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THE ELECTROPHILICALLY INITIATED RING OPENING OF SOME CYCLOBUTANONE DERIVATIVES

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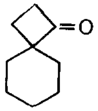
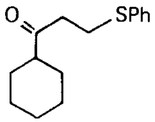
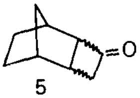
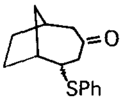
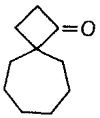
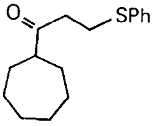
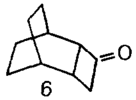
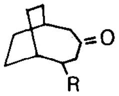
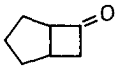
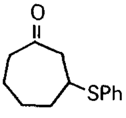
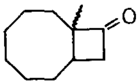
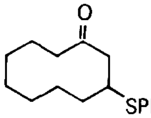
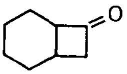
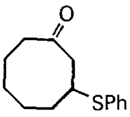
Cyclobutanone derivatives by virtue of their reactivity have proved to be valuable synthetic intermediates, and recent synthetic advances have increased their accessibility.[1] Most useful transformations of these compounds are initiated by addition of reagents to the strained carbonyl and subsequent ring expansion, contraction or opening. Ring enlargement usually involves bond migration to an election deficient center (e.g., Baeyer-Villiger oxidation) while ring contraction or opening occurs by cleavage of the initial carbonyl adduct.[2] In many cases, the regiospecificity of these processes is high enough to be synthetically valuable. In addition, the reactivity of cyclobutyl systems has been demonstrated by the facile rearrangement of the corresponding cations which also often show high and predictable regioselectivity.[3,4] Since cyclobutanones themselves are potential sources of oxycyclobutyl cations upon reaction with strong electrophiles, it seemed reasonable that the ring opening of these derivatives could be electrophilically initiated. This phenomenon has been reported only for a limited number of highly substituted derivatives in very strongly acidic media.[5]

Preliminary mechanistic studies suggested that the combination of anhydrous hydrogen chloride and zinc chloride in the presence of a nucleophile such as thiophenol initiated the ring opening of certain spirocyclobutanones to yield γ-ketosulfides. We now report the general application of this technique to a variety of cyclobutanone derivatives (see Table 1).[6]

In each case the rearrangement product is a γ-ketosulfide which is a useful intermediate in many synthetic transformations. For example, simple desulfurization with Raney nickel in acetone produced the saturated ketones, while sequential oxidation with sodium metaperiodate and subsequent heating generated the corresponding enones in good yield. In each case examined, the regioselectivity of the electrophilically initiated rearrangement was high. Examination of the crude reaction mixtures by nmr and glpc failed to reveal significant quantities of the methyl ketones. This regioselectivity is particularly useful for the bicyclo [n.2.0] ketones (e.g., 3, 4 and 7), which are easily prepared from the corresponding cyclic olefin via addition of dichloroketene and subsequent dechlorination,[7] since it allows a simple two carbon ring expansion to the corresponding cyclic ketone derivatives.

Table I.

 1	 8 (70%)[a]	 5	 12 (70%)
 2	 9 (65%)	 6	 13 R = SPh and Cl (75%)[b]
 3	 10 (61%)	 7	 14 (75%)
 4	 11 (45%)		

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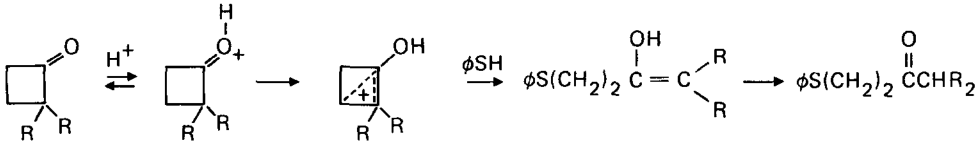
[a] Isolated yields of purified products

[b] Isolated as a 4/1 mixture of sulfide and chloride

While the mechanism of this conversion is unclear at this point, a reasonable hypothesis is shown below.



Protonation of the ketone in the acidic medium would generate a cation potentially capable of ring opening. In this respect, substituent scrambling and ring openings have been reported for a limited number of highly substituted cyclobutanones in sulfuric acid.[5] In these cases, where a suitably nucleophilic counterion was lacking, the products were unsaturated ketones. Under our conditions, the observed regioselectivity of the ring opening was correctly predicted by the formation of the more highly substituted enol. The presence of thiophenol is essential for the successful transformation of the ketones in Table I. For example, the treatment of 3 with the HCl-$ZnCl_2$ reagent alone led to the recovery of considerable starting material even after 5 days. Under these conditions, even the material which had reacted produced a complex reaction mixture. The function of the nucleophile seems most reasonably to be the capture of a rearranged cationic species rather than simple nucleophilic displacement on the protonated ketone. This is suggested by the facile reaction of the bicyclo [n.2.0] ketones resulting in nucleophilic capture at the relatively sterically hindered former bridgehead site. Also consistent with this suggestion was the isolation of the γ-ketosulfides 12 as an empimeric mixture from the rearrangement of endo-tricyclo[4.2.1.$0^{2,5}$]nonan-3-one (endo-5). In a similar fashion exo-5[8] generated the same epimeric mixture of sulfides.

General Procedure for the Electrophilic Rearrangement of Cyclobutanones

Anhydrous hydrogen chloride was bubbled through a well-stirred suspension of 1.0 mmole of freshly fused zinc chloride in 10 ml of CH_2Cl_2 for 1 hr at 25°. To this mixture which had been cooled to 0° was added the cyclobutanone derivative (1 mmole). A solution containing 1.1 mmole of distilled thiophenol dissolved in 2 ml of CH_2Cl_2 was added at 0° over 1 hr, and the resulting mixture was stirred at 0° for 3 hrs. The reaction mixture was then allowed to warm to room temperature and stirred vigorously until infrared analysis indicated the complete consumption of the cyclobutanone. The mixture was then poured into ether and washed with 5% sodium hydroxide and 10% brine solution. After drying, the solvent was removed and the residue distilled (0.05 mm) to yield the desired γ-ketosulfide.

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