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SYNTHESIS AND STEREOCHEMISTRY OF 4-ETHOXY-2-OXAZOLINES[1]

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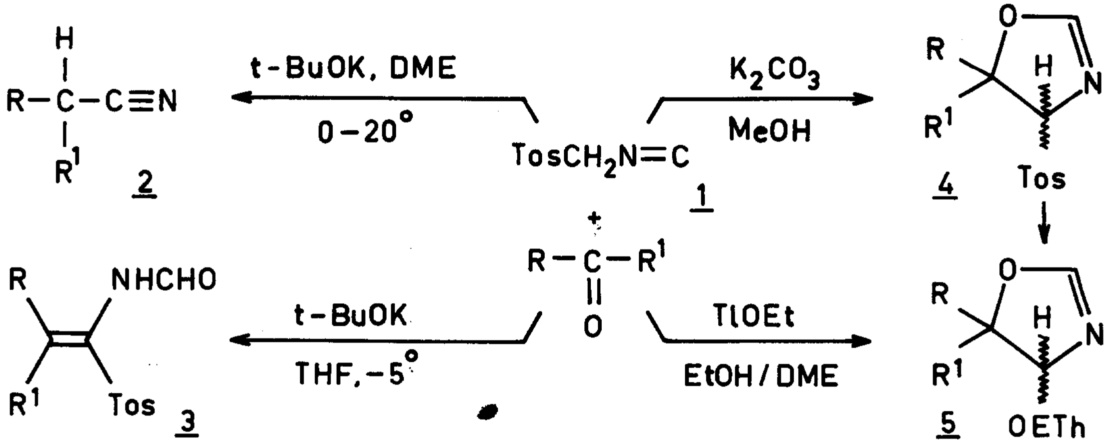
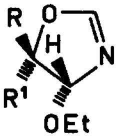
A number of reactions of tosylmethylisocyanide (TosMIC, 1) with ketones has been discussed in previous papers. Different products, i.e. nitriles (2)[1b,2], 1-formylamino-1-tosylalkenes (3)[3] or 4-tosyl-2-oxazolines (4)[1b,3], were obtained by changing the conditions of the reaction. In continuation of our search for synthetic applications of TosMIC, we now wish to add to these possibilities the synthesis of 4-ethoxy-2-oxazolines (5) from the same reactants, but again under different circumstances.



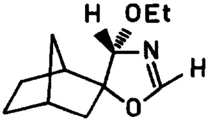
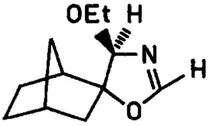
2-Oxazolines with a 4-ethoxy substituent (not reported previously[4]) are of interest because of their utility as starting materials in an attractive, new synthesis of (monomeric) α-hydroxy aldehydes (see accompanying letter[5]).

The 4-ethoxyoxazolines 5, listed in the Table, were prepared simply by stirring equimolar quantities of a ketone, TosMIC and thallium (I) ethoxide in a 4 : 1 mixture of absolute ethanol and 1,2-dimethoxyethane (DME) at room temperature. Under the same conditions 5 is formed from

TABLE[a]



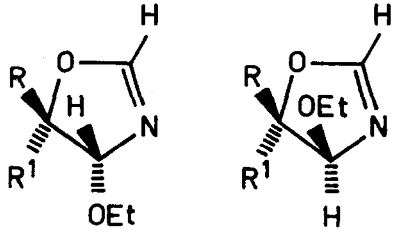
5

	R	R'	ratio of epimers[b]	yield[c]	b.p. °C.[d]
5a	Me	Me	-	60%	54°/12 mm
5b	-(CH$_2$)$_5$-		-	72%	99°/10 mm
5c	n-Pr	n-Pr	-	75%	112-114°/16 mm
5d			-	92%	m.p. 71-76°
5e	t-Bu Me	Me t-Bu	e	35%	88-90°/12 mm
5f	Ph Me	Me Ph	E 82% Z 18%	60%	84-88°/0.5 mm
5g	p-BrPh Me	Me p-BrPh	E 84% Z 16%	55%	129-131°/0.5 mm
5h	p-MeOPh Me	Me p-MeOPh	E 85% Z 15%	40%	104°/0.1 mm
5i			Z[f] ~ 80% E[f] ~ 20%	62%	114-115°/10 mm

