

KETENE BIS(TRIMETHYLSILYL) ACETALS. CROSS-ALDOL TYPE CONDENSATION REACTIONS
 WITH ALDEHYDES AND SCHIFF BASES

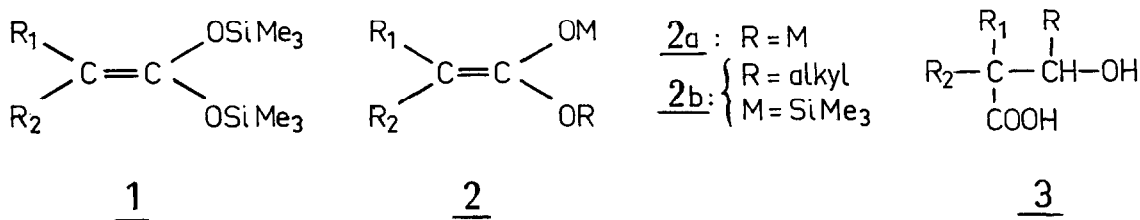
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ABSTRACT : Condensation of the title acetals with aldehydes and Schiff bases in the presence of titanium tetrachloride is reported for the first time. It leads to β -hydroxyacids and to β -lactams via a cross-aldol type reaction, with good yields.

During the last decade, impressive progress has been made in the construction of C-C bonds via the aldol condensation reaction and, in particular, in the discovery and development of new reagents.¹

Continuing our previous investigations in this field,² we report a new and effective compound for cross-aldol condensations : the ketene bis(trimethylsilyl) acetals 1.³



Reagents of type 1 correspond to masked carboxylic acid dianions 2a, reported⁴ to condense with aldehydes leading to β -hydroxyacids 3 and they are analogous to ester silyl acetals 2b which have been employed for aldol condensations with both aldehydes⁵ and Schiff bases⁶ and which lead to 3 and to β -lactams 4, respectively.

The mechanism of cross-aldol reactions of 2 is not yet well known. In the case of 2a it has been suggested^{4,7} that the reaction proceeds via a pericyclic transition state, but cycloaddition without cycloadduct formation cannot be excluded.⁴ Likewise, the exact mechanism of the titanium-promoted aldol condensation of 2b is not well established despite the interesting proposals of Ojima et al.⁶ who postulate that reactions are proceeding via titanium enolates derived from ligand exchange by $TiCl_4$ on the silyl ketene acetal. It is however possible that metal enolates may not be involved.⁵

In view of these uncertainties and in order to subsequently clarify the condensation mechanism of compounds 1, we have investigated the reaction of 1 with various aldehydes and Schiff bases in the presence of titanium tetrachloride. The results are listed in the Table.

TABLE : Reaction of 1 with aldehydes RCHO and Schiff bases R'CH = NR''

R'	R''	R	Yield ^{a,b} of <u>3</u>	Ref.	R'	R''	Yield ^{a,b} of <u>4</u>	Ref.
		Ph	86	8a	Ph	Ph	75	8d,6a
Me	Me	t-Bu	85	8b	i-Pr	Ph	66	6a
		n-Pr	89	8a				
		-(CH ₂) ₅ -	75	8c	Ph	Ph	60	6a
		Me	90	4c	Ph	Ph	69	8e,6a
Ph	H ⁹	Ph	91	4c	i-Pr	Ph	65	6a
		t-Bu	88	4c				

a) Non optimized yields in pure isolated products. b) Spectral data (NMR, IR) and physical constants are in agreement with the literature.

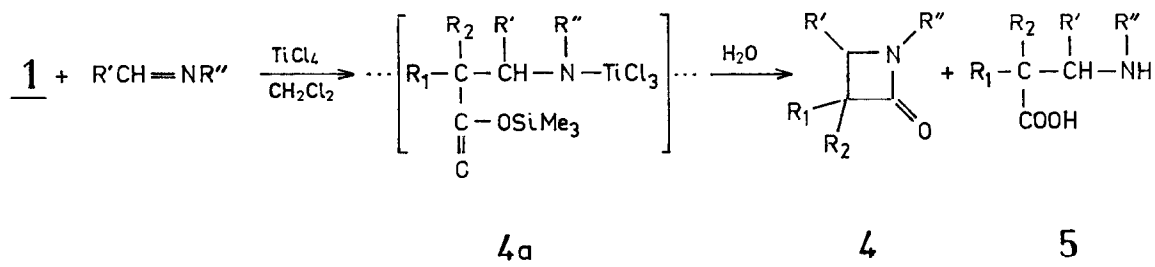
A typical procedure involves adding a 1M solution of aldehyde (or imine) in thoroughly dried dichloromethane to a 1M solution of titanium tetrachloride at room temperature. 10 minutes later, a 1M solution of 1 in dichloromethane is added dropwise and the mixture is stirred for about 2 h at room temperature. Hydrolysis is conducted with 10 ml of cold water, followed by extraction with ether, drying over anhydrous magnesium sulfate, removal of the solvent under reduced pressure and analysis of the resulting residue.

The reaction of 1 with aldehydes leads to β -hydroxyacids 3 in high yields which are not notably affected by the bulkiness of R nor by the temperature of the reaction^{10a}.

Schiff bases have been far less studied in aldol condensation reactions¹. When condensed with 1 as previously described^{10b}, they lead exclusively to β -lactams 4 in all cases. The exact mechanism of this reaction is not known. It could involve addition of 1 to the imine double bond and formation of an entity like 4a intermediately. This could lead either to β -lactams 4 or to β -aminoacids 5. We have never observed the formation of acids 5 under these reaction conditions. It seems obvious that lactams 4 are formed by intramolecular cyclization of species like 4a and not by cyclization of 5 during the hydrolysis. This alternative seems improbable as we proceed in strongly acid media.

