Remote Participation in Electrophilic Reactions of 'Protected' Polyols

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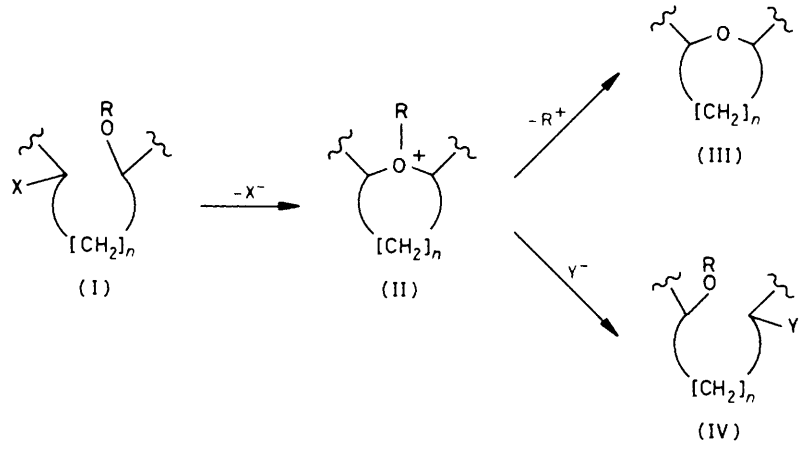
Oxygens present in ethers, esters, and pyranose rings participate efficiently in electrophilic reactions at remote centres leading to five- and six-membered heterocycles.

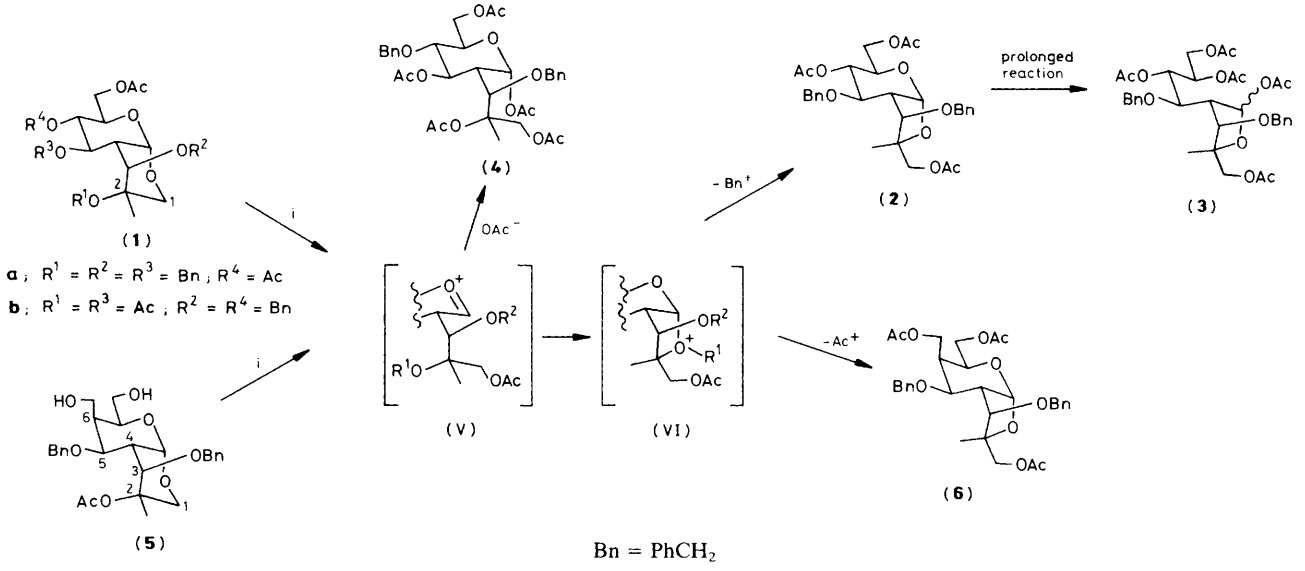
Electrophilic reactions of a wide variety of polyoxygenated systems show that formation of oxygen heterocycles, for example, (III), is a widespread process, even where the oxygen in the precursor, (I), is protected as an ether, and where the ring formation is not stereoelectronically favourable.[1] An oxonium ion, such as (II), is the postulated intermediate[2] and this is consistent with the fact that benzyl ethers (I; R = $PhCH_2$) are particularly prone to cyclization, a result which is attributed to the (incipient) benzylic carbocation ion released in going to (III) (R^+ = $PhCH_2^+$). An alternative pathway, leading to the product of oxygen migration (IV), is usually seen with methyl ethers[3] and is again consistent with the comparatively unstabilized oxonium ion in (II; R = Me). A further generalization is that the process is most prevalent when n = 2.[2] We now describe additional examples, not all of which conform to these generalizations, indicating the need for extra caution when dealing with complex polyoxygenated systems.

Prolonged acetolysis of the bicyclic acetal (**1a**)[4] afforded the furanosyl acetate (**3**), a result which is consistent with the intermediate oxonium ions (V) and (VI) (R^1 = R^2 = Bn). Loss of $PhCH_2^+$ from (VI; R^1 = R^2 = Bn) would be consistent with the mechanism in Scheme 1. Indeed, if the reaction was interrupted after 10 minutes, compound (**2**) was isolated in 60% yield.

