Radical Cyclisation of Some Unsaturated Carbohydrate Derived Acetals

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Haloacetals derived from pyranosidic allylic alcohols or allylic hemiacetals were stereospecifically cyclized using tributyltin hydride as radical promotor to give fused furanoses; the reaction was also applied to a propargylic glycoside which cyclized readily into a vinylstannane, precursor of methylene furanose.

The utility of free radical reactions in carbon–carbon bond formation is now widely recognized and has been recently reviewed.[1] Radical cyclizations are of special interest because they allow carbocyclization or regio and stereospecific introduction of carbon chains on a suitable template.[2] An elegant method starting from allylic alcohols and using 'a detachable radical' cyclizing to a five membered ring has been proposed by Stork,[3] and led to some achievements in the synthesis of natural products.[4] Very recently McDonald and Dugger have described a radical cyclization of a haloacetal derived from an unsaturated sugar,[5] and another approach to radical cyclization on sugar templates has also been recently reported.[6] This prompts us to disclose results of our current investigations on the stereoselective introduction of functionalized carbon chains on a sugar template.[7]

We first tested the ability of a double bond of an unsaturated pyranoside to behave as a radical acceptor using the readily available iodoacetals (**1**) and (**3**) (diastereisomeric mixtures).[8] Treatment of (**1**) or (**3**) with tributylstannyl radicals generated with azoisobutyronitrile (see Table 1) gave the expected cyclized products (**2**) and (**4**) respectively, in *ca.* 80% yield as a separable 1/1 mixture of anomers at C-7. Further synthetic use of these compounds will depend upon the selective cleavage of one of the two glycosidic bonds. This was assumed to be rather difficult and thus other substrates in

Table 1. Radical cyclization of some unsaturated sugars.

Substrate	Product	Method	Time/h	Yield/%
(**1**)	(**2**)	a	0.5	84
(**3**)	(**4**)	a	1	85
(**3**)	(**4**)	b	1	78
(**5**)	(**6**)	b	1.5	83
(**8**)	(**9**)	a	6	76
(**8**)	(**9**)	b	6	88
(**11**)	(**12**) + (**13**)	a	0.5	66 + 12

Method a: Bu_3SnH, (1.1 equiv.) AIBN catalyst, 0.02 M in degassed benzene, reflux. Method b: $NaBH_3CN$, (2 equiv.) AIBN catalyst, Bu_3SnCl (0.1 equiv.) in degassed t-butanol.[8]

(**1**) (**2**) (**3**) (**4**) (**5**) (**6α**) (**6β**)

(**7**) (**8**) $n = 1$ (**10**) $n = 2$ (**9**) (**11**) (**12**) X = $SnBu_3$ (**14**) X = H (**13**)

which the two acetal functions would be imbricated or in which there was only one acetal (or glycoside) were elaborated. Towards this end, the iodoacetal (**5**) was prepared from the corresponding hemiacetal as a mixture of four diastereoisomers. When treated with tributyltinhydride in the above conditions, two sets of products were obtained (83%) and separated. Compound (**6α**) was obtained as a 1/1 mixture of epimers at C-7 whereas (**6β**) was obtained as a pure *exo*-(7*S*) isomer on the basis of its ^{1}H n.m.r. spectrum.† The acetals (**6α**) were hydrolysed to the corresponding hemiacetal which retained the bicyclic structure and was oxidized by Hanessian's procedure[9] to a single lactone (**7**). All attempts to prepare anomerically pure iodoacetal (**5**) have been unsuccessful, so another approach has been devised. Several unsaturated glycosides have been prepared using the Ferrier rearrangement[10] of commercially available tri-O-acetyl-D-glucal. Different alcohols, suitably functionalized to serve as a radical generator such as bromo and acetylenic alcohols, were used giving the glycosides (**8**), (**10**), and (**11**). Upon treatment with tributyltin hydride as usual, compound (**8**) (α/β 7/1) readily cyclized into (**9**) (α/β 11/1) whereas (**10**) was only debrominated to give the unsaturated glycoside. Finally addition of tributyltin radical to the triple bond of (**11**),[11] generated the corresponding vinylstannyl radical which smoothly cyclized into the vinylstannane (**12**) as a single isomer. Some uncyclized vinylstannane (**13**) (12%) was also isolated as a mixture of *E* and *Z* isomers. Destannylation of (**12**) on silica gel proceeded slowly to give (**14**) in 82% yield.

In summary the radical cyclization of various unsaturated iodoacetals derived from sugars proceeds well, giving a new solution to the problem of the stereoselective introduction of functional carbon chains on a sugar template. The use of suitable unsaturated glycosides, easily available from glucal, also allows the chain extension of the sugar at position C-2 providing interesting intermediates such as (**12**) or (**14**).

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† No *endo* isomer was detected in the cyclization products. This could be explained in terms of an electrostatic repulsion, in the transition state, between the ring oxygen and the oxygen of the ethoxy group of the 7(*R*) iodoacetal (**5**).

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