239. The Reaction of Cyclopropyl Ketones with Acetyl Methanesulfonate. An Efficient Ring Opening under Neutral Conditions with Regiospecific Enol Acetate Formation and Stereo-controlled Nucleophilic Addition

Preliminary communication[1])

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Summary

Cyclopropyl ketones are readily cleaved under neutral conditions at room temperature by the combined action of acetyl methanesulfonate and nucleophiles such as Br^-, I^-, and MsO^-. The high-yield reaction involves regiospecific enol acetate formation with a stereoselectivity of nucleophile addition which is compatible with an S_N2-type opening of the cyclopropyl ring.

Nucleophilic ring opening of cyclopropyl carbonyl compounds, which has attracted much attention over the past years, has been undertaken in three principal ways: *a*) Doubly activated cyclopropyl moieties undergo cleavage with numerous nucleophiles [1] [2]; *b*) A limited number of monoactivated cyclopropane derivatives may be opened if the ring system itself is sufficiently strained, or by particularly powerful nucleophiles [1]; *c*) Cyclopropyl ketones undergo electrophile-assisted nucleophilic reactions [3] [4][2])[3]). Our own work was aimed at the elaboration of versatile ring cleavages of the third category (*c*), with particular regard to the cyclopropyl ketones which are readily available from acetone-sensitized oxadi-π-methane photorearrangements [7]. Appropriate functionalisations of, *e.g.*, **4a** and **4b** *(Table)* would provide access to a series of natural products.

One literature example appeared especially interesting. Here a cyclopropane (**1**; *Scheme*) is opened with the *Mazur* reagent (acetyl methanesulfonate (AcOMs) [8]) with intramolecular participation of a donor double bond ($\rightarrow$**2**) affording (epi-)cedrone (**3**) [3]. Activation of the ketone with AcOMs (*cf.* **4**$\rightarrow$**5**) should have the general effect of increasing the electrophilicity of the cyclopropane moiety towards nucleophiles which are insufficiently reactive to attack **4** alone. At the same time, when no intramolecular ring closure as in **1**$\rightarrow$**3** is involved, regiospecific enol acetate formation could be an additional synthetic feature ($\rightarrow$**6**).

Indeed, Br^- and I^- are successfully introduced from their tetramethylammonium salts in the case of several cyclopropyl ketones (**4a–e**; *Table*). Quaternary

[1]) Presented at the ESOC I Conference, Köln (1979).

[2]) A specific example of acid-catalyzed ring cleavage is the treatment of **4a** with HBr [5].

[3]) S_N2 ring-opening of *Lewis* acid-activated cyclopropyl ketones was originally proposed by *Stork* [6] and confirmed in [3].

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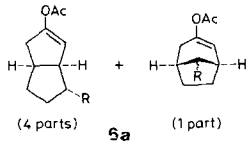
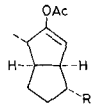
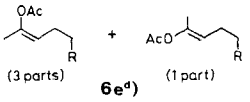
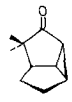
ammonium salts were chosen as the nucleophilic source because of their solubility and their potential to effect configurational equilibration in organic solvents [9]. In the case of products such as **6a** (mixture of two structural isomers) and **6b** it could therefore be expected that the C(8)-*exo*-epimer would be very much favoured over the *endo*-isomer.

The influence of the substitution pattern on the behaviour of the cyclopropyl ketones **4a**, **4b** and **4f** was of particular mechanistic interest. The unsubstituted tricyclo[3.3.0.$0^{2,8}$]octan-3-one (**4a**) was cleaved at C(1) and C(8) in the same ratio

Table[a])

Starting Cyclopropyl Ketones	Products[b]) R = Br, I	Yield[c]) %	Reaction time h
 **4a**	 (4 parts) **5a** (1 part)	87 (95)	24
 **4b**	 **6b**	72 (89)	24
 **4c**	 **6c**	82 (93)	72
 **4d**	 **6d**	94	48
 **4e**	 (3 parts) **6e**[d]) (1 part)	81[e])	80
 **4f**	no reaction	-	-

[a]) The starting ketones **4** in CH_3CN under argon were treated at room temperature with a two-fold excess of AcOMs [8] (which can be stored for several months in a deep freeze) and an equivalent excess of tetramethylammonium bromide or iodide. In general the best yields were achieved in CH_3CN, but CH_2Cl_2 can also be used. In the work-up, the solvent was removed *in vacuo* and the residue taken up in ether/H_2O. The iodo compounds are labile and should be used for further transformations shortly after isolation.

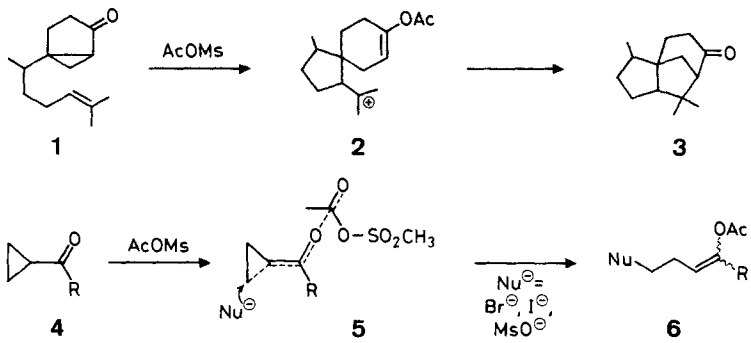
[b]) All products gave satisfactory analytical data (GLC., IR., 270 MHz, ^{1}H-NMR., MS.).

[c]) Yields of isolated bromo products (the yields of the corresponding iodo compounds did not differ significantly); GLC. analysis of crude reaction mixture in parentheses.

[d]) The 3:1 ratio reflects the preferential conformation of the three-membered ring parallel to the carbonyl π orbital (bisected conformation); *cf.* [9].

[e]) GLC. of crude reaction mixture showed 15% of unreacted **4e**.

Scheme



(1:4) as upon treatment with HBr [5]. The result most likely reflects thermodynamic control. Only one epimer of the bicyclo[3.3.0]oct-1-en-1-yl acetate, the major component of the mixture **6a**, was found, which is compatible with either S_N2 nucleophilic addition at C(8) or an S_N1 opening mode followed by stereoequilibration at C(8). In either event, the C(8)-group should be *exo*-oriented. In the case of **4b**, only one regioisomer (**6b**) was found. A plausible explanation for this high regioselectivity can be found for an S_N2 mechanism if a build-up of repulsive interaction between the hydrogen atom at C(1) and the methyl group at C(4) is assumed in the transition state for ring cleavage at C(1). Finally, substrate **4f** was unreactive under the conditions used. Possibly, sterically unfavourable interactions prevent sufficient activation of the ketone by AcOMs.

A further observation is also in accord with an S_N2 mechanism. When **4b** was treated by AcOMs in the absence of any additional nucleophile, **6b** (with R=OMs) was isolated as the sole product in 80% yield. In this particular case, no subsequent inversion at C(8) is possible.

In summary, we present a general and high-yield method for the ring opening of cyclopropyl ketones under neutral conditions and at room temperature. The combination of AcOMs and nucleophiles such as Br^-, I^- and OMs^- affords with two ketones the results expected for an S_N2 mode of opening. An additional synthetic feature is the possibility of regiospecific enol acetate formation. This renders the method superior to the strategically related use of $(CH_3)_2SiI$, where efficient 'enolate trapping' has not yet been proved to be general [4] [10].

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