However, pyranosyl acetate (**4**) was our desired acetolysis product and it seemed that the appropriate reaction pathway would be favoured by use of the triacetate (**1b**), which should prevent the formation and decomposition of the acetyl oxonium ion (VI; R^1 = Ac, R^2 = Bn). Indeed, (**1b**) underwent acetolysis smoothly to give (**4**), with no trace of the derivative corresponding to (**2**).

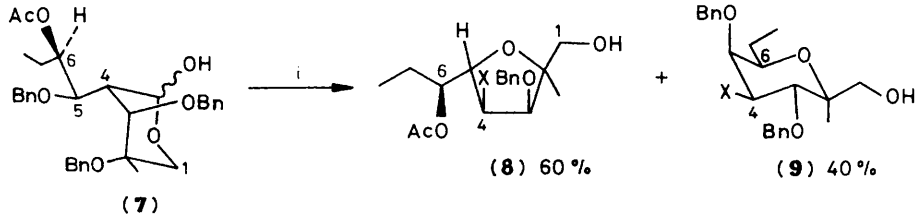


Scheme 1

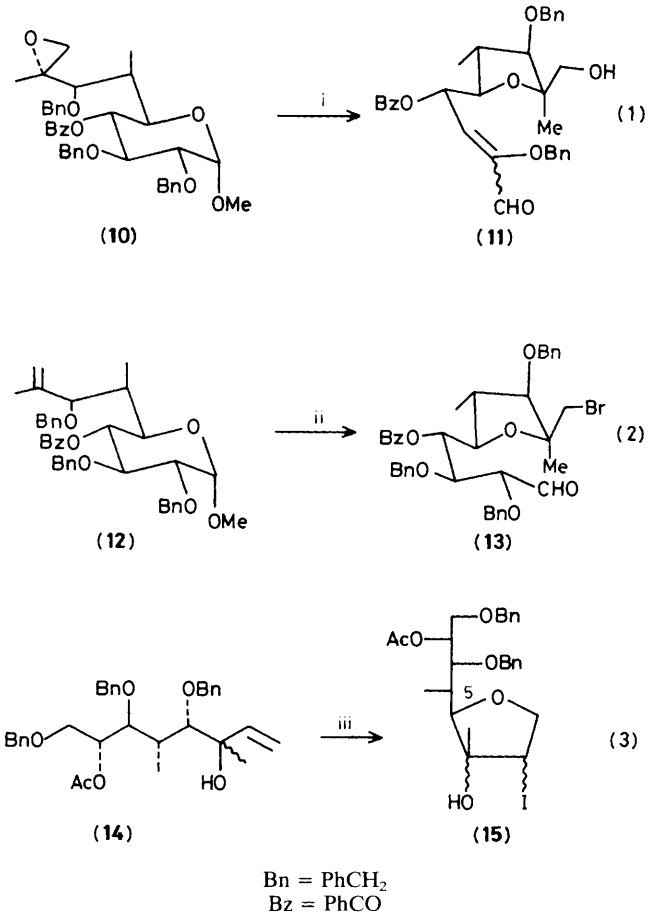


Bn = $PhCH_2$

Scheme 2. i, $BF_3{\cdot}OEt_2$, Ac_2O, 0 °C.



Scheme 3. i, $BF_3 \cdot OEt_2$, $HS[CH_2]_3SH$.



Reagents and conditions: i, HOAc–H_2O (4 : 1), 80 °C, 30 min; ii, NBS, THF, H_2O; iii, I_2, MeCN.

However, the tenuous nature of this rationalization was revealed in the case of (**5**), which is sterically different from (**1b**) only in the axial hydroxymethyl group at the remote C(6) centre. The product of acetolysis was compound (**6**), which implies that formation and decomposition of the acyl oxonium intermediate (VI; R^1 = Ac, R^2 = Bn) → (**6**) was occurring with great ease.

The last result undoubtedly was spurred by a pronounced Thorpe–Ingold effect[5] of the geminal substituents at C(2) of (**5**). *However, acetoxy participation may be encountered even in the absence of such a driving force.* Thus, the formation of (**8**) and (**9**) in 3 : 2 ratio during mercaptolysis of (**7**) indicates that the acetoxy group can be competitive with the benzyloxy group (Scheme 3).

The cases shown in equations (1) and (2) are novel. Pyranose oxygens have been known to participate in trans-annular displacements at C(2)[6] and C(4),[7] but the normal requirements for this process are a highly nucleofugal substituent and an anti-periplanar relationship to the migrating oxygen; these are standard prerequisites for ring contraction [*cf.* (**1a**) → (**2**)]. However, the reaction of (**10**) reveals that the ring oxygen of the pyranose unit displays surprising nucleophilicity. This trend was even more apparent in the case of alkene (**12**), which, upon treatment with *N*-bromosuccinimide (NBS) in tetrahydrofuran (THF), afforded (**13**) quantitatively as a 1 : 1 mixture of diastereoisomers.

Finally, the reaction of compound (**14**) may proceed *via* 6-*exo-tet* and 5-*endo-tet* pathways, depending on which benzyloxy group participates in the reaction. Although the former is usually the more favourable,[8] treatment of (**14**) with iodine led to (**15**) quantitatively *via* the 5-*endo-tet* route, equation (3).

In summary, the participation of the acetoxy groups [(**5**) → (**6**) and (**7**) → (**9**)], the predominance of stereoelectronically unfavourable reaction pathways [(**14**) → (**15**)], and the nucleophilicity of the ring oxygen of pyranosides [(**10**) → (**11**) and (**12**) → (**13**)] are reaction pathways which cannot be ruled out in dealing with complex, polyoxygenated derivatives.

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