ALUMINIUMCHLORIDE-INDUCED ADDITIONS OF FORMALDEHYDE TO ALKENES

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Dedicated to Professor H.G. Viehe on the occasion of his 65th birthday

ABSTRACT

The addition of formaldehyde to alkenes induced by AlCl3 is a simple route to alkylsubstituted tetrahydropryanos. Additions of two equivalents of formaldehyde to 1-alkenes and 1,2-dialkylsubstituted alkenes give 3-alkyl-4-chlorotetrahydropryanos and 3,5-dialkyl-4-chlorotetrahydropryanos, respectively. The products are obtained as a mixture of diastereomers. 2,5-Dialkyl-4-chlorotetrahydropryanos are obtained in AlCl3-induced additions of one equivalent of formaldehyde to homoallylic alcohols. Reductive dechlorination gives the corresponding 3-, 3,5- and 2,5-alkylsubstituted tetrahydropryanos, respectively.

INTRODUCTION

The acid-catalyzed addition of aldehydes to olefins is usually called the Prins reaction (1-3). Generally the reaction gives a complex mixture of products consisting of 1,3-dioxanes, 1,3-glycols and unsaturated alcohols as main products. Cyclic ethers such as tetrahydropryanos and tetrahydrofurans were identified occasionally as minor products. It should be of interest to find reaction conditions giving with high selectivity only one of the formaldehyde-alkene addition products.

There are known Lewis acid induced reactions - e.g. SnCl4 and BF3, Et2O - giving as main products the corresponding unsaturated alcohols (4-6). Primary homoallylic alcohols are obtained in good yields and with high selectivity in allylaluminium halide induced one reactions (7-9). We reported recently the allylaluminium halide induced one addition of formaldehyde to readily available unsaturated fatty compounds (10,11), for example oleic acid and 10-undecenoic acid which are of interest as renewable raw materials (12) and obtained in good yields the corresponding primary homoallylic alcohols.

3-Alkyl-4-halotetrahydropryanos are obtained in reactions of paraformaldehyde and α-olefines in the presence of hydrogen halides (13a). Using hydrogen chloride at -60° to -70°C the products were obtained in yields of 70-80% as mixtures of diastereomers. The condensation of cis- and trans-2-butene with formaldehyde and hydrogen chloride affords the diastereomeric chloroalcohols and their formals as main products while the corresponding alkyls substituted chlorotetrahydropryanos were formed only in small amounts (14). The reaction of formaldehyde and cyclohexene in the presence of hydrogen chloride gives a mixture of two chlorinated bicyclic ethers along with a small amount of the corresponding formaldehyde acetal (15). Addition of formaldehyde to 3-butanol-1-ol catalyzed by hydrochloric acid gives 4-chlorotetrahydropryanos (16). 2-Alkyl-4-chlorotetrahydropryanos are obtained in analogous reactions with aldehydes such as acetaldehyde, propionaldehyde and butyraldehyde. The corresponding reactions catalyzed by sulphuric acid afford the substituted tetrahydropryan-4-ols as major products. Additions of aldehydes and ketones to the substituted alcohol 4-methyl-4-penten-2-ol in the presence of p-toluenesulfuric acid give 3,6-dihydro-2H-pyrans (17).

In the present paper we describe the addition of formaldehyde to olefins induced by AlCl3 to give with high selectivity alkylsubstituted tetrahydropryanos.

