Tetrahedron Letters No. 36, pp 3761 - 3763, 1972. Pergamon Press. Printed in Great Britain.

A NEW PROCEDURE FOR THE DARZENS SYNTHESIS OF GLYCIDIC ESTERS

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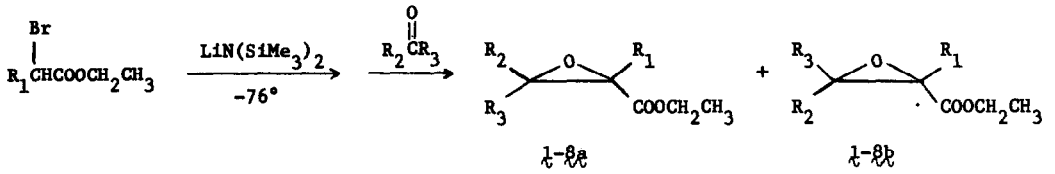
(Received in USA 14 July 1972; received in UK for publication 3 August 1972)

The Darzens condensation is a well-established method for the synthesis of glycidic esters.[2] Unfortunately, the method fails for acetaldehyde and monosubstituted acetaldehyde derivatives presumably due to competing base-catalyzed self-condensations of the aldehydes. Our need for a convenient route to ester 1 for a synthesis currently under investigation prompted the development of an alternate synthesis based on prior generation of the α-haloester anion.

The α-bromoester anion was smoothly generated by reaction with lithium bis(trimethylsilyl) amide in tetrahydrofuran at -78°.[3] Quantitative conversion to the anion was generally complete in less than 15 min, and the anion remained stable at -78° for approximately 1 hr; at higher temperatures (-40°) or for longer times at -78°, extensive decomposition occurred. Addition of the requisite aldehyde or ketone at -78° followed by workup afforded high yields of the corresponding glycidic esters. The major isomer was the "trans" isomer a in each case, the ratios showing only slight variation over the range of compounds studied. The major isomer was assigned on the basis of the oxirane proton (R_3 in the "a" isomers) being shifted to lower field than the R_3 proton in "b" isomers by the cis ester group. The results are summarized in the Table.

To a nitrogen-flushed 50-ml 3-necked flask equipped with nitrogen inlet, septum inlet, and magnetic stirrer was added a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (11 ml of a 0.7 M solution[4]) and an additional 5 ml of THF. The flask was immersed in an acetone-dry ice bath, and a solution of ethyl α-bromobutyrate (1.46 g, 7.5 mmol) in 3 ml of THF was added dropwise over 5 min at -70°. Stirring was continued for 10 min at -70° and for 10 min more after removal of the cooling bath. The reaction mixture was poured into ice water and ether and the organic layer washed with dilute HCl and water. The solution was dried (K_2CO_3) and evaporated to give 1.14 g (96%) of crude product which contained only glycidic esters 1a and 1b by glpc analysis. Short-path distillation afforded 970 mg of product, bp 88-90° (20 mm).



1-8a 1-8b

Table

Bromoester	Carbonyl Compound	Product No.	R_1	R_2	R_3	% Yield Anal.[a]	% Yield Isol.	Ratio[a,b] a : b
Et								
BrCHCOOEt	CH_3CHO	1	Et	Me	H	96	82	55:45
"	CH_3CH_2CHO	2	"	Et	H	95	83	60:40
"	$(CH_3)_2CHCHO$	3	"	i-Pr	H	97	85	70:30
"	PhCHO	4	"	Ph	H	92	86	70:30
"	CH_3COCH_3	5	"	Me	Me	94	81	—
$BrCH_2COOEt$	CH_3CHO	6	H	Me	H	91	73	70:30
"	CH_3CH_2CHO	7	H	Et	H	86	72	60:40
"		8[b]	H	$-(CH_2)_4-$		92	83	—

[a] Analytical yields and isomer ratios based on glpc analysis. [b] Isomer ratios varied by ± 5 in different runs. [c] Reaction stirred for 45 min at -70° after ketone addition to ensure complete reaction.

For less reactive carbonyl compounds (e.g., 8 in the Table) it proved convenient to monitor the progress of the addition step by adding 2-3 drops of 0.2% 4-phenylazodiphenylamine[5] to the reaction medium. The treated reaction mixture is pink in the presence of ester anion and rapidly turns yellow when the ester anion is consumed. Using the anion of ethyl bromoacetate, for example, acetaldehyde discharged the color immediately, but cyclohexanone discharged the color only after ca. 30 min.

We assume that ring closure of the halohydrin anion is the slow step in the addition, and that this closure is slower for the bromoacetate than for the bromobutyrate derivatives. Using the indicator technique, reactions of bromoacetate and bromobutyrate with isobutyraldehyde were subsequently treated with excess acetaldehyde after the ester anion had been consumed. The bromoacetate reaction showed significant incorporation of acetaldehyde in the product, indicating that, although the ester anion had been consumed, ring closure was not complete and reverse reaction subsequently occurred. The bromobutyrate reaction, however, showed no trace of acetaldehyde incorporation into the final product.

Finally, it appears that α-chloroesters are less attractive reagents for this reaction sequence because of very slow rates of closure to the oxirane. Reaction of α-chloroacetate anion with propionaldehyde, for example, gave upon normal workup the corresponding chlorohydrin as the major product.

Acknowledgment. Financial support from the National Cancer Institute, National Institutes of Health (CA 10849) is gratefully acknowledged.

References

1. Alfred P. Sloan Foundation Fellow.
2. For reviews see M. Ballester, Chem. Rev., 55, 283 (1955); M. S. Newman and B. J. Magerlein Org. Reactions, 5, 413 (1949).
3. M. W. Rathke, J. Amer. Chem. Soc., 92, 3222 (1970).
4. Solutions of lithium bis(trimethylsilyl)amide may be conveniently titrated with t-butyl alcohol using 4-phenylazodiphenylamine as an indicator.[5] The endpoint color change from pink to yellow is sharp, and duplicate runs show good reproduceability.
5. B. J. Magerlein and W. P. Schneider, J. Org. Chem., 34, 1179 (1969).