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Chlorosulfonic acid as a convenient electrophilic olefin cyclization agent

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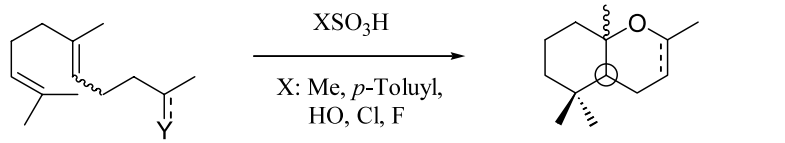
Abstract—Among several sulfonic acids studied ($MeSO_3H$, *p*-TsOH, H_2SO_4, $ClSO_3H$, FSO_3H), the scarcely used chlorosulfonic acid showed to be an efficient agent for electrophilic olefin cyclizations with internal nucleophilic termination, in a similar manner that is well-established with fluorosulfonic acid. Its availability, lower price and relatively lesser handling problems makes $ClSO_3H$ an advantageous cyclizing agent particularly for high-scale applications. The stereochemical outcome of these cyclizations has been rationalized.

Synthesis of many polycyclic isoprenoids has been accomplished following the electrophilic polyene cyclization methodology, the success of which depends on a combination of factors related to the method of initiation, the nucleophilicity of the double bonds involved, and the mechanism of termination.[1] Among the great variety of protonic and Lewis acids used as external electrophiles to initiate the cyclization, fluorosulfonic acid has shown to be a highly effective reagent for obtaining fully cyclized compounds in a structurally and chemically selective, and stereospecific way.[2] In addition, when termination of cyclization is achieved by an appropriately placed internal nucleophile, the method has been proved to be also efficient to add a final heteroatom to the polycyclic skeleton.[2b,c] In contrast to the extensive amount of work developed with FSO_3H much less research has been carried out on related protonic acids such as chlorosulfonic, sulfuric, *p*-toluenesulfonic and methanesulfonic acids, among others. Thus, the superacid $ClSO_3H$ has extensively been used as a strong sulfating, sulfonating, dehydrating or chlorinating agent,[3,4] but rarely as a cyclizing agent. It has only been used in the synthesis of several cyclic terpenoids[5] and *trans*-γ-lactonization of two homoterpenic acids.[6] Different cyclizations have been described using H_2SO_4,[7] *p*-TsOH[8] and $MeSO_3H$,[8b,9] most of them involving the generation of a single ring. Furthermore, in the course of our research on the synthesis of several odorants[10] we were able to learn about the effectiveness of *p*-TsOH, in the monocyclization of alkenols,[10c,d] and H_2SO_4 and $ClSO_3H$, in the bicyclization[10b,c] and tricyclization[10c] of polyalkenols and polyalkenones.

The general information on sulfonic acids is somewhat confused and contradictory. For example, the weak



1 Y:OH

2 Y:O

3 Octahydrobenzopyrans

4 Hexahydrobenzopyrans (Δ^2)

Scheme 1.

