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A NEW SYNTHESIS OF α-HYDROXY ALDEHYDES FROM KETONES AND TOSYLMETHYLISOCYANIDE[1]

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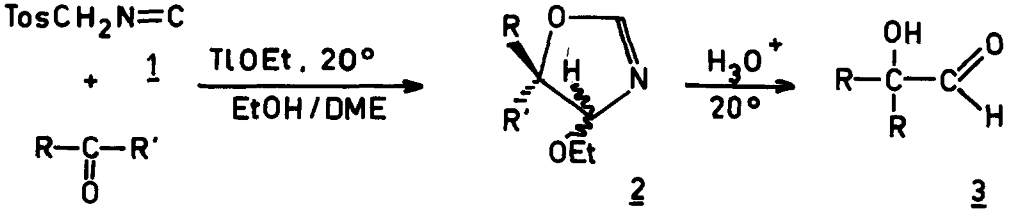
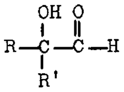
In the preceding letter[1b] we reported the synthesis of 4-ethoxy-2-oxazolines (2) from TosMIC (1) and ketones with thallium (I) ethoxide. Due to the presence of a 4-ethoxy substituent, acid catalyzed hydrolysis of these oxazolines leads directly to the formation of α-hydroxy aldehydes (3). Since 4-ethoxyoxazolines (2) are easily obtained in good yields[1b], and because hydrolysis is achieved under mild conditions, we here have at hand a new and simple synthesis of α-hydroxy aldehydes. This method moreover has the advantage of providing most of the hydroxy aldehydes in monomeric form.



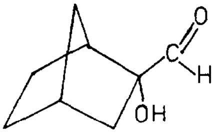
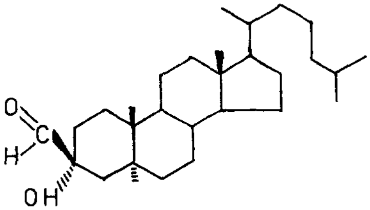
For obvious reasons, much work was done in the past to develop methods for the synthesis of α-hydroxy aldehydes. Only a few approaches have been successful, with the restriction however, that mostly dimeric products were obtained.[2,3] Recently, synthetic methods have been reported based on the hydrolysis of 1,1-dichloro-2-hydroxy compounds[4], oxidative hydrolysis of α-hydroxy mercaptals[5,3], and hydrolysis of the mono-S-oxides of α-hydroxy mercaptals.[6] These methods — applied to aryl α-hydroxy aldehydes only — are less general and more laborious than the present procedure.

TABLE[a]



$$\mathrm{R{-}\overset{OH}{\underset{R'}{C}}{-}\overset{O}{\overset{\|}{C}}{-}H}$$

3

	R	R'	yield[b]	b.p./m.p. °C
3a	$-(CH_2)_5-$		38%	80-82°/12 mm DNPH, m.p. 217.5-218.5° [d]
3b	n-Pr	n-Pr	52%	73°/12 mm
3c	t-Bu	Me	70%	130°/760 mm
3d	Ph	Me	70%	108-110°/0.3 mm (lit.[5] 116-120°/0.7 mm)
3e	p-BrPh	Me	71%	m.p. 60-61°
3f			78%	97-100°/12 mm
3g			70%[c]	m.p. 176-176,5°

a) Satisfactorily elemental analyses were obtained for all new compounds.

b) Yields based on the amount of monomer obtained after diluting the reaction mixture with water, extraction with ether and distillation or crystallization.

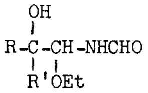
c) Mixture of dimer and monomer.

d) Lit.[2] DNPH, m.p. 218-219°.

The conversion of the 4-ethoxyoxazolines (2) to α-hydroxy aldehydes is accomplished simply by stirring a solution of 2 in a mixture of THF and dilute hydrochloric acid at room temperature overnight. The results are summarized in the Table.

With the exception of 3g, all α-hydroxy aldehydes were obtained in monomeric form. The tendency to dimerize was most pronounced for 1-hydroxycyclohexane-1-carboxaldehyde (3a) and for 3,α-hydroxy-5,α-cholestane-3,β-carboxaldehyde (3g). In all other compounds little dimer was present after storing samples for 3 days at -20°.