This reaction is advantageous in comparison with the reaction described by Ojima et al.⁶ with compounds 2b. They reported that in many cases and under analogous reaction conditions, 2b

leads to an intermediate β -aminoester (acid) 5 which has to be treated by a strong base in order to provide 4. The facility of cyclization which we observe is probably due to the better leaving group character of trimethylsilyloxy compared to alkoxy groups.¹¹



We have demonstrated that compounds 1, reported for the first time in a cross-aldol condensation, can be profitably employed for this class of reactions leading to β -hydroxyacids 3 or to β -lactams 4. 3 are structural units of many natural products and their synthesis has attracted the attention of several research groups^{4,12}. β -lactams are particularly interesting intermediates in the synthesis of naturally occurring compounds, such as penicillin, cephalosporin and many analogs, and elaboration of new methods of synthesis of 3 remains a very active area¹³.

The use of acetals 1 seems promising. A detailed study of the mechanism of this reaction including its stereoselectivity is under active investigation.

REFERENCES AND FOOTNOTES

- For excellent recent reviews on the aldol condensation see, inter alia :
 a) D.A. Evans, J.V. Nelson and T.R. Taber, *Topics in Stereochemistry*, Vol. 13, J. Wiley and Sons, New York (1982) ; b) C. Heathcock, *Science*, 214, 395 (1981) ; c) C. Heathcock, *Asymmetric Synthesis*, Vol. 2, J.M. Morisson, Ed. Academic Press Inc., New York (to be published).
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- Prepared according to C. Ainsworth and Yu-Neng Kuo, *J.Organometallic Chem.*, 46, 73 (1972), but in our hands yields did not exceed 60% in all cases.
- a) J. Mulzer, J. Senger and G. Bruntrup, *Tetrahedron Lett.*, 4651 (1977) ; b) J. Mulzer, G. Bruntrup, J. Finke and M. Zippel, *J.Am.Chem.Soc.*, 101, 7723 (1979) ; c) J. Mulzer, M. Zippel, G. Bruntrup, J. Senger and J. Finke, *Justus Liebig's Ann. Chem.*, 1108 (1981).

5. T.H. Chan, T. Aida, P.X.K. Lan, V. Gorys and D.N. Harp, *Tetrahedron Lett.*, 4029 (1979).
6. a) I. Ojima, S. Inaba and K. Yoshida, *Tetrahedron Lett.*, 3643 (1977) ; b) I. Ojima and S. Inaba, *ibid*, 2077 (1980) ; c) *ibid*, 2081 (1981).
7. For an interesting discussion on transition state hypotheses, see ref. 1c) and references cited therein.
8. a) D.A. Cornforth, A.E. Opara and G. Read, *J.Chem.Soc.(C)*, 2799 (1969) ; b) m.p. (Ligroin 35°-65°) 157-158°C ; N.M.R. (CD_3COCO_3) : 4.10 (large s, 1H, OH) ; 3.65 (s, 1H, CH) ; 1.20 (s, 3H, CH_3) ; 0.95 (s, 9H, tBu) . I.R. (KBr) : 3420 (OH) ; 1700 (C=O). c) N.M.R. (CD_3COCD_3) : 10.00 (s, 1H, COOH) ; 7.10-8.00 (m, 10H, arom) ; 4.65 (s, 1H, CH) ; d) F. Dardoize, J-L. Moreau and M. Gaudemar, *Bull.Soc.Chim.Fr.*, 3841 (1972) ; e) H. Kagan, J-J. Basselier and J-L. Luche, *Tetrahedron Lett.*, 941 (1964).
9. These reactions lead to the formation of the two diastereoisomers of reported 3 or 4, detectable by N.M.R. Indicated yields in all these cases concern the mixture of the two diastereoisomers, isolated by column chromatography on silica gel.
10. a) Comparable yields are obtained with aldehydes by hydrolysis after about 1 h at - 50°C. b) There is no reaction when Schiff bases are condensed with 1 at - 78°C after 1 hour stirring.
11. Lower yields observed with Schiff bases than with aldehydes are due to the formation of not always identified by-products. For instance, with 1 where $\text{R}_1 = \text{R}_2 = \text{Me}$, we isolated a solid whose spectral data are in agreement with the structure 2,2,3,3-tetramethyl succinic acid : N.M.R. 1.25 (s, CH_3) ; I.R. 3350 large (OH), 1705 (C=O). This compound could be formed by dimerization of 1 under the reaction conditions. Such dimerizations have been reported with compounds 2b under similar conditions : S. Inaba and I. Ojima, *Tetrahedron Lett.*, 2009 (1977).
12. Inter alia : C. Heathcock, C.T. White, J.J. Morisson and D. Van Derveer, *J.Org.Chem.*, 46, 1296 (1981) and references cited therein ; b) R.E. Ireland, R.H. Mukaiyama, *Angew. Chem.Int.Ed.Engl.*, 16, 817 (1977) and references cited ; S. Masamune, W. Choy, F.A.J. Kerdesky and B. Imperiali, *J.Amer.Chem.Soc.*, 103, 1566 (1981).
13. See, inter alia : a) Recent Aspects of the Chemistry of β -Lactams, *Tetrahedron*, 39, 2445-2606 (1983) and references cited ; b) A.K. Bose, K. Gupta and M.S. Manhas, *J.Chem.Soc., Chem.Comm.*, 86 (1984) ; c) A. Knierzinger and A. Vasella, *ibid*, 9 (1984).

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