Novel Application of Alkyl Dihalogenoacetates; Chain Extension with an α-Ketoester Unit of Carbohydrates

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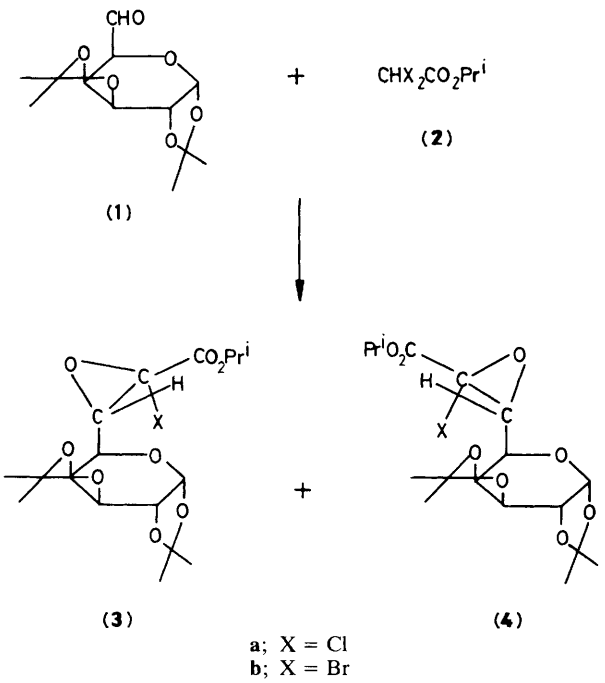
Darzens reaction between dialdosugar (**1**) and alkyl dihalogenoacetates afforded, in high yields, α-halogenoglycidic esters, which can be easily transformed into pyruvic derivatives.

Ketoesters are useful intermediates in organic synthesis,[1] especially in the construction of heterocycles.[2] They also interfere in various biological processes.[3] Although many syntheses have been designed,[4] few α-ketoester derivatives of sugars are known.[5] Furthermore the introduction of an α-ketoester moiety as a part of carbohydrate structures may provide a facile route to C-glycosylated aminoacids.

We have previously reported on several applications of dihalogenoacetate carbanions,[6] and developed a general synthesis of α-ketoesters, from carbonyl compounds using alkyl dichloroacetates.[7] As a part of a programme directed towards the chain elongation of carbohydrates,[8] the application of this methodology to dialdosugar derivatives was undertaken. The readily available 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (**1**)[a] was chosen as model substrate. Darzens condensation between (**1**) and the anions derivated from the isopropyl dihalogenoacetates (**2a**) (X = Cl) or (**2b**) (X = Br) cleanly afforded in high yields (92 and 82% respectively) diastereoisomeric mixtures of α-halogenoglycidic esters (**3**) and (**4**) (Scheme 1).

The ratios of the epimers (**3**) and (**4**) were determined from the integration of the 1-H doublets in the ^1H n.m.r. spectra.



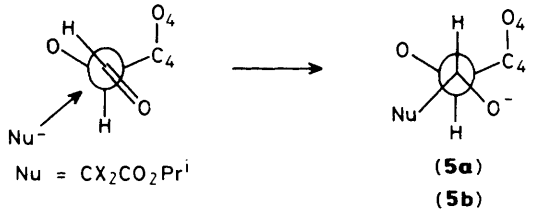
Scheme 1. *Reagents and conditions:* (**1**) (0.775 mmol), (**2**) (1.55 mmol), Pr^{i}OK (1.55 mmol) in PrOH (3 ml) and ether (1.5 ml) under N_2, 90 min at room temperature.

The values which were obtained [(**3a**):(**4a**) = 84:16; (**3b**):(**4b**) = 75:25] clearly indicated that the Darzens condensation exhibited a strong diastereoselection.

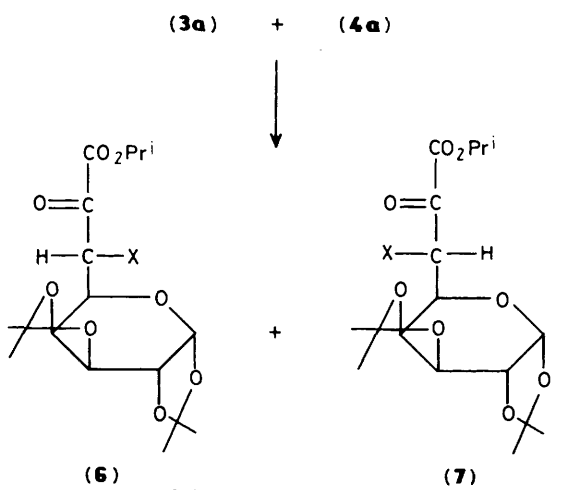
The *trans* relationship of the two carbon chains linked to the oxirane ring was assigned by analogy with previous results in aliphatic series.[6,10]

The configuration at C-6 of the major α-halogenoglycidic esters (**3**) was tentatively assigned as D-*glycero* on the basis of both mechanistic considerations and ^1H n.m.r. data.

