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ALDOL ADDITION REACTION OF A LITHIUM ESTER ENOLATE IN THE SOLID STATE

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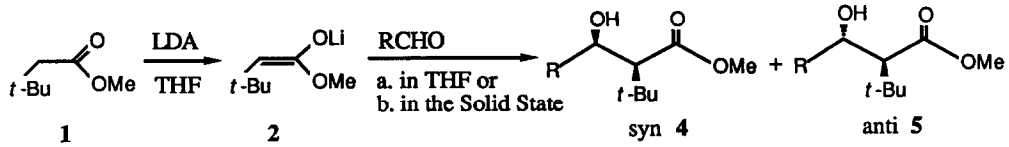
Summary: The first solid state aldol addition of the lithium enolate of methyl 3,3-dimethylbutanoate to aromatic aldehydes is reported. The diastereoselectivity of the reactions in the solid state is similar to that in solution, suggesting that the same reacting species and transition states might be involved.

Metal enolates play important roles as reactive intermediates in synthetic organic chemistry. There are many excellent articles on the topics such as aldol addition,[1-3] Michael addition,[4] and oxidation[5] reactions, which focus on the central importance of enolate structure and geometry in relation to the reactivity and stereochemical outcome of the reactions. Seebach's[6,7] and Williard's[8] groups have carried out extensive work on the determination of crystal structures of a variety of metal enolates and on the structure-reactivity relationship of these enolates. All the crystalline enolates for which the X-ray structure analysis data are available consist of dimeric, tetrameric or hexameric aggregates. Many pioneering studies have unequivocally demonstrated that enolates exist as aggregates in solution.[9] However, the identity of the form that actually reacts in solution is still not fully elucidated.

In this connection, we have investigated for the first time the aldol addition reactions of a crystalline lithium ester enolate with aldehydes in the solid state and the results are directly compared with those of the same reactions carried out in solution media. In this study, the lithium ester enolate **2** (*E*-isomer) was chosen since it can be readily prepared from the reaction of methyl 3,3-dimethylbutanoate **1** with LDA, it is stable at room temperature, and its structure has been well established *via* X-ray crystallography.[7] The crystalline enolate **2** is a tetrameric aggregate and has a cubic structure in which lithium and oxygen atoms occupy the alternate corners of the cube and each lithium atom is attached to a tetrahydrofuran molecule as depicted in the structure **3**.[7]

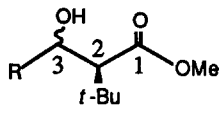


1 **2**

The lithium enolate **2** was prepared according to the procedure described in the literature.[7] The isolated enolate was a pale yellow solid which was ground to a fine powder under an argon atmosphere. The various aromatic aldehydes employed in this study were also ground to a fine powder before mixing with the lithium enolate. As a typical procedure for the solid state reactions, the freshly ground lithium enolate **2** (1.2 equiv.) was mixed with *o*-anisaldehyde (1 equiv.) in argon at room temperature. The reaction was allowed to continue at room temperature under vacuum for three days, quenched with aqueous NH_4Cl and extracted with three portions of diethyl ether. The combined organic extract was washed with water and dried with anhydrous Na_2SO_4. The solvent was removed using a rotary evaporator at reduced pressure to yield the crude product. In the ^{1}H-NMR spectrum of the crude product in $CDCl_3$, a relatively large difference in coupling constant values was observed for syn (10.1 Hz) and anti (3.3 Hz) protons attached to C(2) (Table I). The syn/anti ratio was determined from the ^{1}H-NMR spectrum based on the integrations of the C(2)H doublets in the aldols **4** and **5**. The crude product was found to contain mainly anti aldol product (syn/anti ratio 8:92). Further purification was carried out using preparative TLC with methanol-benzene (5:95 in volume) as eluent (R_f value 0.7-0.8). The purified product thus isolated was a colorless solid (m.p. 64-65 °C) (yield 70%) with the same syn/anti ratio as that of the crude product. The syn/anti ratios of both the crude and purified products were further confirmed by gas-liquid chromatography. Similar results were obtained for the solid state reaction of the lithium enolate **2** with other aldehydes as summarized in Table I. In all the cases, a high diastereoselectivity was observed in favor of the anti isomer. The solid state reaction of other aldehydes gives an isolated yield of about 20%, which is not unexpected because reactions in the solid state usually afford low yields.[10]

