## SELECTIVE SYNTHESIS OF 2-CHLORO-2,3-EPOXY-2-OXAZOLINES AND ISOMERIC 3-CHLORO-2-OXO-2-OXAZOLINES

Jean Claude Combret\*, Abdelhamid Meghni, Didier Postaire, Jacques Tekin

Laboratoire de Synthèse Organique IRCOF, U.F.R. Sciences et Techniques, Université de Rouen, B.P. 118 - 76134 MONT SAINT AIGNAN

ABSTRACT : The reaction of 2-dichloromethyl-4,4-dimethyl-2-oxazoline with carbonyl compounds in basic media has been investigated. Phase transfer catalysis allows fast and selective formation of 2-chloro-2,3-epoxy-2-oxazolines (with aliphatic aldehydes) or 3-chloro-2-oxo-2-oxazolines (mainly with ketones) in high yields.

Numerous recent reports have been dedicated to the description of selective methods of access to 2,3-dihydroxy (or 3-amino-2-hydroxy) acids and esters <sup>1</sup>, which leads us to describe the results obtained as to the formation and selective reactions of functional oxazolines. In fact, such synthetic intermediates with protected functions are the very precursors of functional diols and aminoalcohols, allowing stereochemical control in the case of chiral oxazolines <sup>2,3</sup>. We have already reported on the preparation of a new oxazoline, 2-dichloromethyl-4,4-dimethyl-2-oxazoline 1a, and its O- 1b and S- 1c derivatives as well as the elaboration of corresponding carbanions and access to the alkylated products 2 of these oxazolines 4-6.



2

1a X = C11b  $X = OCH_3, OC_2H_5$ 1c  $X = SC_2H_5, SC_6H_5$  We describe here a selective synthesis of protected compounds 3, 4 and 5 using the conjugated anion of oxazoline 1a and its reaction with aldehydes and ketones under suitable conditions.



This straightforward and valuable route to protected species represents a development of the DARZENS reaction, already described in the case of dichloracetic esters <sup>7</sup> and recently extended to the dichloracetic dianion itself <sup>a</sup>.

However, reaction of oxazoline 1a with carbonyl compounds according to usual conditions (base in aprotic solvent or sodium alkoxide in the corresponding alcohol) does not provide satisfactory results. Using potassium t-butoxide in t-butanol together with THF/HMPT at  $-5^{\circ}C$  allows formation of epoxide 4; yet, the reaction is limited to a few cases (ethanal, 2-methylpropanal, 2,2-dimethylpropanal) and is not selective : the competitive appearance of the isomeric compound 5 can be checked using capillary GC-MS and <sup>1</sup>H NMR.

On the other hand, reaction of 1a with isopropylmagnesium chloride (or halide-magnesium exchange between the same reagent and 2-trichloromethyl-4,4-dimethyl-2-oxazoline 1d) enables to observe a selective reaction with carbonyl compounds. Oxazolines 3 are readily isolated in high yields, as in similar cases already observed with di- and trichloracetic esters °.



**1a:** X=H; 1d: X=C1

Cyclisation from 3 to 4 can be easily performed with potassium t-butoxide in t-butanol, partial isomerisation of 4 into 5 being still difficult to avoid.

Difficulties encountered in preliminary attempts have led us to investigate phase transfer catalysis conditions, owing to the good stability of oxazolines in basic aqueous media. This experimental technique used to elaborate glycidic nitriles or esters in some cases 10-12, has been successfully carried out with la yielding selectively oxazolines 4 (from aliphatic aldehydes) or 5 (mainly from ketones).