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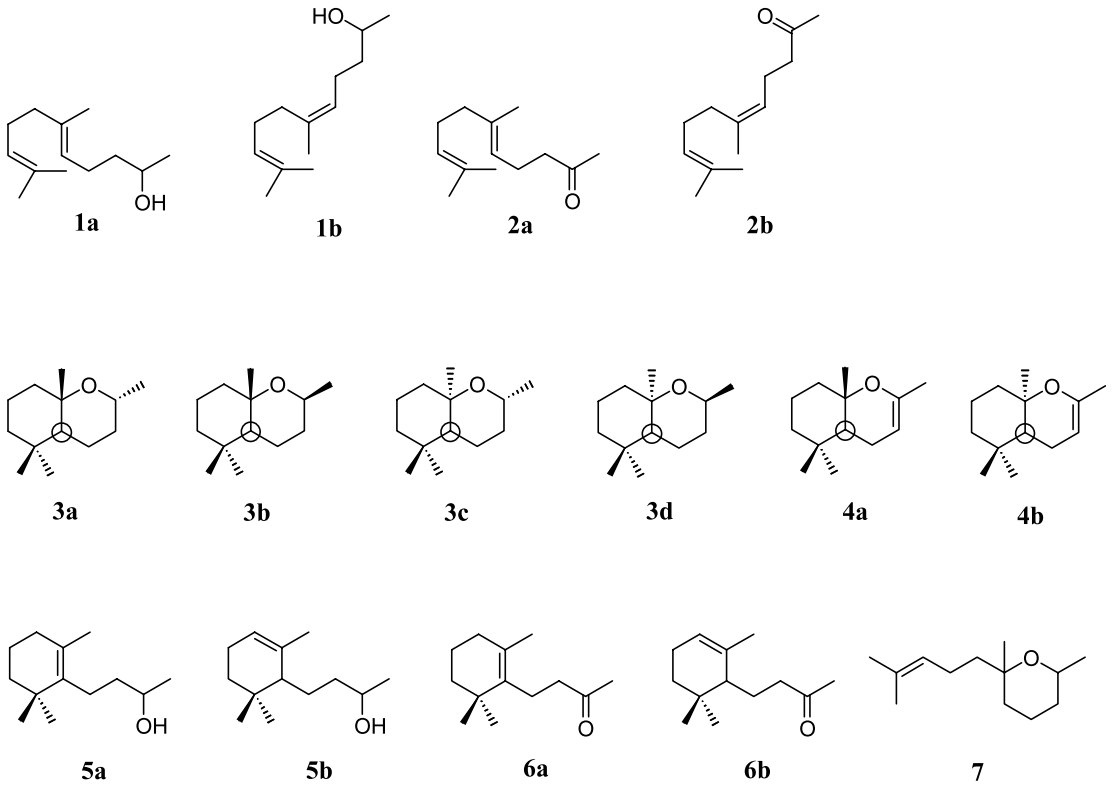
acid $MeSO_3H$[9b] has been shown to be as efficient as the superacid FSO_3H;[2b] the main purpose of this work is to know the relative cyclizing capabilities of several sulfonic acids of increasing acidity ($MeSO_3H$, *p*-TsOH, H_2SO_4, $ClSO_3H$), in comparison with that of the effective well-known FSO_3H. For that, dienols **1** and dienones **2** were chosen as starting acyclic substrates because they are able to lead to monocyclic or bicyclic compounds. The different configuration of the C_5–C_6 double bond would allow to reach conclusions on stereospecificity and the presence of internal nucleophilic functional groups enables to combine polyene and electrophilic heteroatom cyclizations.[11] In addition, the anticipated fully cyclized benzopyran derivatives **3** and **4** seem to be of some interest for the fragrance industry (Scheme 1).[12] Thus, the cyclization reactions of **1** and **2** were conducted with 5 equiv. of sulfonic acid in 2-nitropropane at −78°C.[13] The use of a considerable excess of cyclizing agent at low temperature has been used in FSO_3H-mediated cyclizations and, hence, it was assumed here as standard cyclization conditions for both stronger (H_2SO_4, $ClSO_3H$, FSO_3H) and weaker ($MeSO_3H$, *p*-TsOH) acids. However, for the latter acids the reaction temperature had to be changed to room temperature as lower values led to prolonged reaction times. In such conditions the cyclizations were normally completed after 10 min (stronger acids) or 30 min (weaker acids). As certain amounts of uncharacterized polymeric compounds always appear in FSO_3H cyclizations,[2] we decided to add a final filtration through a silica gel pad of all crude reaction mixtures in order to know the weight lost in every reaction.[13] This practice gave product recovering in the range of 70–75% for the three stronger acids and 85–90% for the weaker ones.

The acid cyclizations of alcohols **1** and ketones **2** with several sulfonic acids are summarized in Table 1. All final products **3**–**7** were identified by comparison of their chromatographic and spectroscopic data with those reported in the literature.[14,15] As may be deduced from entries 1–5 all cyclization agents mainly promoted the cyclization of the (*E*)-alcohol **1a** into bicyclic compounds **3**, although this conversion was clearly more effective when $ClSO_3H$ (entry 4) and FSO_3H (entry 5) were used. With these latter agents the cyclization of **1a** mainly yielded the *trans*-fused octahydrobenzopyran **3a**, along with a lower amount of the C-2 epimer **3b**. Although $MeSO_3H$, *p*-TsOH or H_2SO_4 are comparatively less efficient agents in the cyclization of **1a** it is worth noting that reasonable yields of **3** (60.5–73.0%) were obtained. This means that behaviors of weaker acids (entries 1–3) under the experimental conditions used here are not too different from those of the superacids, although lesser stereoselectivities (certain amounts (9.5–17.0%) of the *cis*-fused octahydrobenzopyrans **3c**,**d** are formed) and selectivities (significant amounts (26.0–34.0%) of the monocyclic compounds **5** and **7** are formed) have been observed. Before drawing a final conclusion on the comparative cyclizing abilities of all these sulfonic acids, the cyclization of the (*E*)-ketone **2a** was also studied (entries 6–10). Again, a parallel behavior could be observed, although the ratio between the *trans*-fused hexahydrobenzopyran **4a** and the *cis*-fused stereoisomer **4b** was larger in all cases