RESULTS AND DISCUSSION

The AlCl3-induced reaction of formaldehyde and 1-octene (1a) or methyl 10-undecenoate (1b) gave the corresponding 3-alkyl-4-chlorotetrahydropryanos trans-2a/cis-2a and trans-2b/cis-2b, respectively. The diastereomers were obtained in a ratio of [cis]:[trans] = 1:2.5. The isomers could be assigned by their 13C NMR data. The chemical shifts of the ring carbons were identical to those of cis- and trans-4-chloro-3-propyltetrahydropryan (13b). The reaction takes place by addition of two equivalents of formaldehyde to the double bond of the alkene. In the first step one equivalent of formaldehyde should be added to give the ene adduct, the homoallylic alcohol. It is known that homoallylic alcohols cyclize to give 4-chlorotetrahydropryanos on reaction with formaldehyde and hydrogen chloride (18). This reaction sequence was confirmed by the following experiment: Methyl 12-hydroxydodec-9-enoate obtained by ethylaluminium dichloride-induced addition of formaldehyde to methyl 10-undecenoate (10), reacted with formaldehyde induced by AlCl3 to give 3-alkyl-4-chlorotetrahydropryan...
trans-2b/cis-2b. Reductive dechlorination of trans-2a/cis-2a and trans-2b/cis-2b for example with Bu₃SnH afforded the 3-alkyl-tetrahydropyran 3a and 3b, respectively.

The addition of formaldehyde to 1,2-dialkylsubstituted alkenes 4, 6a and 6b gave the corresponding 3,5-dialkyl-4-chlorotetrahydropyran 5, 7a/8a and 7b/8b in good yields. The reaction of cis-2-heptene (4) afforded regioselectively 4-chloro-5-methyl-3-propyltetrahydropyran (8) as a diastereomeric mixture of (3α, 4β, 5β)-5 and (3α, 4α, 5α)-5 in a ratio of 4:1. The addition products with methyl oleate (6a) and methyl petroelite (6b) were obtained as regioisomers (1:1 mixture) and as diastereomers. Reductive dechlorination of 7a/8a and 7b/8b with Bu₃SnH gave the corresponding 3,5-dialkyltetrahydropyran 9a/10a and 9b/10b.

The diastereomeric mixture of 7a/8a was separated by column chromatography and obtained as (3α, 4β, 5β)-7a/(3α, 4β, 5β)-7b (3α, 4α, 5α)-8a and (3α, 4α, 5α)-8b in a ratio of 3:1.

The addition of formaldehyde to methyl ricinoleate (11), an alkene with β-hydroxy functionality took place regioselectively to position C-9 of the oleine. Cyclization and elimination of H2O afforded 2,5-dialkyl-4-chlorotetrahydropyran 12 as a mixture of diastereomers. (2α, 4α, 5β)-12 was obtained by recrystallization of 12 from petrolether. Reductive dechlorination of 12 gave a mixture of the 2,5-dialkyltetrahydropyran trans-13 and cis-13 in a ratio of 3.8:1.

The stereochemistry of the main products can be explained by anti-attack of the formaldehyde·AlCl3-complex to the homoallylic alcohol existent in the preferred conformation avoiding allylic strain (19). The minor products are formed by syn-attack.
The AlCl₃-induced addition to formaldehyde to alkenes gives high selectivity the corresponding alkylsubstituted 4-chlorotetrahydropyrans. In this study the synthesis of 3-, 3.5- and 2.5-alkylsubstituted tetrahydropyrans is described. By variation of the alkenes on the one hand and of the carbonyl compound on the other hand it should be possible to synthesize the complete set of alkylsubstituted tetrahydropyrans.

**EXPERIMENTAL**

Melting points (uncorrected): Leitz Laborlux 12. - Refractive indices nD: Zeiss-Abbe-Refractometer. - ¹H and ¹³C NMR: Bruker AM 300 (2a, 2b, 3a, 3b, 9a/10a and 9b/10b), Bruker AMX R 500 ((3x, 4x, 5x, 7a/8a)/3x, 4x, 5x, 7a/8a), TMS as internal standard: selected data are given. Full ¹H- and ¹³C-NMR data are available from the authors on request. The signals of the regiosomers 7b and 8b were distinguishable in the ¹H- and ¹³C-NMR spectra but they could not be assigned unambiguously to the respective products. NMR-data of the minor products cis-2a, cis-2b, (3x, 4x, 5x, 7a/8a)-5 and (3x, 4x, 5x, 7b/8b)/3x, 4x, 5x, 7b/8b) were signed by ⁸. Analytical GC: Carlo Erba GC 6000 Vega Series 2 with a FID (DB1 column, 28 m). - Mass spectra: Finnigan MAT 212 mass spectrometer. -

