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Armed/Disarmed Effects in the Solvolysis of Caged 1,6-Anhydro Pyranoses

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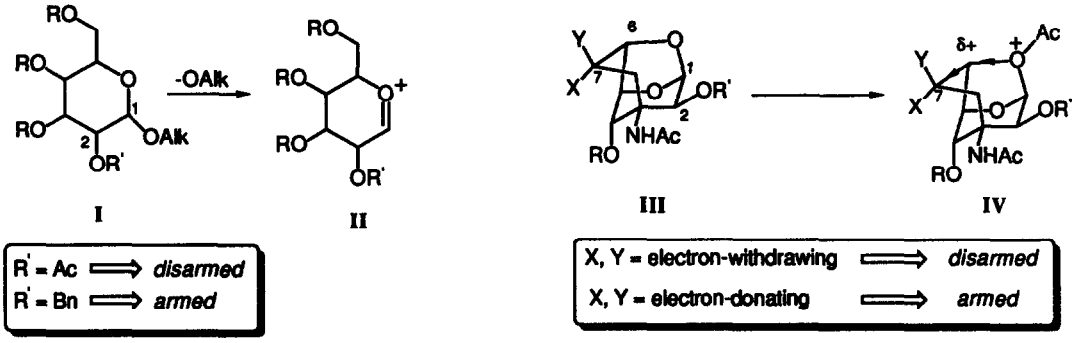
Abstract: A systematic study of the effect of ether and ester protecting groups upon the acetolysis of several caged 1,6-anhydro sugar derivatives reveals the profound effect that these protecting groups have upon the reactivities of such systems.

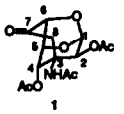
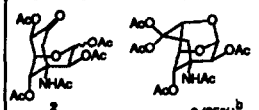
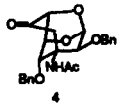
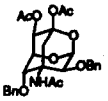
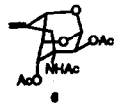
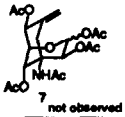
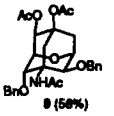
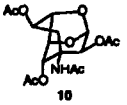
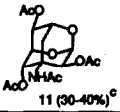
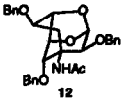
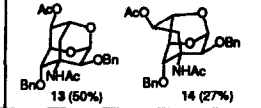
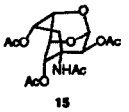
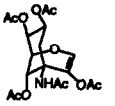
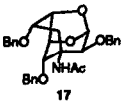
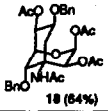
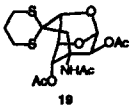
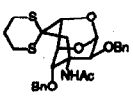
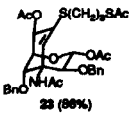
In connection with a total synthesis underway in our laboratory we have recently described the preparation of compound **1** (Table).[1] As with many internal acetals,[2,3] substituents can have an influence on hydrolytic cleavage.[4] In the case of **1** we anticipated that there might be some difficulty because of the rigid tricyclic framework. "Armed/disarmed" principles have emerged[5] as powerful determinants in glycosidic cleavage,[6] (Scheme 1, I->II) and it was of interest to see whether these successes could be applied to facilitate the cleavage of structures such as **III**. In this manuscript we describe some of our studies relating to this issue.

Scheme 1



We recently reported that the use of acetic anhydride and triethylsilyl trifluoromethanesulfonate (Ac_2O/TESOTf) readily achieved acetolysis of 1,6-anhydro sugars.[7] However when ketone **1** was subjected to these conditions, we did not obtain the glycosyl acetate **2** (Table), but the diacetyl ketal **3** which was resistant to further acetolysis (*vide infra*). That **3** was obtained, and not **2**, was immediately ascertained by the absence

Table Acetolysis of Some Armed and Disarmed Tricyclic Acetals[9]

Substrate	Conditions TESOTf eq.	Temp. °C	Time h	Product(s)[a]
 1	2	23	24	 2 not observed; 3 (25%)[b]
 4	2	23	12	 5 (50%)
 6	2	65	1	 7 not observed
 8	2	0	1	 9 (58%)
 10	8	23	60	 11 (30-40%)[c]
 12	2	0	0.25	 13 (50%); 14 (27%)
 15	8	23	48	 16 (40-50%)[d]
 17	2	0	1	 18 (64%)
 19	2	23	12	 20; 21 (64%)
 22	2.2	0	<0.5	 23 (86%)