Taking account of the usual stereochemical outcome of reactions of (**1**) towards nucleophiles,[8,11] we believe that the major attack at C-6 will arise from the less hindered side of the dialdose which adopts the conformation of Felkin's model,[12] thus leading predominantly to the D-*glycero*-olates (**5**) (Scheme 2).

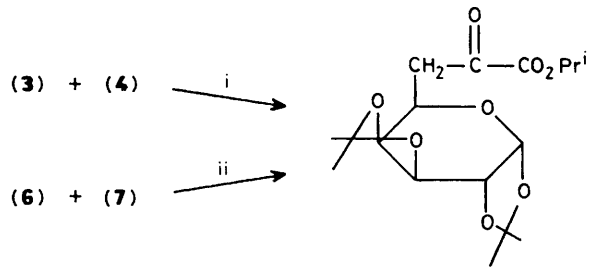


Scheme 2



	X in (6) or (7)	Yield (%)	(6):(7)
a	Cl	72	80:20
b	Br	81	65:35
c	I	78	55:45

Scheme 3. *Reagents and conditions:* (**3a**):(**4a**) (84:16) (0.5 mmol); **a**, $MgCl_2$ (2 mmol), tetrahydrofuran (4 ml), 50 °C, 24 h under N_2; **b**, $MgBr_2$ (1 mmol), ether (5 ml), reflux, 2 h under N_2; **c**, MgI_2 (1 mmol), ether (5 ml), reflux 1 h, then water only (5 ml).



Scheme 4. *Reagents and conditions*: i, (**3**), (**4**) (0.5 mmol), MgI_2 (1 mmol), ether (5 ml), reflux 1 h, then aqueous saturated $NaHSO_3$ (10 ml); ii, (**6**), (**7**) (0.5 mmol), MgI_2 (0.6 mmol), ether (5 ml), reflux 30 min, then aqueous saturated $NaHSO_3$ (10 ml).

Furthermore, in the ^1H n.m.r. spectra, the 5-H signals of the major α-halogenoglycidic esters (**3**) are at higher field than the corresponding signals for the minor epimers (**4**). A similar pattern was previously observed for a number of 2-substituted nitriles derivated from (**1**).[8]

Treatment of the chloroglycidic ester (**3a**)–(**4a**) with magnesium halides, then water, afforded halogenoketoesters (**6**) and (**7**) in high yield (Scheme 3). The ratios of the epimers (**6**) and (**7**) were determined from the integration of the 1-H doublets in the ^1H n.m.r. spectra. The values recorded above clearly indicated that the oxirane opening and the subsequent substitution at the C-6 atom of the chloroglycidic esters (**3**)–(**4**) is not a simple S_N2 mechanism. Since the 5-H signals of the major isomer (**6**) were at lower field than those of (**7**), the L-*glycero* configuration could be assigned to C-6 of the major isomer (*vide supra*).

Treatment of the mixture (**3**) and (**4**) with magnesium iodide followed by saturated aqueous sodium hydrogen sulphite yielded the α-ketoester (**8**) (90% yield) *via* the epimeric iodoketoesters (**6c**)–(**7c**) as demonstrated by separate experiments (Scheme 4).

The reaction of magnesium iodide with the α-bromoketoesters (**6b**)–(**7b**) followed by aqueous work-up afforded the iodoketoesters (**6c**)–(**7c**) (57:43) in 99% yield, which were reduced ($NaHSO_3$) to give (**8**) (80%).

A study of the 400 MHz ^1H n.m.r. spectra of the α-ketoester (**8**) shows that the crude (**8**) exists as a tautomeric mixture of keto–enol forms. Purification of the crude product by flash chromatography on silica gel affords the pure keto form.

In summary this methodology introduces a two carbon unit in a sugar moiety in high yield. The high degree of functionality would allow a variety of chemoselective transformations, the study of which is in progress.

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