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Allylation of Oxepane Rings

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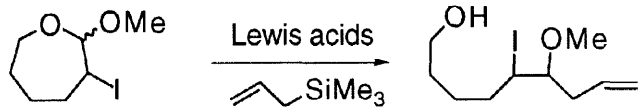
Abstract: 2-Allyloxepanes have been prepared by reaction of 2-(4-nitrobenzyloxy)oxepanes with allyltrimethylsilane in acetonitrile in the presence of BF_3-Et_2O or from 2-ethoxyoxepane in liquid sulphur dioxide without catalyst.

Introduction of a carbon chain on the oxepane ring in 2-position has been reported by nucleophilic additions of ketene acetals on the carbonyl of lactones [1] or organometallic compounds on the carbon-sulphur bond of thiolactones,[2] by alkylations of 2-carboalkoxyoxepan-3-one,[3] or 2-cyanooxepane.[4] However, further chemical transformations were necessary to obtain the desired 2-C oxepanes. These latter compounds were also recently obtained by ring expansion of pyran derivatives.[5] The direct approach to these compounds by nucleophilic substitution of the anomeric sulphone was also reported in moderate yields.[6] The electrophilic substitution at the anomeric carbon atom from acetal, widely studied in the tetrahydropyran chemistry,[7,8] does not seem to have been reported in the case of upper membered heterocycles.

We decided to study the allylation of oxepanes, using the well known Lewis acid catalysed electrophilic substitution of allyltrimethylsilane.[8] The oxepanes **1**, **2** were prepared [9] in three steps from δ-valerolactone, by reduction with diisobutylaluminum hydride followed by a Wittig reaction using methoxymethylenetriphenylphosphorane on the intermediate lactol, and haloetherifications using biscollidineiodine(+1) (84 % yield) and biscollidinebromine(+1) hexafluorophosphate (74 % yield). In the two cases, mixture of diastereomers (80-20) corresponding to the E-Z mixture of the starting olefin were isolated.

Our first studies on the electrophilic allylations with allyltrimethylsilane were conducted in acetonitrile or nitromethane. Degradation of oxepane **1** was observed with Lewis acids such as $AlCl_3$, $ZnCl_2$, $SnCl_4$ or $SnCl_2$, while with Lewis acids such as $F_3CSO_2SiMe_3$, SnF_2, $BF_3 \cdot Et_2O$ only the ring cleavage compound **3** was isolated (Scheme 1).



1 **3**

Scheme 1

The replacement of the methoxy group by the benzyloxy or 4-nitrobenzyloxy group was next examined. The desired acetals **4** (80% yield), **5** (65% yield) were obtained by reaction of acetal **1** with the corresponding alcohols, in cyclohexane at reflux in the presence of p-toluenesulfonic acid and 20% of 3-*tert*-butyl-4-hydroxy-5-methylphenylsulphide, used as radical inhibitor. If the radical inhibitor was omitted large amounts of deiodinated oxepanes were observed. The subsequent allylation with allyltrimethylsilane

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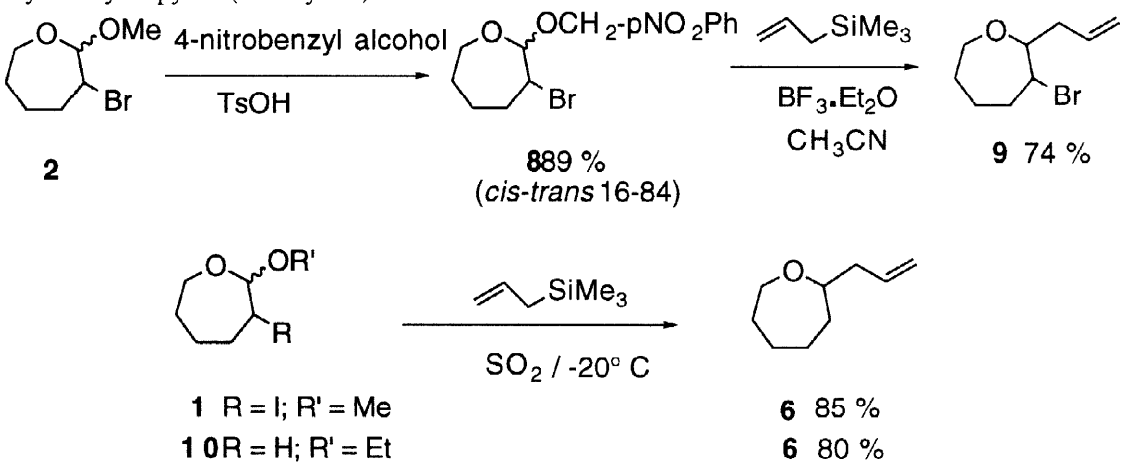
conducted in acetonitrile in the presence of boron trifluoride diethyl etherate and the radical inhibitor led to a mixture of 2-allyloxepane **6** [2] and 2-allyl-3-iodooxepane **7** in low to moderate yields (30-50%). However, 2-allyloxepane **6** was isolated (80% yield) as the unique product when the allylation of compound **1** was carried out without catalyst in liquid SO_2[10] at -20°C (Scheme 2). This easy halogen removal was not observed with the bromooxepane **2**. Heating of this latter overnight at reflux in toluene in the presence of p-toluenesulfonic acid and 4-nitrobenzylalcohol led to the transacetalization product **8** in good yield. The subsequent allylation to the bromooxepane **9**[11] was then smoothly accomplished in acetonitrile using boron trifluoride diethyl etherate as catalyst (Scheme 2). Only one diastereomer of unknown configuration was isolated. The bromooxepane **2** did not reacted with allyltrimethylsilane in liquid sulphur dioxide at - 20°C. The desactivation of anomeric carbon in **2** by the bromine atom was confirmed by the fact that 2-ethoxyoxepane **10**[12] reacted smoothly with allyltrimethylsilane in liquid SO_2 at - 20° C (1h) to give 2-allyloxepane **6** without any trace of the open product. This new allylation procedure appeared general and was also successfully applied to 2-methoxytetrahydropyran (75 % yield).



Scheme 2

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11. **9**: ^{1}H NMR (200 MHz, $CDCl_3$)δ 1.60-1.90 (m, 4H); 2.08-2.40 (m, 2H); 2.60-2.75 (m, 2H); 3.40-3.55 (m, 1H); 3.64 (ddd, J = 9, and 3.9Hz, 1H); 4.00-4.20 (m, 2H); 5.05-5.20 (m, J = 2.5, 10.5, and 17Hz, 2H); 5.78-6.00 (m, 1H). ^{13}C NMRδ 22.57, 30.54, 37.13, 38.54, 57.42, 72.85, 86.32, 117.27, 134.46.
12. This compound was prepared following the procedure described for the preparation of 2-methoxyoxepane: Inoue, Y.; Matsumoto, N.; Hakushi, T.; Srinivasan, R. *J. Org. Chem.* **1981**, *46*, 2267-2272.