4

Rı	R²	t(mn)	Yield (a) (b)	b.p. °C/mmHg	NMR <sup>⊥</sup> H ( 4	ppm/TMS) 5(d)
Me	н	15	60	74/2	1.3(m,6H) 2.5(d,3H) 4.2(s,2H) 3.1(m,1H)	1.3(s,6H) 2.5(d,3H) 4.2(s,2H) 4.5(m,1H)
Et	н	15	75	80/2	1.3(m,9H) 2.5(m,2H) 3.2(t,1H) 4.2(s,2H)	1.3(m,9H) 2.5(m,2H) 4.2(s,2H) 4.6(t,1H)
i-Pr	н	15	95	85/2	1.3(m,12H) 2,5(m.1H) 3.1(d,1H) 4.2(s,2H)	1.3(m,12H) 2.5(m,1H) 4.2(s,2H) 4.65(d,1H)
Ph	н	30	80	40(c)		1.2(d,6H) 4 (s,2H) 6.4(s,1H) 7.35(m,5H)
Me	Me	60	95	60/0,2	1.4(m,9H) 1.9(s,3H) 4 (m,2H)	1.35(s,6H) 1.9(s,6H) 4.1(s,2H)
(CH <sub>2</sub> ) <sub>5</sub>		30	95	95/0,2		1.3-2.5(m,16H) 4 (s,2H)
Ph	Me	75	83	57(c)		1.35(s,6H) 1.75(s,3H) 4.1(s,2H) 7.35(s,5H)

a) yields (% calculated from 1a after purification) correspond to 4 (lines 1,2,3,5) or to direct formation of 5 (lines 4,6,7)

b) oxazolines 4 and 5 gave satisfactory analyses and mass spectral data (molecular ion, fragments) in good agreement with the proposed structures (HP 5890 GC - 5970 MS detector)

c) uncorrected melting pointsd) after quantitative isomerisation of 4 using zinc chloride in boiling ether (lines 1,2,3,5).

5

The following procedure for the synthesis of 4 or 5 is representative : to a vigorously stirred solution of 50% NaOH in water was added a mixture of la (5g ; 27.5 mmol) and benzyltributylammonium chloride (0.4g ; 1.3 mmol) in 20 ml of dichloromethane. After five minutes, the carbonyl compound (30 mmol) was added and reaction carried out at room temperature for the time indicated in the table. Water (20 ml) and ether (20 ml) were added, then the organic layer was separated, washed with a saturated solution of ammonium chloride in water (3x10 ml) and dried on magnesium sulfate. Ether was evaporated under reduced pressure before distillation or crystallization. Oxazolines 4 were refluxed in ether with stoechiometric amounts of zinc chloride to give a quantitative yield of isomeric compound 5.

## BIBLIOGRAPHY

- B.R.MATTHEWS, H.GOUNTZOS, W.R.JACKSON, K.G.WATSON, Tetrahedron Letters, 5157 (1989)
  G.GUANTI, L.BANFI, E.NARISANO, C.SCOLASTICO, Tetrahedron, 44, 3671 (1988)
- 2) A.I.MEYERS, E.D.MIHELICH, Angew.Chem.Int.Ed., 15, 270 (1976) A.I.MEYERS, J.SLADE, J.Org.Chem., 45, 2785 (1980)
- 3) J.C.COMBRET, J.TEKIN, C. MALHIAC, unpublished results
- 4) J.C. COMBRET, J.TEKIN, Comptes Rendus Acad.Sciences, C 285, 249 (1977)
- 5) J.C. COMBRET, J.TEKIN, D. POSTAIRE, Bull.Soc.Chim.Fr., II-371 (1984)
- 6) D.POSTAIRE, Thèse Doctorat, Rouen (1983) J.TEKIN, Thèse Doctorat, Rouen (1981)
- 7) J.VILLIERAS, B.CASTRO, N.FERRACUTTI, Bull.Soc.Chim.Fr., 1450 (1970)
- 8) P.COUTROT, A.EL GADI, Synthesis, 115 (1984)
- 9) J. VILLIERAS, B.CASTRO, Bull.Soc.Chim.Fr., 246 (1968)
- 10) A.JONCZYK, M.FEDORYNSKI, M.MAKOSZA, Tetrahedron Letters, 23, 2395 (1972) M.FEDORYNSKI, K.WOJCIECHOWSKI, Z.MATACZ, M.MAKOSZA, J.Org.Chem., 43, 4684 (1978)
- 11) E.D'INCAN, J.SEYDEN-PENNE, Comptes Rendus Acad.Sc., C 281, 1081 (1975)
- 12) S.GLADIALI, F.SOCCOLINI, Synthetic Communications, 12, 355 (1982)

(Received in France 19 July 1990; accepted 7 November 1990)