Tetrahedron Letters, Vol.31, No.15, pp 2181-2184, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

CINE SUBSTITUTION IN FUSED CHLOROCYCLOBUTANONES BY N, S AND C NUCLEOPHILES. OXYALLYL CATIONS AND AN UNUSUAL DIMER FORMATION.[1]

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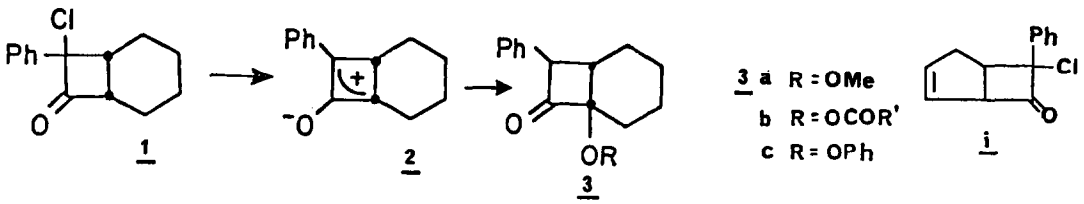
Abstract: Chlorocyclobutanone 1 was shown for the first time to react with S-, N-, and C-nucleophiles to produce cine substitution products, which apparently arise via an oxyallyl cation species 2. With some nucleophiles, the cine product is accompanied by an unusual dimer involving bond formation between two tertiary carbons.

α-Halocyclobutanones of type 1 have been shown to undergo reactions with alcohols or with carboxylic acids to produce α'-alkoxy or α'-acyloxy-cyclobutanones 3a or 3b.[2,3] The facile introduction and subsequent removal of an acyloxy group as in 3b, can be used for protection of carboxylic acids.[4] It has been proposed that such cine substitutions proceed via oxy stabilized allyl cations 2.[3]



1 2 3

3 a R = OMe
b R = OCOR'
c R = OPh

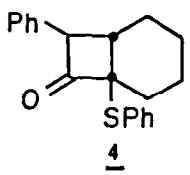
i

While open chain oxyallyl cations have been studied extensively[5-7] and have proved of immense synthetic utility, because they can be trapped with dienes or electron rich olefins, much less is known about their cyclic analogs[8] and in particular the fused system 2.[3] Our attempts to trap 2 with dienes or dienophiles have so far been unsuccessful. This may be ascribed to the strain imparted by fusion of the cyclobutanone to a cyclohexane ring. Though reaction of α-halocyclobutanones with O-nucleophiles or halide ions takes place readily, reports of analogous reactions with other nucleophiles have been conspicuosly absent. We found that the fused cyclobutanone i was unreactive even toward MeO^-, AcO^- or N_3^-.[9] We felt that chloroketone 1 offers a better possibility than i of forming oxyallyl cations such as 2 that might react with a variety of nucleophiles and therefore holds out some promise of synthetic utility.

We report now that a variety of N-, S-, as well as C- nucleophiles are capable of undergoing reaction under mild conditions at room temperature with α-chlorocyclobutanones 1, apparently via oxyallyl cations, leading to cine substitution.

Treatment of 1 with 1.1 molar equiv. of phenylthiol in the presence of Et_3N in acetone overnight at room temperature produced the ketosulfide 4 in 90% yield. Phenol, under identical conditions, led only to the unsaturated ketone 5 and unreacted chloro ketone 1. Potassium phenoxide in THF, on the other hand, did provide the ether 3c in 75% yield. Reaction of 1 with KNCS-Et_3N proceeded by C-N rather than C-S bond formation with the isolation of an unstable thioisocyanate 7a, which was converted by heating with EtOH to the fused oxazolidinethione 6. By contrast KNCO gave 5 together with decomposition products.

Amines likewise led to cine substitution products, e.g. isolation of 7b in 70% yield, formed in the reaction of pyrrolidine with 1 at room temperature. Sodium azide gave an unstable azido ketone 7c. The addition of lithium perchlorate to the reaction mixture had a beneficial effect (faster reaction) for the nitrogen nucleophiles.