Table 1. Acid cyclizations of alcohols **1** and ketones **2**

Entry	Starting material[a]	Cyclization agent[b]	Products distribution (%)[c]						
			3a	**3b**	**3c**	**3d**	**4a**	**4b**	Others
1	**1a**	$MeSO_3H$	49.5	0.5	15.5	1.5			**1a** (3.5), **5a** (6.5), **5b** (3.0), **7** (19.5)
2	**1a**	*p*-TsOH	55.5	0.5	11.0	6.0			**1a** (0.5), **5a** (5.0), **5b** (3.0), **7** (18.0)
3	**1a**	H_2SO_4	26.5	24.5	4.0	5.5			**1a** (3.0), **5a** (31.0), **5b** (3.0)
4	**1a**	$ClSO_3H$	70.0	21.0	-	4.0			**1a** (1.5), **5a** (1.5)
5	**1a**	FSO_3H	68.0	23.0	-	5.0			**1a** (–), **5a** (1.0), **5b** (1.0)
6	**2a**	$MeSO_3H$					50.0	5.4	**2a** (5.0), **6a** (4.0), **6b** (2.1)
7	**2a**	*p*-TsOH					51.0	2.0	**2a** (3.0), **6a** (5.5), **6b** (4.0)
8	**2a**	H_2SO_4					72.5	9.0	**2a** (4.0), **6a** (1.9), **6b** (3.0)
9	**2a**	$ClSO_3H$					92.5	2.2	**2a** (–), **6a** (2.0)
10	**2a**	FSO_3H					95.0	3.0	**2a** (–), **6a** (1.6)
11	**1a**	$ClSO_3H$[d]	63.0	22.0	1.0	4.5			**1a** (1.0), **5a** (3.0), **5b** (3.0)
12	**1a**	$ClSO_3H$[e]	29.5	31.0	5.5	5.0			**1a** (13.0), **5a** (12.0), **7** (1.5)
13	**1a**	$ClSO_3H$[f]	22.0	20.5	10.0	4.5			**1a** (9.0), **5a** (21.5), **5b** (5.0), **7** (5.0)
14	**1b**	$ClSO_3H$	61.3	6.8	2.9	22.4			**1b** (0.5), **5a** (1.0), **7** (2.5)
15	**1b**	FSO_3H	65.0	14.0	2.5	16.5			**1b** (–), **5a** (1.5)
16	**2b**	$ClSO_3H$					16.0	64.7	**2b** (–), **6a** (2.0), **6b** (1.0)

[a] Alcohols **1a** and **1b** were prepared by reducing **2a** and **2b**, respectively, with $NaBH_4$ in MeOH at −10°C; ketones **2a** and **2b** were obtained by column chromatography on 20% $AgNO_3$–silica gel of a commercial sample of geranylacetone (**2a**) which contained ca. 35% of nerylacetone (**2b**).
[b] See general procedure in Ref. 13.
[c] Percentages directly deduced from the GC analysis of the crude reactions. Compounds **3**–**7** were identified by comparison of their GC retention times with those from authentic samples prepared in authors' lab.
[d] **1a**:$ClSO_3H$ ratio, 1:2.5; reaction temperature, −78°C; reaction time, 25 min.
[e] **1a**:$ClSO_3H$ ratio, 1:2.5; reaction temperature, −45°C; reaction time, 25 min.
[f] **1a**:$ClSO_3H$ ratio, 1:2.5; reaction temperature, −17°C; reaction time, 25 min.