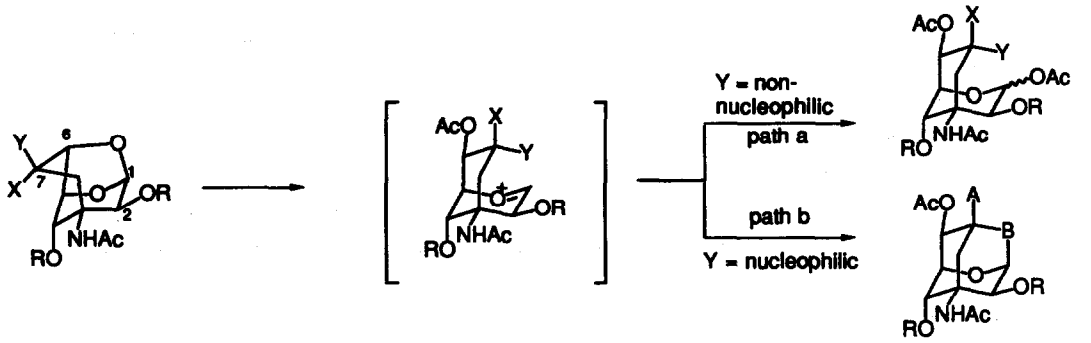
a. yields are not optimized; b. plus 30% recovered 1; c. plus 30% recovered 10; d. plus 10% recovered 15

of a carbonyl resonance, and the presence of a second acetal signal at 101.4 ppm in the ^{13}C NMR spectrum. Additionally, $J_{5,6}$ was unchanged in the product (for **1**, 6.4 Hz; for **3**, 6.2 Hz), which clearly ruled out structure **2**. That disarming effects were operative was clearly apparent when the dibenzyl analog **4** was studied since it readily yielded the dioxoadamantane **5**.

The armed/disarmed effect was first identified for the influence of C2 substituents upon O1 (Scheme 1).[5] However according to our rationalization of the phenomenon,[8] an electron-withdrawing group at C7 would also be expected to exert a disarming influence on the acetolysis by draining electron density from O1/O6, as illustrated in **IV** (Scheme 1). That acetolysis of **4** was slow relative to **12** and **17**, *vide infra*, is therefore readily understood, as is the complete resistance to hydrolysis of the pentaacetate **3**.

The corresponding methylene derivatives **6** and **8** are not similarly disarmed at C7; however the former remained unaffected even at elevated temperatures where there was no evidence for the glycosyl acetate **7**. By contrast the dibenzyl analog **8** reacted completely at 0°C in one hour to give the oxoadamantane **9**.

Scheme 2



Reduction of ketones **1** and **4** followed by acetylation or benzylation led to the pairs of epimers **10/15** and **12/17**. Compounds **10** and **12**, with pseudo axial substituents at C7, reacted to give the tricyclic acetals **11** and **13**, respectively, formed, presumably, by attack of the C7 oxygen on the intermediate C1 oxocarbenium ion (Scheme 2, path b). (Notably, the monoacetate **14** was obtained in substantial amounts.) However, while the armed substrate **12** reacted at 0°C in 15 min, the disarmed analog **10** required 60 h at a higher temperature (23°C).

In the case of the epimeric derivatives, **15** and **17**, the pseudo equatorial C7 substituents cannot attack the anomeric center, therefore they should give bicyclic structures (Scheme 2, path a). Indeed compound **17** reacted at 0°C in 1 h to give pyranoside **18**, while the tetraacetate **15** required 48 h at 23°C to give the enol acetate **16** in 40-50% yield.

The reaction times for **15** versus **17**, and **10** versus **12** are fully consistent with armed/disarmed influences upon reactivity. However formation of the adamantane-like structures **5**, **9**, **11**, and **13** reveals the ease with which the C7 substituent can trap the reactive intermediate, leading to products which are even more stable than the corresponding starting materials.

Compounds **15** and **17** indicated that proper orientation of the C7 substituent was one way of avoiding this problem. In seeking an additional, alternative strategy, we examined the cyclic dithioacetals **19** and **22**.

After 12 h at 23°C, a 64% yield of the thioenol ether **21** was obtained from acetolysis of the former. However acetolysis of the armed counterpart **22** occurred much more smoothly, affording **23** in less than 30 min at 0°C in 86% yield. Presumably the dithioacetals react first to give the enol thioethers, i.e. **20**, which then react further with cleavage of the internal acetal yielding the observed products.

We have demonstrated that the proper combination of protecting groups on the pyranose ring and substitution on the carbocyclic ring can greatly facilitate solvolytic cleavage of caged systems.

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References and Notes

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4. See for example, Černý, M.; Pacák, J.; Stanék, J. *Collect. Czech. Chem. Commun.* **1965**, *30*, 1151. Carlson, L.J. *J. Org. Chem.* **1965**, *30*, 3953. James, S.P.; Smith, F.; Stacey, M.; Wiggins, L.F. *J. Chem. Soc.* **1946**, 625. Jeanloz, R.W.; Schmid, D.M.; Stoffyn, P.J. *J. Am. Chem. Soc.* **1957**, *79*, 2586.
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9. Typical experimental procedure: The anhydro sugar is dissolved in Ac_2O and triethylsilyl trifluoromethanesulfonate (TESOTf) (2 eq) is added at the appropriate temperature. The reaction is followed by TLC and further equivalents of TESOTf are added in the cases of **10** and **15**. Upon completion, a solution of saturated sodium bicarbonate is then added and after being stirred for 30 min, the aqueous mixture is extracted three times with ethyl acetate. The organic extracts are combined and washed with saturated sodium bicarbonate solution followed by brine. The material is then recovered in the usual way.

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