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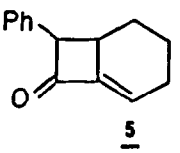

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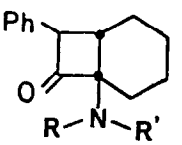
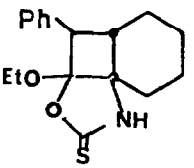


7 a; R,R'= C=S
b; R,R'=$(CH_2)_3$
c; R,R'= N_2
d; R=H, R'= allyl
e; R=H, R'= n-propyl

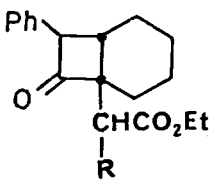


6

All these reactions are consistent with initial formation of an oxyallyl cation 2 from 1 by an enolization-solvolysis step, followed by trapping with a good nucleophile. Our initial attempts to establish if C nucleophiles can be used effectively were disappointing. Thus, reaction of 1 with KCN or with diethyl malonate-Et_3N in acetone led to elimination product 5 and decomposition products. However, diethyl potassiomalonate in THF reacted readily at room temperature within 20 min with C-C bond formation to produce 8a in 60% yield. Similarly 8b resulted when ethyl acetoacetate-potassium tert butoxide in THF was used.

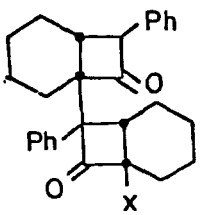
The stereochemical cis, cis assignment in the above cine substitution products is based on analogy with 3b, for which an X-ray diffraction analysis was reported.[3c] Their structure was verified by ^1H and ^{13}C NMR, NOE experiments and mass spectra.

A surprising result was the co-formation of a dimer in 25% yield, together with **10**, in the reaction of water-Et_3N in acetonitrile with chloroketone **1**. The structure of the dimer was determined as **9a** by COSY and one-bond and long range hetero-COSY NMR experiments. All ^1H and ^{13}C resonances may be thus assigned and three-bond CH couplings (see Fig.1) clearly indicated a C-C linkage between the benzylic carbon of unit **11** and the bridgehead carbon of an oxyallyl species **2**. The ^1H-NMR also revealed one of the hydrogens (H_m) to be at very high field (-0.33 ppm), while its geminal neighbor was at 1.20 ppm. The unusual shielding is apparently due to the location of H_m directly above the plane of the phenyl ring on the second cyclobutane moiety, which is confirmed by examination of stereomodels.



8 a ; R = CO_2Et

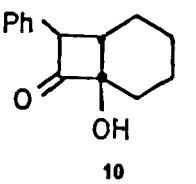
b ; R = COMe



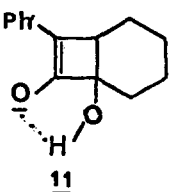
9 a: x = OH

b; x = NH

c; x = NH



10



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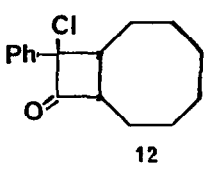

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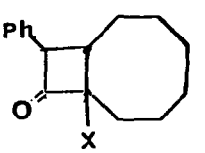
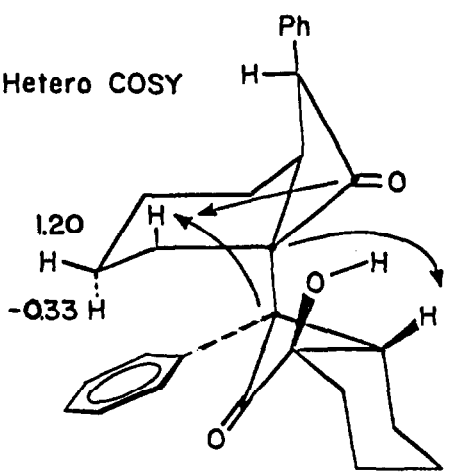


13 a x = SPh

b x = $N(CH_2)_4$



9a

3-bond coupling

Figure 1

A plausible mechanism for the unusual dimer formation involves trapping of the initially formed oxyallyl cation by hydroxide ion, followed by formation of an enolate 11. Formation of the latter might be favored due to intramolecular H-bonding with the adjacent OH. Complexation or electron transfer between enolate 11 and a molecule of the oxyallyl cation 2 would lead to the dimer **9a**, by what appears to be a highly hindered approach of two tertiary carbon centers.

Consistent with this explanation is the formation of analogous dimers **9b** and **9c** in 30% yield in the reaction of allylamine or propylamine with 1. The presence of a H-bonding donor group at the bridgehead to stabilize an intermediate enolate (see above) seems to be important, since a dimer was not observed during formation of 3 or **7b**.

In an analogous manner the homologous chloroketone 12 reacted with Ph-SH and pyrrolidine to produce **13a** and **b** respectively. The further synthetic potential of these reactions is being explored.

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(Received in UK 30 January 1990)