than that observed with **1a**. Invariably, $ClSO_3H$ (entries 4, 9) seemed to have a closer behavior to FSO_3H (entries 5, 10), justifying previous complementary results.[5,6,10b,10c] This allows us to propose that $ClSO_3H$ is a convenient cyclizing agent with a very similar degree of efficiency as the well-established FSO_3H. Furthermore, the considerably lower price of $ClSO_3H$ and relative lesser handling problems[16] makes it more advantageous than FSO_3H, particularly for high-scale applications. In order to improve the experimental use of $ClSO_3H$ we explored different substrate:acid ratios and reaction temperatures. The **1a**:$ClSO_3H$ ratio could be decreased up to 1:2.5 (entry 11) without loosing efficiency, however, rising temperature (entries 12, 13) resulted in continuous loss of selectivity; less *trans*-fused **3a**,**b**, more *cis*-fused **3c**,**d** and more monocyclic compounds (**5**, **7**) were progressively obtained. Although we have previously shown that $ClSO_3H$ may

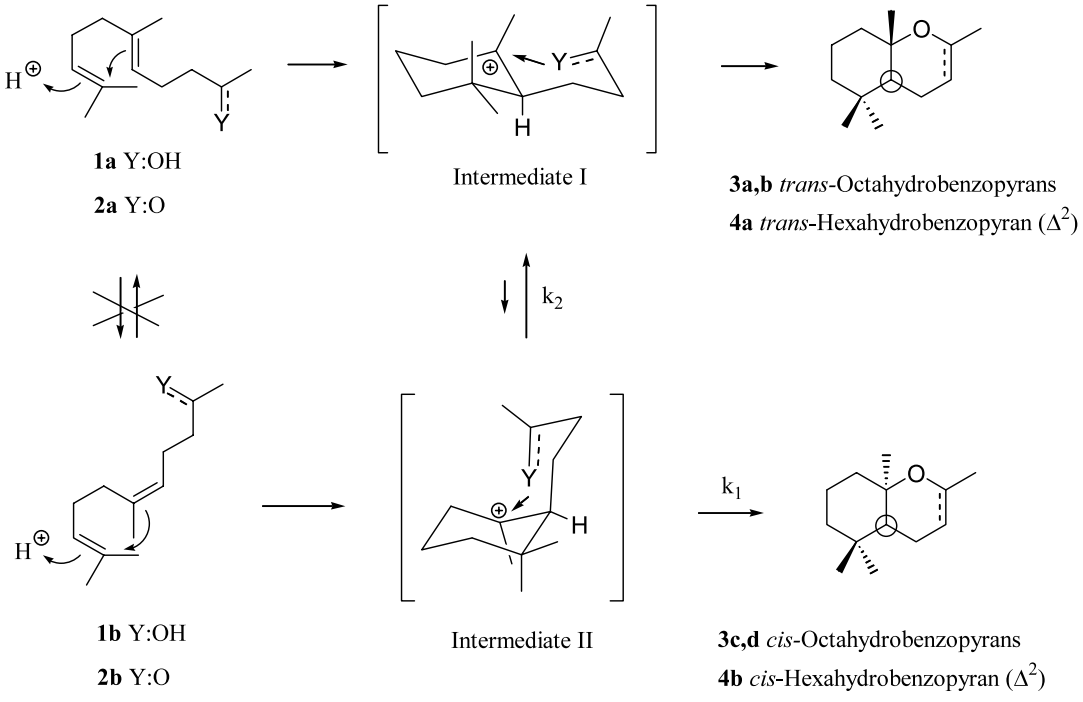


Figure 1. Proposed mechanism for the acid-mediated cyclization of alcohols **1** and ketones **2**.

perform cyclizations on a stereospecific way[10c] as FSO_3H,[2] we wished to confirm this aspect with **1a**. Thus, the (*Z*)-alcohol **1b** was treated with $ClSO_3H$ using the initial procedure (entry 14) and, surprisingly, we obtained the same major compound (**3a**). However, when the (*Z*)-ketone **2b** was reacted with $ClSO_3H$ the *cis*-fused hexahydrobenzopyran **4b** was stereospecifically formed in good yield (entry 16).

