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TANDEM REFORMATSKY REACTIONS OF 2-BROMOPROPIONATES IN THE PRESENCE OF CHLOROTRIMETHYLSILANE

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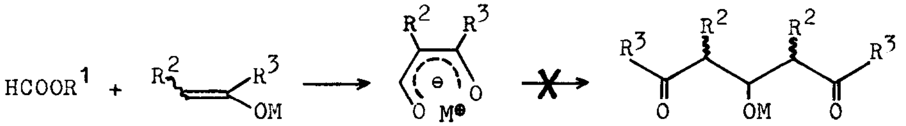
Summary: Tandem aldol-like reactions are accessible through the addition of the Reformatsky reagent derived from 2-bromopropionate to either formate /eq 2/ or orthoformate /eq 3/ acceptor in the presence of chlorotrimethylsilane.

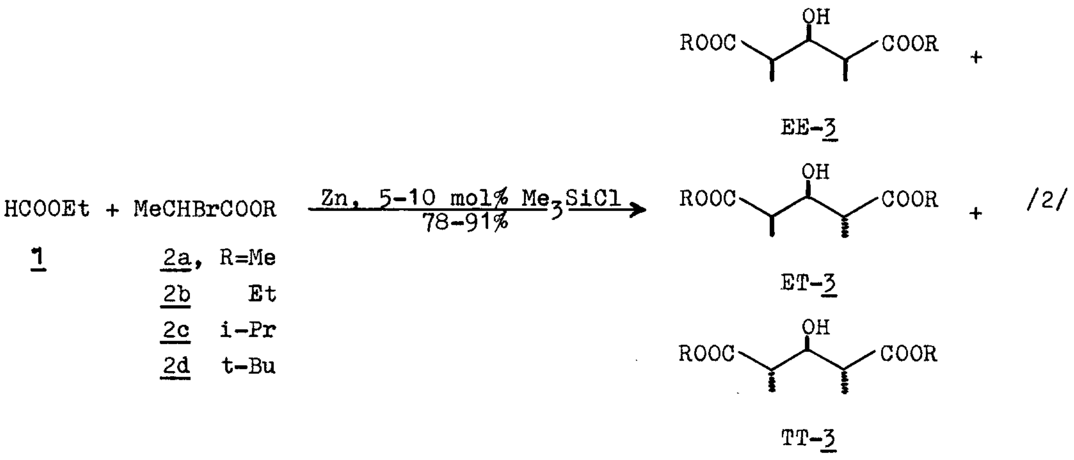
In recent years, as a result of extensive investigations, we have witnessed extraordinary progress in aldol reactions, especially in improving aldol stereoselection.[1] Despite of that, tandem enolate additions to a formate acceptor are quite uncommon, due to the expected interception of the initially formed aldehyde as a stable metal enolate.



/1/

The general interest in the synthesis of chiral units having alternate arrangement of methyl and hydroxy substituents, commonly found in macrolide and polyether antibiotics, prompted us to study condensation reactions of formates with enolate type reagents derived from propionic acid. Our initial efforts to achieve tandem addition of lithium enolates or ketene silyl acetals of propionic esters to ethyl formate were unsuccessful /eq 1, R^1=Et, R^2=Me, R^3=OMe or OEt, M=Li or $SiMe_3$+Lewis acid/.

It was anticipated that the use of less basic zinc reagents generated in Reformatsky reaction[2] should overcome this problem. Indeed, we have found that the classical Reformatsky procedure, giving tandem aldol product 3 in low yield[3] can be significantly improved by the addition of small amount Me_3SiCl to activate the system prior to addition of the bromoester.[4] This simple and inexpensive modification allows to run Reformatsky reaction below room temperature, thus eliminating side reactions and improving its stereoselectivity.[5]



Typical procedure: To a stirred suspension of Zn dust /3.9 g; acid-washed and dried[6]/ in dry diethyl ether /50 mL/ was added Me_3SiCl /0.5 mL/ and the mixture stirred 15 min. at room temp. After cooling with ice-bath to 0° 25 mmol /2.1 mL/ 1 was added, followed by 55 mmol /7.0 mL/ 2b. Reaction started immediately and stirring was continued 15 min. at 0° and 1 hr. at room temp. The resulted milky mixture was quenched with sat. NH_4Cl, extracted with 6N HCl, washed with brine and dried over $MgSO_4$. Distillation at 85-90°/0.55 mm Hg afforded 3b, 5.3 g /91%/.

No reaction takes place under these conditions in the absence of Me_3SiCl. In the presence of 1:1 Me_3SiCl to Zn no 3b is formed in the reaction conducted between -20° and 0°.[7]

Stereoselectivity of the reaction, represented by the ratios of the EE/ET/TT diastereomers, is affected to some extent by reaction conditions /see Table below/.[8]

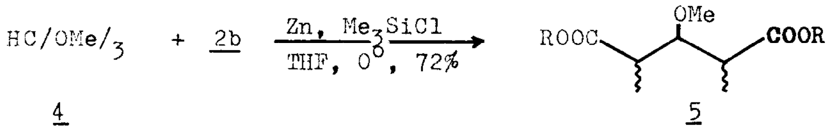
Table

Entry	Solvent	2	3, EE :	ET :	TT
1	tetrahydrofuran	2b	36	49	15
2	diethyl ether	2a	49	42	9
3	diethyl ether	2b	42	46	12
4	diethyl ether	2c, 2d	43	47	10
5	dichloromethane	2b	45.5	44	10.5
6	benzene	2b	47	43	10
7	benzene[§]	2b	40	46	14

[§] at room temp., all other at 0°

Data of the Table reveal erythro preference for the formation of the three consecutive chiral centers of the product 3. This preference diminishes with the increase of solvent polarity /entries 1, 3, 5, 6/ and with the increase of the reaction temperature /entries 6, 7/.