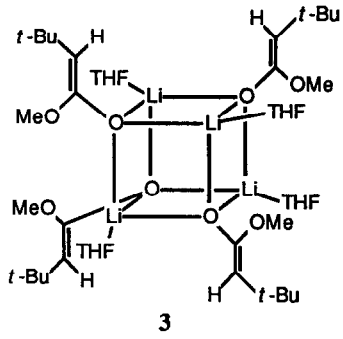
The same aldol reactions were also conducted in solution with THF as solvent at both -78 and 22 °C for 4 hours under argon. In general, the reactions at -78 °C showed a low diastereoselectivity with the syn/anti ratios ranging from 56:44 to 39:61 (Table I). However, when the reactions were carried out at 22 °C, the syn/anti ratios changed greatly to 20:80 - ~0:100. The stereochemical outcome of the solution reaction at 22 °C is comparable to that of the solid state reactions. The aldol reaction of *o*-anisaldehyde with the lithium enolate **2** in THF solution was further studied at different temperatures. At -78 °C, the reaction gave the aldol product with a syn/anti selectivity of 56:44 in 94% yield. Essentially the same results were obtained at -45 °C (syn/anti 58:42) except the yield was lower (76%). Further increase in temperature up to -10 °C resulted in little change (syn/anti 53:47, yield 74%). The anti isomer became the major product at 0 °C (syn/anti 31:69, yield 75%) and at 22 °C. These results clearly indicate that the diastereoselectivity is temperature dependent and that at the higher temperatures, anti selectivity becomes favored. When the aldol addition of the enolate **2** to *o*-anisaldehyde in the solid state was performed at -20 °C, the syn/anti ratio was found to be 56:44 (yield 12%), which is close to that in solution. Mulzer *et al.*[11] reported that the diastereoselection was thermodynamically controlled in the aldol reaction of carboxylic acid dianions with aldehydes in solution at high temperatures (e.g. 22 °C) and long reaction times (e.g. 48 h). To examine whether the reactions were thermodynamically or kinetically stereoselective in our system, the reaction mixture was quenched at various time intervals. At temperatures lower than -10 °C, the syn/anti selectivity was essentially independent of the reaction time, but at 0 and 22 °C the amount of the anti isomer increased greatly with time. These observations suggest that kinetic stereoselection is mainly responsible for the stereochemical outcome at low temperatures while thermodynamic stereoselection dominates at the higher temperatures.

Table I. Aldol Products from Addition of Aldehydes (RCHO) to the Lithium Ester Enolate 2 in the Solid State and in THF Solution.

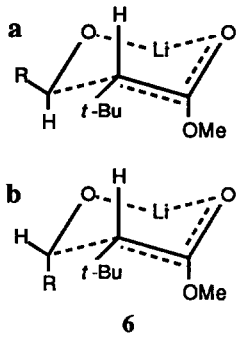


entry	R =	syn/anti ratio			J HC(2) (Hz)		yield (%)		
		a	b	c	syn	anti	a	b	c
1	2-$MeOC_6H_4$-	56:44	8:92	~0:100	10.1	3.3	94	70	75
2	4-ClC_6H_4-	51:49	9:91	1:99	10.0	3.4	73	22	60
3	4-$NO_2C_6H_4$-	44:56	2:98	20:80	9.5	2.9	96	22	54
4	3-$NO_2C_6H_4$-	56:44	~0:100	12:88	9.8	2.4	98	16	57
5	2-$NO_2C_6H_4$-	45:55	~0:100	3:97	10.1	1.8	97	23	71
6	5-NO_2-2-thienyl	39:61	~0:100	d	9.6	2.3	66	29	d

(a) Reaction in THF at -78 °C; (b) Reaction in the solid state at 22 °C; (c) Reaction in THF at 22 °C; (d) Not a clean reaction.



