

A SIMPLE ROUTE TO SPIROKETALS VIA ALKYLATION OF DIHYDROPYRAN

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Abstract - 3,4-Dihydro-2H-pyran was alkylated, via its 2-lithio derivative, with several 0-protected β - or γ -iodo alcohols in excellent yields. Acidic treatment of the resultant 2-substituted dihydropyrans produced both the deprotection of the hydroxyl group and the cyclization to spiroketals.

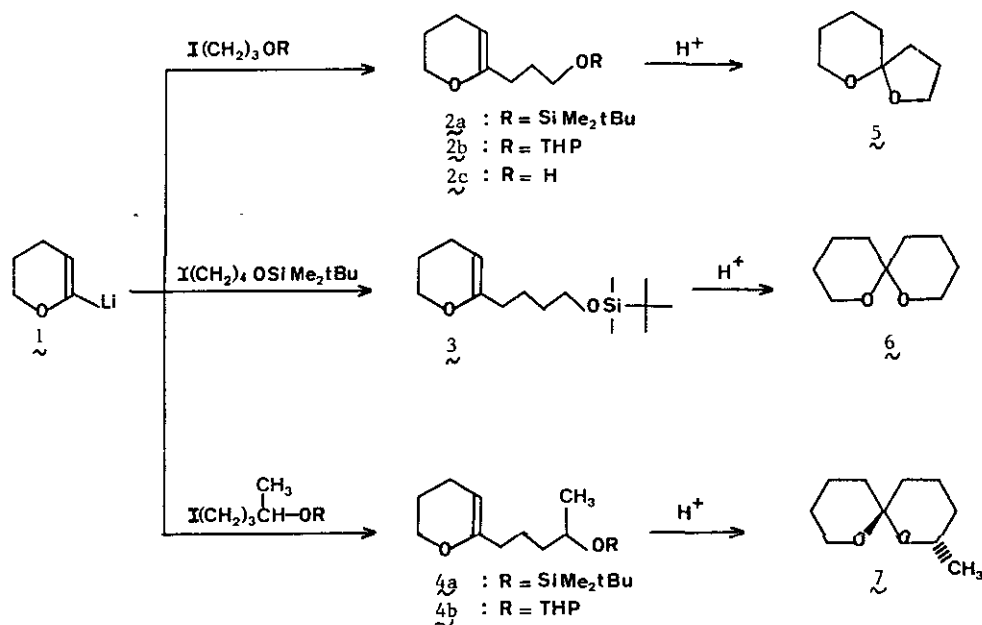
The synthesis of spiroketals has been of continuing interest over the recent years owing to the presence of this type of structure in biologically active natural products including several insect pheromones¹⁻⁴ and polyether ionophore antibiotics⁵⁻⁷. Recently, a new methodology using spiroketals as key intermediates for the synthesis of natural macrolides has brought increasing interest to this class of compounds⁸.

A variety of synthetic routes to dioxaspiroalkanes have been reported. Most of them utilize lactones as starting materials^{4,9,14} or keto diols and their equivalents as intermediates^{5,6,15,17}. However, some less classical methods have been described: cyclization of furan derivatives³, photocyclization of aldehydo-ketals¹⁸, hetero-Diels-Alder condensation⁷, organoselenium mediated cyclization of unsaturated keto alcohols¹⁹ and finally an electrochemical synthesis²⁰.

We propose here a new approach for the construction of spiroketal structures using a simple and straightforward synthesis giving better yields than most of the reported methods. The two-step procedure starts with the condensation of the pyranyl or *t*-butyldimethylsilyl ether of a β - or γ -iodo alcohol with 3,4-dihydro-2H-pyranyllithium **1** (scheme I). Acidic treatment of the resulting substituted dihydropyran promotes both the deprotection of the hydroxyl group and the subsequent cyclization of dioxaspiroalkane²⁸. We applied this method to the preparation of the following known spiroketals: 1,6-dioxaspiro[4,5]decane^{18,25}, 1,7-dioxaspiro[5,5]undecane^{4,12,26} (major component of the sex pheromone of the olive fly) and 2-methyl-1,7-dioxaspiro[5,5]undecane^{12,26}. The lithiation of 3,4-dihydro-2H-pyran exclusively at the 6-position (vinylic carbon