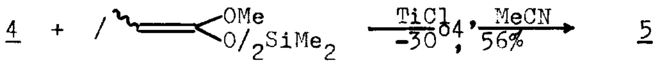
Tandem Reformatsky reaction was also performed with methyl orthoformate in the presence of two molar equivalents of the Reformatsky reagent and chlorotrimethylsilane.



/R=Et/ EE:ET:TT = 4:4.6:1 /3/

Again, no 5 is formed in the absence of Me_3SiCl. The side product detected in the reaction is $/MeO/_2CHCHMeCOOEt$, obtained from 4 as the main product in the absence of Me_3SiCl;[2] it appears that Me_3SiCl enhances electrophilicity of the carbon atom in orthoformate. However, as the nature of the Reformatsky reagent derived from 2-bromopropionate remains unknown,[10] we are not in position to propose mechanistic details of the reaction.

Related double aldol-type reaction of ketene silyl acetal 6[11] with 4 catalyzed by $TiCl_4$ /eq 4/[12] shows higher erythro-preference, but certainly lacks the simplicity of the reaction outlined in eq 3.



/R=Me/ EE:ET:TT = 8.5:7:1 /4/

Acknowledgements: We thank A. Pięta for skillful technical assistance. This work was supported in part by the Polish Academy of Sciences.

References and Notes

1. Recent reviews: /a/ D.A. Evans, J.V. Nelson and T.R. Taber in "Topics in Stereochemistry, vol. 13", E.L. Eliel and S.H. Wilen, Eds., Wiley-Interscience, New York, 1982; /b/ C.H. Heathcock, Science, 214, 395 /1981/; /c/ C.H. Heathcock in "Comprehensive Carbanion Chemistry, vol. II", T. Durst and E. Buncel, Eds., Elsevier, 1983.

2. For reviews see: /a/ M.W. Rathke, Org. Reactions, 22, 423 /1975/; /b/ K. Nützel in "Houben-Weyl Methoden der organischen Chemie, vol. 13/2a", 809, G. Thieme, Stuttgart, 1973.

3. /a/ S. Reformatsky, *Ber.*, **28**, 3263 /1895/; /b/ K. Gerzon, E.H. Flynn, M.V. Sigal, P.F. Wiley, R. Monahan and U.C. Quarck, *J. Am. Chem. Soc.*, **78**, 6396 /1956/.

4. A similar reaction with the use of ethyl bromoacetate leads to none tandem-aldol product /cf. eq 1/.

5. Other methods which allow to carry-out Reformatsky reaction at low temp. include /a/ use of trimethyl borate as solvent: M.W. Rathke and A. Lindert, *J. Org. Chem.*, **35**, 3966 /1970/; /b/ highly activated Zn: R.D. Rieke and S.J. Uhm, *Synthesis*, 452 /1975/; Et_2AlCl-CuBr: K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto and H. Nōzaki, *Bull. Chem. Soc. Japan*, **53**, 3301 /1980/; /d/ sonic acceleration: B.-H. Han and P. Boudjouk, *J. Org. Chem.*, **47**, 5030 /1982/.

6. R.L. Shriner and W.F. Neumann, *Org. Synthesis*, Coll. Vol. III, 74 /1955/.

7. Detected by-products are homo-alkylation products EtOOCCH/Me/-CHMeCOOEt /meso + d,l/. At higher temperatures Reformatsky reagents are silylated at C/α/: R.J. Fessenden and J.S. Fessenden, *J. Org. Chem.*, **32**, 3535 /1967/.

8. The experimental EE/ET/TT ratios were obtained by GC analysis of 3 on 10% DEGS on Chromosorb W at 140°. The esters 3c and 3d were analyzed after transesterification to 3a with acidic methanol. The isomers 3a were identified according to ref. 9. The EE-diacid can be readily isolated from the hydrolyzed mixture of esters - see ref. 3b and: P. Mohr, N. Waespe-Sarcevic, Ch. Tamm, K. Gawrońska and J.K. Gawroński, *Helv. Chim. Acta*, **66**, 2501 /1983/.
Aldol diastereoselection /erythro:threo/ and aldehyde diastereoface selection /"Cram:anti-Cram"/ could be obtained as x and y from: EE = xy; ET = x/1-y/ + y/1-x/; TT = /1-x//1-y/, but unambiguous assignment of x and y is not possible due to the symmetry of the aldol 3.

9. T. Matsumoto, Y. Hosoda, K. Mori and K. Fukui, *Bull. Chem. Soc. Japan*, **45**, 3156 /1972/.

10. Dimeric structure was recently reported for Reformatsky reagent derived from t-butyl bromoacetate: J. Dekker, J. Boersma and G.J.M. van der Kerk, *Chem. Commun.*, 553 /1983/.

11. Prepared by adding methyl propionate to LDA in THF at -78°, followed by Me_2SiCl_2. Yield 53%, b.p. 45-50° /bath temp./ at 0.4 mm Hg. IR /neat/: 1690 cm^{-1}; ^{1}H NMR /C_6D_6/: 0.29 /3H, s/, 1.66 /3H, d, J=7/, 3.50 /3H, s/, 4.03 /1H, q, J=7/.

12. Side product: /MeO/$_2$CHCHMeCOOMe. This is the sole condensation product /yield 80-90%/ in dichloromethane at -78° in the presence of $TiCl_4$ or $BF_3 \cdot Et_2O$.

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