3



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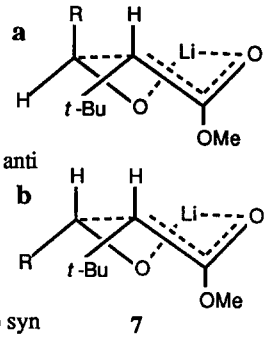

E to anti

E to syn

7

In order to explain kinetic stereoselectivity in aldol addition reactions conducted in solution, several types of transition state models have been proposed in the literature.[2] The closed or chelated transition states, proposed by Zimmerman and Traxler,[12] for *E* and *Z* enolates leading to syn and anti aldols suffice to explain the observed stereoselectivity trends when the group attached to C(2) carbon is small. Yet another closed transition state model was proposed by Evans *et al.*[1] which considers both chair and boat arrangements. The stereochemical outcome can be explained by assuming that the *E* enolate **2** can choose either the chair (**6**) or the boat transition states (**7**). Increase in the bulk of the group attached to C(2) atom would tend to favor the boat (**7a**) rather than the chair transition states because of the steric interaction between the groups attached to the C(2) and C(3). Under such circumstances, according to Evans *et al.*,[1] the *E* enolate would either have no effect on stereoselectivity or would increase the anti selectivity. The results of this investigation demonstrate that there is essentially no stereoselectivity at low reaction temperatures. The fact that the diastereoselectivity of the aldol reaction in the solid state is close to that in solution suggests that the same

reacting species and transition states might be involved in both solid state and solution reactions. Further investigation is in progress to explore other types of enolate reactions in the solid state.

All the aldol products were fully characterized by spectroscopic methods.

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References and Notes

(1) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

(2) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D. Ed.; Academic Press: Orlando, Fl, 1984; Vol. 3, pp. 111-212.

(3) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1. Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 488.

(4) Heathcock, C. H.; Oare, D. A. *Top. Stereochem.* **1989**, *19*, 227.

(5) Davis, F. A.; Sheppard, A. C.; Chen., B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679.

(6) Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624. Seebach, D.; Amstutz, R.; Schweizer, W. B.; Dunitz, J. D. *Helv. Chim Acta* **1981**, *64*, 2617. Seebach, D.; Laube, T.; Dunitz, J. D.; *Helv. Chim. Acta* **1985**, *68*, 1373. Seebach, D.; Haner, R.; Laube, T. *J. Am. Chem. Soc.* **1985**, *107*, 5396 Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *Chem. Ber.* **1986**, *119*, 434. Maetzke, T.; Hidber, C. P.; Seebach, D. *J. Am. Chem. Soc.* **1990**, *112*, 8248.

(7) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403.

(8) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 3345. Williard, P. G.; Salvino, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 3931. Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462 Williard, P. G.; Salvino, J. M. *J. Chem. Soc., Chem. Commun.* **1986**, *153*. Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539 Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602.

(9) Jackman, L. M.; Smith, B. D. *J. Am. Chem. Soc.* **1988**, *110*, 3829. Arnett, E. M.; Palmer, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7354 and references cited therein.

(10) Toda, T.; Yagi, M.; Kiyoshige, K. *J. Chem. Soc., Chem. Commun.* **1988**, *958*. Toda, T.; Kiyoshige, K.; Yagi, M. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 320. Toda, T.; Shigesmasa, T. J. *Chem. Soc., Perkin Trans. I* **1989**, 209 Toda, F.; Akai, H. *J. Org. Chem.* **1990**, *55*, 3446.

(11) Mulzer, J.; Zippel, M.; Brüntrup, G.; Segner, J.; Finke, J. *Liebigs Ann. Chem.* **1980**, 1108.

(12) Zimmerman, H.E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 192

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