α to oxygen atom) is well documented^{21,23}. For instance, selective metalation of dihydropyran can be achieved with *t*-butyllithium in a pentane-tetrahydrofuran mixture at -78°C ²¹ or with *n*-butyllithium in hexane and a catalytic amount of tetramethylethylenediamine (TMEDA) at room temperature²². An alternative route consist of adding *n*-butyllithium in hexane to a solution of dihydropyran in tetrahydrofuran at 0°C and then heating the mixture at 50°C for 1h²³. We chose this last metalation procedure with, however, a slight modification. In preliminary essays carried out under the reported conditions²³, we observed side reactions in the alkylation step (condensation of *n*-butyllithium with the iodide and coupling reaction of the iodide chain), due probably to the presence of an excess of *n*-butyllithium. Therefore we decided to use rather an excess of dihydropyran(1.2 equivalent) with respect to *n*-butyllithium²⁴. The alkylation was performed by adding a solution of the protected iodo alcohol (0.8 equivalent) in tetrahydrofuran to the solution of dihydropyranyllithium **1** cooled at -10°C . At the end of the addition, the mixture was warmed at 50°C . The reaction was generally complete after 1 h and yields of alkylated dihydropyrans **2-4** exceeded 90% based upon the iodide. The crude products were pure enough to be involved directly in the deprotection-cyclization step. The alkylation can be carried out with 0.4 equivalent of an unprotected β -iodo alcohol (i.e. **2c** from 3-iodo-1-propanol). On the other hand protection of γ -iodo alcohols is essential, since these compounds undergo a spontaneous ring closure to tetrahydrofurans under basic conditions.

Scheme I



Cyclization of compounds 2-4 spiroketals have been effected by various acidic agents depending on the protection mode of the hydroxyl group²⁹. The alcohol 2c stirred with a catalytic amount of pyridinium para-toluenesulfonate (PPTS) in dichloromethane affords the 1,6 dioxaspiro[4,5]decane 5 in 78% overall yield of purified product. The t-butyl dimethylsilyl ethers 2a, 3, 4a are cleaved and cyclized in acetonitrile with a small quantity of aqueous hydrofluoric acid leading to the spiroketals 5, 6 and 7 (66, 67 and 63 overall yields respectively). The spiroketals 5 and 7 are also obtained from the cleavage and cyclization of pyranyl ethers 2b and 4b with hydrochloric acid in ether (respectively: 69 and 74% yields). Although 2-methyl-1,7-dioxaspiro[5,5]undecane can exist in two diastereoisomeric forms, formation of only one isomer of 7 from 4a or 4b is evident from ¹³C NMR analysis. This result is in accord with the prediction of Deslongchamps et al.¹², since the acid promoted cyclization occurs probably under thermodynamic conditions. Owing to the anomeric and usual steric effects, the configuration of the spirotal 7 should be trans in the conformation where the two oxygen atoms are axial and the methyl group equatorial¹².

In addition to the good yields observed, the ready accessibility of the iodo alcohols and their corresponding ethers makes this dioxaspiroalkanes synthesis very convenient. The 3-iodo-1-propanol was prepared from the commercially available chloride (sodium iodide in methyl ethyl ketone, 8h at reflux). The t-butyl dimethylsilyl ethers of 3-iodo-1-propanol, 4-iodo-2-pentanol was obtained directly by ring opening of oxetane, tetrahydrofuran and 2-methyltetrahydrofuran respectively with t-butyl dimethylsilyl chloride and sodium iodide in acetonitrile. Likewise the ring opening of 2-methyltetrahydrofuran by chlorotrimethylsilane and sodium iodide afforded, after hydrolysis, 4-iodo-2-pentanol. The regioselectivity of 2-substituted heterocycles ring cleavage by "in situ" iodoalkylsilanes is currently under investigation in our laboratory and will be published in a separate paper. Conversion of iodo alcohols to tetrahydropyranyl ethers was carried out in dichloromethane with pyridinium para-toluenesulfonate as catalyst²⁷.

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