

THE CHROMOUS CHLORIDE PROMOTED ADDITION OF N-CHLOROCARBAMATES TO ENOL ETHERS

THE SYNTHESIS OF N-ALKOXYCARBONYLDERIVATIVES OF 2-AMINO SUGARS

AND OF α -AMINO KETONES AND ALDEHYDES¹

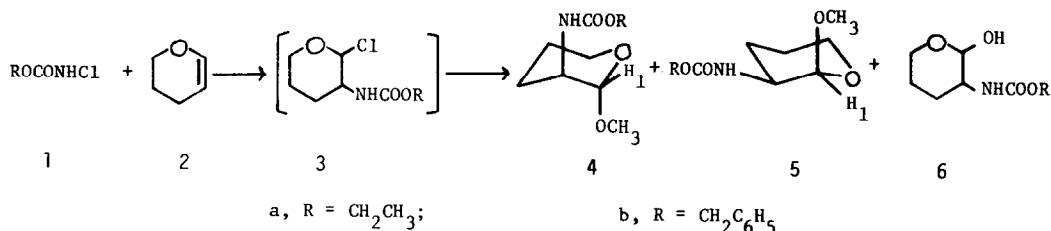
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In the preceding communication (1), we describe a new reaction which utilises chromous chloride to promote the addition of N-chlorocarbamates to olefins in good yields. We have applied this reaction to four enol ethers which illustrate the synthetic importance of the novel reaction.

Dihydropyran. - N-chlorourethane (NCU) (1a) and dihydropyran (2) in a 1:2 molar ratio (CH_3OH , -78°C , 30 min) gave the adducts 4a³, 5a (m.p. $62-63^\circ\text{C}$) and 6a (2) in 77%, 3% and 5% yields respectively (scheme I). Equilibration of either the trans isomer 4a or the cis isomer 5a with



Scheme I

dry hydrogen chloride in absolute methanol gave a 1:2 mixture of 4a and 5a thus implying that the more stable isomer is 5a. The methoxy groups in both isomers assumes an axial orientation [4a: δ (H_1) 4.41 (doublet, $J = 2.8$ Hz); 5a: δ (H_1) 4.61 (doublet, $J = 3.0$ Hz)] consequential of the anomeric effect (3). With N-chlorobenzylcarbamate (1b), a 60% yield of adduct 4b (m.p. 59°C) was obtained.

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² Holder of a Studentship from the Arts Council of Canada, 1969-1971.

³ All compounds had I.R. and N.M.R. (CCl_4 or $\text{CDCl}_3\text{-TMS}$) spectra consistent with their structures. All new compounds gave satisfactory analytical data. Liquids were purified by microdistillation.

Triacetyl-D-glucal. - The reaction of N-chlorocarbamates and triacetyl-D-glucal (7) in a 2:1 molar ratio ($\text{CHCl}_3\text{-CH}_3\text{OH}$, -78°C , 8 to 10 hr) is illustrated in scheme II. The N.M.R. spectrum of the crude product indicated the presence of mainly the α -chloride 8 [$\delta(\text{H}_1)$ 6.25 (doublet $J = 3.8 \text{ Hz}$)] in addition to some unreacted glucal 7; the β -chloride 9 is presumably formed also but it was not possible to observe the signal of its anomeric proton¹. The Koenigs-Knorr reaction performed directly on the above crude reaction mixture gave the derivatives 10 in reasonable yield together with some unreacted glucal 7 (scheme II, table I). In some of the chromatographic fractions, the presence of small amounts of the manno derivatives 11 could be inferred from an examination of their N.M.R. spectra; the mannopyranoside 11 ($\text{R} = \text{CH}_2\text{CH}_2\text{Cl}$, $\text{R}_1 = \text{CH}_3$) [m.p. $140^\circ\text{-}141^\circ\text{C}$; $[\alpha]_{578}^{25} + 38^\circ$

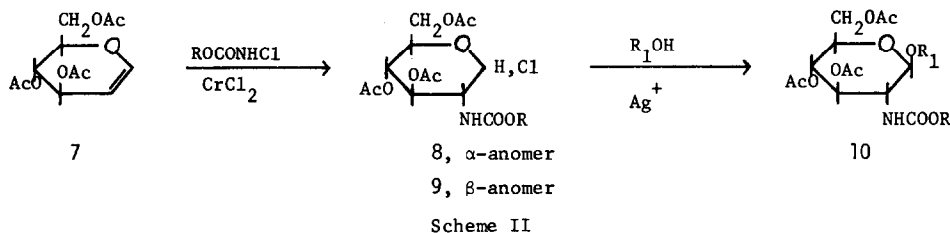


Table I

R	R ₁	Recovered 7	Yield ^{a)}	Isolated 10 m.p.	$[\alpha]_{578}^b$	m.p.	Litterature $[\alpha]_D^b$	(Ref)
C ₂ H ₅	CH ₃	18%	42% ^{c)}	136.5-137°C	+6.0°			
C ₂ H ₅	COCH ₃	18%	49%	144-144.5°C	+18°	144-145°C	+16.1°	(4)
C ₂ H ₅	CH ₂ C ₆ H ₅	18%	46%	157-158°C	-28°			
CH ₂ C ₆ H ₅	CH ₃	13%	43%	149-150°C	+17.5°	147-149°C	+17°	
CH ₂ CH ₂ Cl	CH ₃	2%	43% ^{d)}	122-123°C	+9.4°			

a) These yields do not take into account the recovery of the starting glucal 7. The N.M.R. spectrum of the mother liquors shows that they still contain appreciable amounts of compound 10.