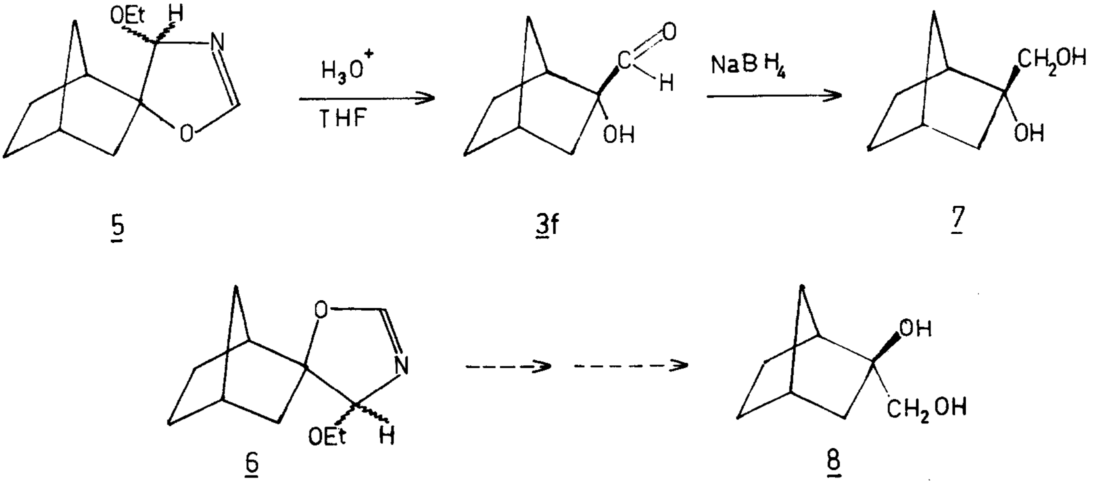
Hydrolysis of 2 was shown, by monitoring with GLC, to involve rapid formation of an intermediate (4), which was converted more slowly to 3. By quenching the reaction leading to 3a at an early stage, the intermediate was isolated and identified as 4 [R-R' = -(CH$_2$)$_5$-] on the basis of PMR, IR and MS.



$$\mathrm{R{-}\overset{\displaystyle OH}{\underset{\displaystyle R'}{C}}{-}\underset{\displaystyle OEt}{CH}{-}NHCHO}$$

4

As was discussed in the preceding letter[1b], 2-norbornanone could give in principle two different pairs of epimeric 4-ethoxy-2-oxazolines (5 and 6), depending on the side of attack of TosMIC-anion. The oxazoline actually formed was an epimeric mixture of 5, since hydrolysis gave 2-endo-hydroxynorbornane-2-exo-carboxaldehyde (3f) only.[7] The structure of 3f was proven by reduction with NaBH$_4$ in absolute ethanol to give 2-endo-hydroxy-2-exo-hydroxymethylnorbornane (7), [70% yield, m.p. 69-70°, δ (CDCl$_3$) 3.34 (d, 2 H, J = 2 Hz, CH$_2$OH)], which was shown to be the epimer of the known 2-exo-hydroxy-2-endo-hydroxymethylnorbornane (8) by comparison with an authentic sample.[8]



In a similar manner only 3,α-hydroxy-5,α-cholestane-3,β-carboxaldehyde (3g) was obtained from TosMIC and 5,α-cholestanone-3. α-Hydroxy aldehyde 3g was reduced likewise in 71% yield to 3,α-hydroxy-3,β-hydroxymethyl-5,α-cholestane (m.p. 185-186°).

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Notes and References.

1. a. This letter is considered Chemistry of Sulfonylmethylisocyanides, Part 9;
   b. For Part 8, see O.H. Oldenziel and A.M. van Leusen, this journal, preceding letter.
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7. The spectral data (CMR, PMR) clearly showed that only one of the two possible epimeric 2-hydroxynorbornane-2-carboxaldehydes was formed. The same was found for 3-hydroxy-5,α-cholestane-3-carboxaldehyde.
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