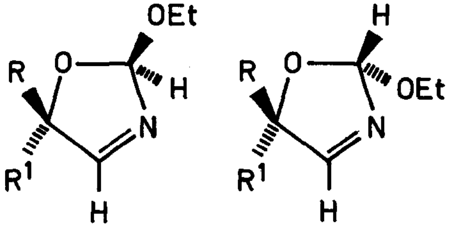
a) The compounds listed gave correct elemental analyses within 0.3%.
b) Ratio of epimers determined by PMR. The epimers have not been separated.
c) Yields after distillation.
d) For epimeric mixtures the b.p. of the mixture is given.
e) Although PMR showed the presence of epimers, the ratio (roughly 4 : 1) could not be determined accurately because of overlapping peaks.
f) E-Z assignment based on sterical arguments only.

(isolated) tosyloxazoline 4 also, as was demonstrated for the compounds with R = R' = Me, and R-R' = $(CH_2)_5$.

The 4-ethoxy-2-oxazoline structure of 5 may be consistent with its formation from 4, however, this reaction does not necessarily exclude the alternative 2-ethoxy-3-oxazoline structure (6). Moreover, the products derived from unsymmetrical ketones have additional stereochemical possibilities — four altogether, not considering enantiomers — as shown in the formulas 5A,B and 6A,B.



A **5** B



A **6** B

The usual spectral data (IR, PMR, CMR and MS) did not permit an unambiguous structural assignment, yet, the detailed structures were elucidated by the following considerations. As is shown in the Table, all symmetrical ketones gave one oxazoline only, whereas a mixture of two (and only two) very similar isomers was formed from the unsymmetrical ketones (based on CMR and PMR). Therefore, the mixture of isomers most likely was an epimeric mixture, either of 5A and 5B, or of 6A and 6B.

The choice for structure 5 was made for the more simple case of the ethoxyoxazoline derived from acetone (5, R = R' = Me, i.e. 5a in Table) on the basis of a Nuclear Overhauser Effect (NOE). A 17% enhancement was observed for the one-proton singlet at δ 4.85 upon irradiation of the C_5-methyls (at δ 1.35), whereas no change was found for a similar singlet at δ 6.90. Since the lower field singlet clearly belonged to the sp^2 bonded hydrogen, 5a must have the 4-ethoxy-2-oxazoline structure.

The epimer ratio is practically the same for all ethoxyoxazolines (5e-i) derived from unsymmetrical ketones (E : Z ≃ 4 : 1). The Z-configuration (i.e. structure 5A, R = Me, R' = aryl) was assigned to the minor epimers in 5f,g,h because of: (i) the observation of a NOE between C_5-CH_3 en C_4-H (which is once more an argument against structure 6 also); (ii) an upfield shift of ca. 0.4 ppm for the ethoxy methyl group due to the C_5-aryl ring in cis-position.

For the spiro-ethoxyoxazoline (5i) derived from 2-norbornanone a similar 4 : 1 mixture of only two epimers was formed (according to CMR and PMR), although here two pairs of epimers would have been possible. The structures of the actual epimers (see Table) follow from the acid catalyzed hydrolysis of the mixture to give only one single product (in 78% yield), which was recognized as 2-*endo*-hydroxynorbornane-2-*exo*-carboxaldehyde (see accompanying letter[5]).

To explain the observed structures of the epimers **5i**, one must assume that in the initial reaction step 2-norbornanone is attacked by TosMIC-anion[6] from the sterically favourable *exo*—position only. Accordingly, camphor with a much less accessible exo-side did not react with TosMIC under the same conditions.

Acknowledgement. This investigation was supported by the Netherlands Foundation for Chemical Research (SON).

Notes and References.

1. a. This letter is considered Chemistry of Sulfonylmethylisocyanides, Part 8;
   b. For Part 7, see O.H. Oldenziel and A.M. van Leusen, Tetrah. Letters **1973**, 1357.
2. O.H. Oldenziel and A.M. van Leusen, Synth. Comm. **1972**, 281.
3. U. Schöllkopf, R. Schröder and E. Blume, Liebigs Ann. Chem. **766**, 130 (1972).
4. Except for the fact that two of them were mentioned briefly in our previous communication, ref. 1b.
5. O.H. Oldenziel and A.M. van Leusen, this journal, succeeding letter.
6. A.M. van Leusen, B.E. Hoogenboom and H. Siderius, Tetrah. Letters **1972**, 2369.