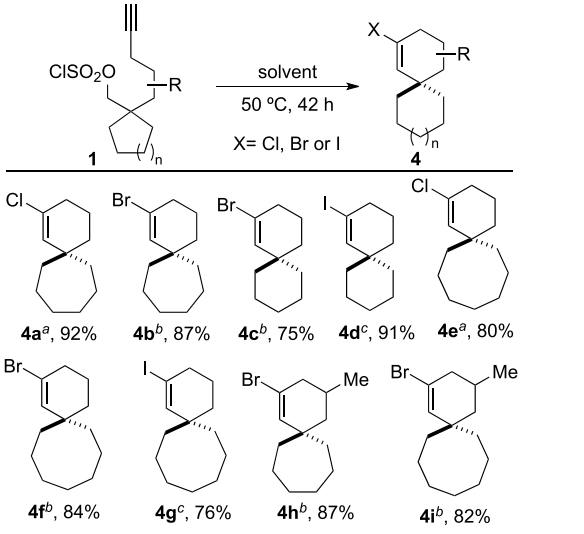
Table 1. Initial Experiments



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	[d]
5[c]	**8**	H	[d]

[a]Based on **1a** and **5**–**8**. [b]Starting material recovered. [c]Reaction performed in the presence of 1 equiv of $HBF_4{\cdot}Et_2O$. [d]Complex mixture of unidentified products.

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.

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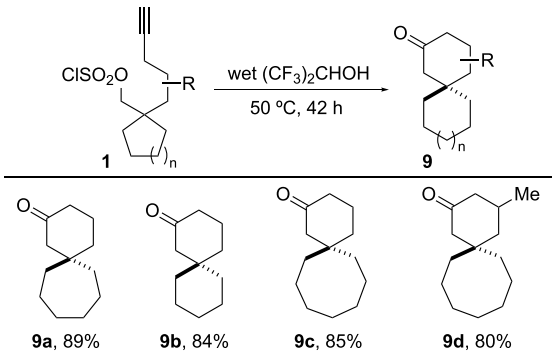
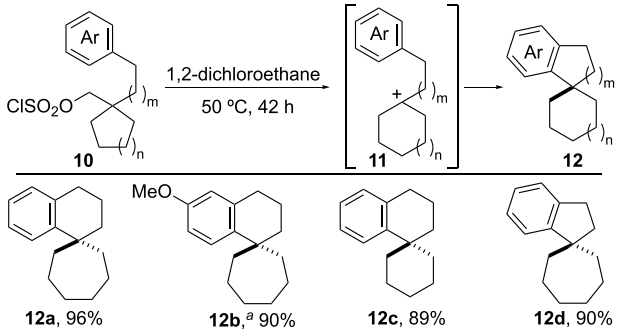
Scheme 3. Synthesis of Ketone-Derived Spirocarbocycles 9



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**.

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, that are 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**, which, after a Friedel–Crafts-type cyclization, should deliver a new type of spirocarbocycles **12** (Scheme 4). In fact, when chlorosulfate

Scheme 4. Synthesis of Aromatic Fused Spirocarbocycles 12



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

derivatives **10** were heated to 50 °C in 1,2-dichloroethane for 42 h, we observed the clean formation of the new [4.6], [5.5], or [5.6] spirocarbocycles **12** in very high yield.

In conclusion, a new method for synthesizing 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 for 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 presented here further expands the utility of these molecules in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01101.

Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the Spanish Ministerio de Ciencia, Innovación y Universidades (grant CTQ2016-76794-P and FPU-predoctoral grant to L.C.) and from the Consejería de Empleo, Industria y Turismo del Principado de Asturias (grant IDI/2018/000231).

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(10) The 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 ref 9.
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