Methyl oleate (new sunflower, 82.8% methyl oleate, 2.6% methyl stearate, 3.5% methyl palmitate, 8.4% C₁₈₂), petroselinic acid (81.3% petroselinic acid, 3.3% palmitic acid, 0.4% stearic acid, 13.5% C₁₈₂), and ricelecnic acid (80 - 85% purity) were obtained from Henkel KGaA. - The amounts of the starting olefins used in the reactions were calculated based on 100% purity. The free fatty acids were converted to their methyl esters by usual esterification. - Methyl 10-undecenolate (Atocom), cis-2-heptenone and 1-octenone (Merck), paraformaldehyde (Janssen), Bu₄SnH, AIBN, AlCl₃, Knorr (Fluka), 18-crown-6 (Aldrich) were used without further purification. - All reactions were run under N₂.

Synthesis of alkylsubstituted chloro-tetrahydropyrans: general procedure:

A mixture of the appropriate alkenes 1a or 4 or of the methyl alkenolate 1b, 6a, 6b or 11 (5 mmol) and paraformaldehyde (0.3 g, 10 mmol; 0.21 g, 7 mmol was used for 11) in CH₂Cl₂ (10 mL) was stirred magnetically in N₂ atmosphere for 5 min at -15°C. After addition of AlCl₃ (0.33 g, 2.5 mmol) the sample was stirred for additional 24 h at r.t. The reaction was quenched by addition for Et₂O (100 mL) and H₂O (40 mL). 10% HCl was added until the precipitated aluminium salts dissolved. The organic layer was separated and the aqueous layer extracted with Et₂O (3x40 mL). The combined organic layers were dried (Na₂SO₄) and evaporated. The product was purified by 'Kugelrohr' distillation (2b, 5, 7a/8a, 7b/8b) or by column chromatography (28 cm x 2 cm) on silica gel (Merck, 70-230 mesh) with petroleum ether/EtOAc (5:5) as eluent (2a, 12). Fractions containing the tetrahydropyrdinolvative were collected, the solvent evaporated and the residue dried at 20°C/0.01 mbar. Reductive dechlorination of the alkylsubstituted 4-chloro-tetrahydropyrans with Bu₄SnH: A solution of the tetrahydropyran 2a, 2b, 7a/8a, 7b/8b and 12 (1-2 mmol), Bu₄SnH (1 mL, 4 mmol) and AlBN (15 mg) in benzene (30 mL) was heated at 80°C for 20 h. The solvent was evaporated and the residue dissolved in Et₂O (10 mL). KF (10% in H₂O, 10 mL) and 18-crown-6 were added. The organic layer was separated and the precipitate washed with Et₂O (80 mL) and evaporated. The combined organic layers were dried (Na₂SO₄) and evaporated.

**trans-4-Chloro-3-pentyltetrahydropyran (trans-2a)** and cis-4-Chloro-3-pentyltetrahydropyran (cis-2a) (2:1 mixture): yield 0.71 g (75%), colorless liquid, nD₂₀ = 1.4635. ¹H NMR (CDCl₃): δ = 4.42 (m, 1H, 4H), 4.02 (dd, J = 11.8, 4.9 Hz, 1H, 2H), 3.94 (m, 1H, 6H), 3.76 (m, 1H, 4H), 3.78 (m, 2H, 6H, 6H), 3.59 (dd, J = 11.5, 4.4 Hz, 1H, 2H), 3.51 (dd, J = 11.5, 9.9 Hz, 1H, 2H), 3.41 (dd, J = 11.5, 11.0, 2.5 Hz, 1H, 6H), 3.11 (dd, J = 11.8, 9.4 Hz, 1H, 2H), 2.16 (m, 1H, 3H), 2.11 (m, 1H, 3H), 1.94 (m, 2H, 5H), 1.94 (m, 2H, 5H), 1.50 (m, 2H, 5H), 1.45 (m, 2H, 5H), 0.85 (m, 2H, 5H). ¹³C NMR (CDCl₃): δ = 72.9 (C-2), 67.1 (C-6), 68.3 (C-8). 62.5 (C-6), 61.8 (C-4), 60.8 (C-4), 44.3 (C-3), 40.0 (C-3), 36.5 (C-5), 34.5 (C-5). MS/Cl (isobutane): m/z (%) = 191(100)/193(32) [M⁺], 155(66) [M⁺-HCl]. - Cu₂H₂OCl₂: calc. 191.1224, found 191.1323 (M₂/O₂Cl). -