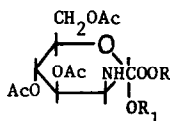
b) Chloroform ($c = 0.5$ to 2%).

c) An additional 19% (total yield of 61%) was obtained by deacetylation of the mother liquors, recrystallisation of the deacetylated product and then reacetylation of the crystals.

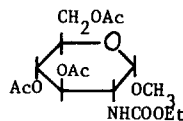
d) An additional 12% (total yield of 55%) was obtained by the procedure described in c).

¹ In the N.M.R. spectrum of a standard 2:2:1 mixture of the α -glucopyranosyl chloride 8 ($\text{R} = \text{Et}$), the β -anomer 9 ($\text{R} = \text{Et}$) and triacetyl-D-glucal (7), the doublet of the anomeric proton of the β -anomer at 5.53 ppm ($J = 8.8 \text{ Hz}$) is masked by other signals. By taking the quantity of glucal 7 recovered after the subsequent reaction as the amount present in the crude reaction mixture, it was possible to estimate by N.M.R. the yield of the α -chloride 8 ($\text{R} = \text{Et}$) as 50% using the above standard mixture for comparison.

($c = 1.3$, CHCl_3) has been isolated in 9% yield. The β -glucopyranosyl chloride 9 ($R = \text{Et}$) [m.p. $115\text{--}116^\circ\text{C}$; $[\alpha]_{578}^{25} + 17.5^\circ$ ($c = 2.0$, CHCl_3)] was prepared from the β -acetate 10 ($R = \text{Et}$, $R_1 = \text{Ac}$) according to the procedure of Lemieux (6). Anomerisation with titanium tetrachloride in chloroform (7) gave the α -chloride 8 ($R = \text{Et}$) [amorphous, $[\alpha]_{578}^{25} + 470^\circ$ ($c = 1.5$, CHCl_3)]. The anomerisation of the β -D-glucopyranoside 10 ($R = \text{C}_2\text{H}_5$, $R_1 = \text{CH}_3$) under the same conditions was complete after 3 days by following with N.M.R.; the pure α -D-glucopyranoside 12 [amorphous, $[\alpha]_{578}^{25} + 99^\circ$ ($c = 1.5$, CHCl_3)] was isolated in 70% yield.

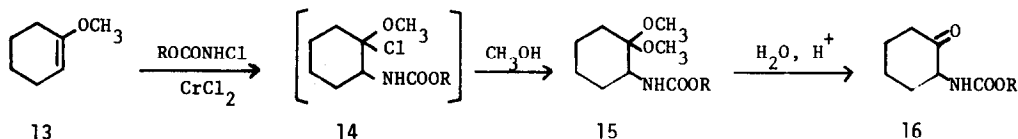


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1-methoxy-1-cyclohexene. - The addition of N-chlorocarbamates to this enol ether (CHCl_3 - CH_3OH , -78°C , 1 hr, 2:1 mole ratio of enol ether to N-chlorocarbamate) is shown in scheme III. When the reaction mixture was stirred for 4 hr at room temperature in presence of water before work up,



Scheme III

hydrolysis of the ketal 15 was nearly complete and the α -carbamido ketone 16 was isolated in very good yield (table II, entries 1 and 2), whereas after 1 hr stirring there was still an appreciable amount of ketal left (entry 3). It was possible to obtain the α -carbamido ketal 15 in good yield by excluding water and neutralizing the acid present in the reaction mixture with sodium methoxide.

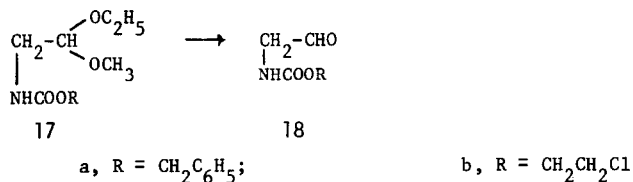
Table II: Addition of N-chlorocarbamates to 1-methoxy-1-cyclohexene (scheme III)

	R	Ketal 15		Ketone 16		(Ref)
		Yield	m.p.	Yield ^{a)}	m.p.	
1	CH_2CH_3			85% (90%)		(8)
2	$\text{CH}_2\text{CH}_2\text{Cl}$	6%		80% (81%)	$49\text{--}50^\circ\text{C}$	
3	CH_2CCl_3	30%		56%	$80\text{--}80.5^\circ\text{C}$	
4	$\text{CH}_2\text{C}_6\text{H}_5$	60%	$58\text{--}59^\circ\text{C}$	3%	$60.5\text{--}61^\circ\text{C}$	

a) Figures in brackets represent yields estimated by VPC (SE-30 on Chromosorb W)

The cleavage of the ketals either with 70% aqueous acetic acid at 70°C for 30 min or with 0.5% hydrochloric acid in 80% aqueous dimethoxyethane at room temperature for 4 hr was nearly quantitative.

Ethoxyethylene. - The addition of N-chlorobenzylcarbamate and N-chloro-β-chloroethyl carbamate to ethoxyethylene ($\text{CHCl}_3\text{-CH}_3\text{OH}$, -78°C, 5 hr, 2:1 mole ratio of enol ether to N-chlorocarbamate) gave the mixed acetals 17a (80% yield) and 17b (74% yield) respectively. The corresponding aldehydes 18a (2,4-DNP: m.p. 192-193°C) and 18b (2,4-DNP: m.p. 188-189°C) were obtained in about 60% yield by heating 1 hr at 70°C in 70% aqueous acetic acid (9).



Further applications of this reaction to carbohydrate and steroid derivatives are being studied.

Enol acetates are less reactive than enol ethers in this type of reaction: the addition of NCU (1a) to 1-acetoxy-1-cyclohexene in the conditions used for the addition of NCU (1a) to 1-methoxy-1-cyclohexene gave a 43% yield of α-ethoxycarbamido cyclohexanone (16, R = Et).

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