A possible explanation of the observed results is shown in Figure 1. The bicyclization of alcohols **1** and ketones **2** to give **3** and **4**, respectively, seems to occur through a nonsynchronous process involving prior ring closure to a cyclohexyl cation as variable amounts of monocyclic compounds (**5**, **6**) are detected in all cases. Thus, the main formation of the *trans*-fused octahydrobenzopyrans **3a**,**b** and hexahydrobenzopyran **4a** from **1a** and **2a**, respectively, may be rationalized by the generation of intermediate I while the smaller amounts of the *cis*-fused isomers **3c**,**d** and **4b**, obtained in the same reactions, could be explained through the conformational inversion of that A-ring cation to intermediate II and subsequent cyclization of the B-ring. In a similar manner, the cyclization of the (*Z*)-isomers **1b** and **2b** may be justified by a nonsynchronous pathway through intermediate II, although clear differences have to be present now as the stereospecificity was lost when alcohol **1b** was the starting material, also with FSO_3H (entry 15), and conserved when ketone **2b** was used. The explanation based on the isomerization of **1b** to **1a** and subsequent bicyclization through intermediate I to give **3a**,**b** was ruled out because no isomerization was observed in the recovered starting material of this reaction (entry 14). Other more probable explanation could be based on the different nucleophilicity of carbonyl and hydroxyl groups in superacidic medium; thus, the comparatively less deactivated carbonyl group (**2b**) mainly gives the *cis*-fused isomer **4b** by a nonsynchronous process where the intermediate II is rapidly attacked by the oxygen atom (k_1 bigger than k_2). However, in the case of the relatively more deactivated hydroxyl group (**1b**) the conformation inversion of the A-ring cation (intermediate II) occurs faster than the B-ring closure (k_2 bigger than k_1) leading to a nonsynchronous process where the most stable *trans*-fused isomers **3a**,**b** are obtained. This latter result along with few FSO_3H-mediated cyclizations of monoterpenoids[2b] are the only exceptions to the regularities described for superacid induced cyclizations.

In conclusion, chlorosulfonic acid is found to accomplish electrophilic olefin cyclizations as efficiently as fluorosulfonic acid and, hence, its protonating superacid properties should be reevaluated.

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13. *Acid cyclization of alcohols* ***1*** *and ketones* ***2***. *General procedure*: To a solution of 2.50 mmol of sulfonic acid (99.5% $MeSO_3H$, 98.5% *p*-$TsOH{\cdot}H_2O$ dehydrated according to Ref. 17, 98% H_2SO_4, 99% $ClSO_3H$, triple-

distilled FSO_3H) in 2-nitropropane (3 mL) was added ($MeSO_3H$, *p*-TsOH) dropwise (H_2SO_4, $ClSO_3H$, FSO_3H) a solution of **1** or **2** (0.5 mmol) in 2-nitropropane (6 mL) at room temperature ($MeSO_3H$, *p*-TsOH) or −78°C (H_2SO_4, $ClSO_3H$, FSO_3H) under argon. After stirring for 30 min ($MeSO_3H$, *p*-TsOH) or 10 min (H_2SO_4, $ClSO_3H$, FSO_3H) at those temperatures a saturated aq. $NaHCO_3$ solution (10 mL) was injected and then further portions of solid $NaHCO_3$ were added to obtain basic pH. Brine (20 mL) and Et_2O (15 mL) were added and the mixture extracted with Et_2O (3×15 mL). After drying the combined organic layers with anhydrous Na_2SO_4 and evaporation of the solvent under reduced pressure, a residue was obtained which was filtered through an SiO_2 (70–230 mesh) pad (1 cm width×2 cm high) using a 1:1 hexane–Et_2O mixture (100 mL) as eluent. This solution was concentrated to dryness, weighed and analyzed directly by GC.

14. Octahydrobenzopyrans **3a**–**d** were purified from several cyclization crude reactions of **1a** and **1b** by successive carefully performed silica gel column chromatographies. Hexahydrobenzopyran **4a** was directly obtained by stereoselective cyclization of **2a** (Table 1, entries 9 and 10) and the stereoisomer **4b** by cyclization of **2b** (entry 16) followed by further purification on silica gel column chromatography. Reference samples of alcohols **5a** and **5b** were prepared by reducing **6a** and **6b**, respectively, with $NaBH_4$ in MeOH at −10°C. Ketones **6a** and **6b** were obtained from commercial β-ionone and α-ionone, respectively, by Raney-Ni induced catalytic hydrogenation.[10b,c] Pyran **7** was purified from crude reactions of **1a** with $MeSO_3H$ and *p*-TsOH (entries 1 and 2). Spectral data of all these purified compounds were according to those reported in the literature.[15]
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16. Both superacids are corrosive and have to be handled in a fume hood with proper protection. However, we have used $ClSO_3H$ for a long time with the same precautions as with H_2SO_4 and taking samples from bottles opened to the air during the process without detecting loss of efficiency, despite some formation of SO_3 (or H_2SO_4) and HCl.[18]
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