3-Pentyltetrahydropyran (3a): Dechlorination of 2a (0.45 g) gave 0.35 g (95%) of 3a, colorless liquid, nD₂₀ = 1.4591. ¹H NMR (CDCl₃): δ = 3.85 (m, 2H, 2H and 6-H), 3.33 (dd, J = 11.2, 9.7, 4.4 Hz, 1H, 6-H), 3.02 (dd, J = 11.0, 10.2 Hz, 1H, 2-H), 1.84 (m, 1H, 3-H), 1.56 (m, 4H, 4-H and 5-H). -
3-7-(Methoxyacarbonyl)ethyl-tetrahydropyran (3b) - Dechlorination of 2b (0.5 g) gave 0.43 g (97%) of 3b, colorless liquid, n\textsubscript{D} = 1.4972. - H NMR (CDCl\textsubscript{3}): δ = 4.20, 2.0, 6.56 (dd, J = 11.5, 5.6 Hz, 1H); 2.86 (dd, J = 7.5, 2H, 6-H\textsubscript{a}); 3.76 (m, 1H, 4-H). - 13C NMR (CDCl\textsubscript{3}): δ = 3.83 (3h, 2, 2-H, 1-H, 4-H\textsubscript{a}); 3.31 (dd, J = 10.6, 10.6 Hz, 2H, 1-H, 4-H\textsubscript{b}); 2.88 (t, J = 7.5, 2H, 6-H\textsubscript{b}); 1.82 (m, 1H, 3-H); 1.56 (m, 6H, 4-H, 5-H, CH\textsubscript{2}CH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{3}). - Cl CH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{3}.

4-Chloro-5-methyl-3-propyltetrahydropyran (3a, 4\alpha, 5\beta)-an (3a, 4\alpha, 5\beta)-an and 3a, 4\alpha, 5\beta)-an, colorless liquid, n\textsubscript{D} = 1.4662. - H NMR (CDCl\textsubscript{3}): δ = 4.08 (dd, J = 5.8, 3.7 Hz, 1H, 4-H\textsubscript{a}); 4.00 (dd, J = 11.5, 4.5, 0.9 Hz, 1H, 2-H); 3.97 (dd, J = 11.6, 3.4 Hz, 1H, 4-H, 6-H\textsubscript{a}); 3.73 (m, 1H, 3-H); 2.90 (t, J = 10.6, 10.6 Hz, 2H, 1-H, 4-H\textsubscript{b}); 2.90 (dd, J = 11.6, 11.5 Hz, 1H, 2-H, 4-H\textsubscript{a}); 2.58 (s, 3H, 5-H; 13C NMR (CDCl\textsubscript{3}) δ = 73.6 (C-2, 72.2 (C-6), 71.0 (C-2\textsuperscript{a}), 67.4 (C-4), 70.3 (C-4), 66.2 (C-4\textsuperscript{a}), 44.3 (C-1), 41.7 (C-3\textsuperscript{a}), 41.4 (C-5). - 3-Chloro-6-(methoxyacarbonyl)hexyl-5-octyltetrahydro- (7a) and 4-Chloro-5-heptyl-3-(methoxyacarbonyl)-heptyl-tetrahydropyran (8a) (1:1 mixture) yield 1.61 g (86%), colorless liquid, n\textsubscript{D} = 1.4723. - MS/Cl (isobutane): m/z (%): 274 (100), 174 (54), 156 (61), 135 (48), 115 (100), 91 (1.7). - CH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{3} (374.2): calcd. C 67.9, H 10.42, found C 67.7, H 10.23. - 4-Chloro-2-hexyl-5-(methoxyacarbonyl)hexyl-5-octyltetrahydro- (trans-13 and cis-13) - Dechlorination of 12 (0.5 g) gave 0.41
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