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REMOTE OXIDATION OF A STEROIDAL AMIDE, ETHER, AND SULFONATE[1]

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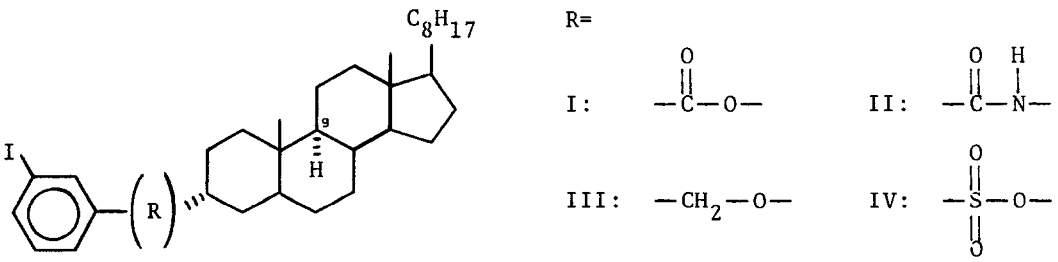
Template directed halogenation of steroids may be performed in the presence of an amide, ether, or sulfonate.

Template directed functionalizations, as introduced by Breslow[3] represented a conceptually novel approach to organic synthesis. The subsequent synthesis of cortisone[4] demonstrated the practical impact of the technique. The procedure, named Remote Oxidation, while providing impressively efficient routes to important steroids, was limited to substrates containing alcohols and carboxylic acid templates. The ester linkage had been convenient and effective. Demonstration of the utility of other linking groups would serve to generalize remote oxidation to a wider range of substrates and templates.

The photoinitiated free-radical chlorination of I by phenyliodine dichloride is directed exclusively to the C-9 position.[5] This is presumably due to the preference of I for conformations which place the chlorine radical, which is complexed to the template iodine, near the C-9 hydrogen, rather than one of the other tertiary hydrogens. The conformations of I and related systems are thus crucial to the success of the remote oxidation. Since the choice of substrate and template is largely dictated by the product desired variation of the linking group offers the greatest potential for control of conformation.

We report that it is possible to use amides, ethers, and sulfonates as linking groups. Using the steroidal ester I, as a model, substitution of the linking moiety gives the template-substrate systems II-IV.



The amide II is quantitatively halogenated at C-9, as indicated by examination of the Δ9,11 olefin produced by treatment with alcoholic base.[6] Apparently the increased rigidity of the amide as compared to the ester did not interfere with the functionalization. The amide might have been expected to undergo halogenation at nitrogen but this reaction was not observed. The amide was also left intact by the dehydrohalogenation.

The ether III is chlorinated at C-9 and can be dehydrohalogenated to the Δ9,11 olefin with an 85% conversion. Halogenation of the benzylic methylene produces m-iodobenzaldehyde. Inasmuch as 3α-cholestanyl benzyl ether gives exclusive halogenation of the benzylic methylene without halogenation of the steroid, III strikingly demonstrates the template direction effect. If desired, III may be halogenated until the benzylic methylene reacts completely so as to provide a convenient hydrolysis of the ether, an otherwise difficult process.

The sulfonate IV is halogenated at C-9 under standard conditions.[6] It is converted to the Δ9,11 olefin in 80% yield with a buffered silver assisted dehydrohalogenation.[7]

The elaboration of these new linking groups not only extends the applicability of remote oxidation to templates and substrates with a wider variety of functionality but broadens the range of strategic options available for the design of an effective template since the new linkages offer a spectrum of conformational flexibilities. Thus, an amide might be substituted for an ester when rigidity is desired or an ether might be used when greater flexibility is considered necessary.

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References:

1. Taken, in part, from the Ph.D thesis of Daniel Michael Wolner, Columbia University, 1979.
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6. The halogenations and dehydrohalogenations were performed according to procedures described in ref. 4.
7. The silver assisted dehydrohalogenation described in ref. 4 was used with the addition of 5. g of sodium bicarbonate to the solution.

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