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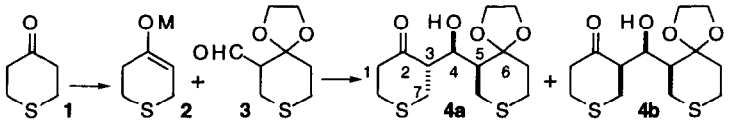
The Thiopyran Route to Polypropionates Revisited: Selective *Syn* and *Anti* Aldol Reactions via 3,6-Dihydro-4-trimethylsilyloxy-2*H*-thiopyran

Dale E. Ward*, Chuk C. Man, and Cheng Guo

Department of Chemistry, University of Saskatchewan,
110 Science Place, Saskatoon SK S7N 5C9, CANADA

Abstract: Aldol reaction of the amine free Li enolate of tetrahydro-4*H*-thiopyran-4-one with 1,4-dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde gives mainly the 2,3-*anti*-3,4-*syn* aldol (7:1) in good yield; reaction of the LDA generated lithium enolate proceeds poorly. Using the trimethylsilyl enol ether and $TiCl_4$ gives the 2,3-*syn*-3,4-*syn* aldol (>10:1). The adducts can be used for polypropionate synthesis.

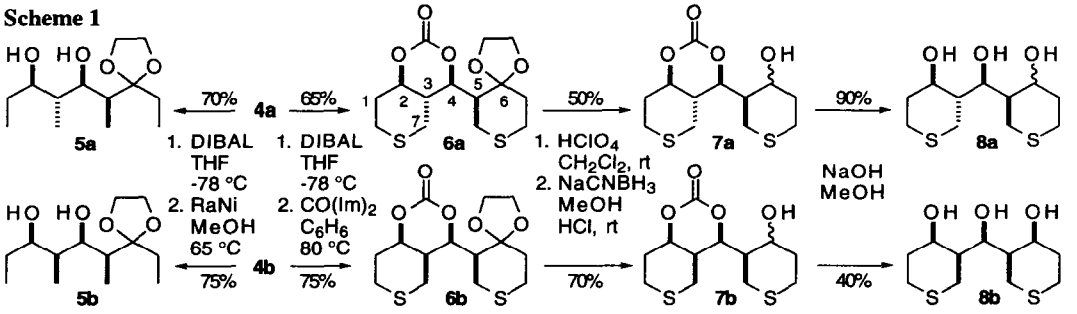
Aldol reactions of tetrahydro-4*H*-thiopyran-4-one derivatives followed by desulfurization is an attractive route to polypropionates.[1,2] We were interested in the aldol coupling(s) of **1** with **3** as a rapid method to produce stereochemically complex bifunctional substrates that might be amenable to desymmetrization.[3] Herein we report that use the amine free Li enolate **2b** is superior to the LDA generated **2a** and that high *syn* or *anti* diastereoselectivity can be obtained in the aldol reaction of **1** with **3** depending on the reaction conditions.



		%yield	4a:4b
2a	M=Li·HN^{i}Pr$_2$	<40	2.5:1
2b	M=Li	75	7.5:1
2c	M=OTMS (with $TiCl_4$)	85	<1:10

Aldol reaction of the LDA generated **2a** with **3** was surprisingly poor, giving a separable 2-3:1 mixture of **4a** and **4b** in 15-40% combined yield.[4] It is well established that the *i*-Pr$_2$NH product from reaction of LDA with ketones is associated with the enolate (i.e. **2a**) and can effect the ensuing chemistry.[5] Any such influences on aldol diastereoselectivity are not well documented. A previous report[2] on improved aldol reactions using an "amine free" lithium enolate (rather than LDA generated) of a thiopyranone type ketone prompted us to examine the reaction of **2b** (1.1 equiv.) with **3**.[6] Under these conditions, a 7-8:1 mixture of **4a** and **4b** was obtained in 70-85% yield. Increased *anti* selectivity was also observed in the aldol reactions of PhCHO with the "amine free" enolates (TMS enol ether + MeLi; cf. note 6) of cyclohexanone (*anti:syn* 12:1, 75%) and **1** (*anti:syn* >10:1, 60%) compared to similar reactions with LDA generated enolates.[4,7] Interestingly, the reaction[8] of **2c** with **3** in the presence of $TiCl_4$ was highly *syn* selective giving a >10:1 mixture of **4b**:**4a** (85%).[9] This *syn* selectivity was not general as reaction of **2c** with PhCHO under the same conditions gave the *anti* aldol (>15:1 *anti:syn*, 75%).[7]

Scheme 1



The experiments summarized in Scheme 1 allowed the stereochemistry for **4a** and **4b** to be assigned unambiguously.[10,11] The cyclic carbonates **6a,b** were readily prepared by reduction[12] of the individual aldol

diastereomers followed by treatment with 1,1'-carbonyldiimidazole. The presence in **6a** of a *trans*-fused dioxathiadecalin with an equatorial substituent was apparent from the large (i.e. axial-axial) coupling constants $^3J_{H\text{-}2,H\text{-}3}$ = 10.5 Hz and $^3J_{H\text{-}3,H\text{-}4}$ = 10 Hz, thereby establishing the *anti* aldol stereochemistry for **4a**. On the other hand, **6b** contained a *cis*-fused dioxathiadecalin with an equatorial substituent ($^3J_{H\text{-}2,H\text{-}3} \approx$ 2 Hz; $^3J_{H\text{-}3,H\text{-}4} \approx$ 2 Hz; +ve nOe: H-2 <---> H-4) confirming that **4b** was a *syn* aldol. Hydrolysis of the ketal in **7** and reduction of the resulting ketone gave, in each case, a mixture of alcohols.[13] The C-5 stereochemistry was determined by hydrolysis of the carbonates in **7** to give the triols **8**. The 4,5-*syn* relationship for **4a** and the 4,5-*anti* relationship for **4b** is established because both of the triols isolated from **7a** were unsymmetrical[14] while the symmetrical triol **8b** (e.g. 6 ^{13}C NMR signals) was obtained from hydrolysis of **7b**.

With reproducible conditions in hand to selectively prepare either **4a** or **4b**, possible application to polypropionate synthesis was demonstrated by the synthesis of the stereotetrads **5a** and **5b**. The aldol adducts **4** present functionality amenable both for two-directional (e.g. **4+3**) and for linear (e.g. **6+3**) iteration of the process. If the stereoselectivity observed in the reactions of **1** with **3** can be extended to further aldol reactions of **4** (or **6**) with **3**, then a useful method for polypropionate synthesis might be at hand.[15]

REFERENCES AND NOTES

1. Hayashi, T. *Tetrahedron Lett.* **1991**, *32*, 5369-5372.
2. For an earlier application of this strategy, see: Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, S. R.; Ong, B. S.; Press, J. B.; RajanBabu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210-3213.
3. Ward, D. E.; Liu, Y.; How, D. *J. Am. Chem. Soc.* **1996**, *118*, 3025-3026.
4. This reaction is reported[1] to give **4a** (96% de) in 85% yield. We used the procedure as described[1] (addition of **1** to LDA in THF at -78 °C, followed by addition of **3**, and then quenching at -78 °C) and with various modifications (i.e. reaction time, concentration, stoichiometry, quench (HOAc, TESOTF, DIBAL), and work up procedure). Calibrating the conditions using cyclohexanone and PhCHO gave the aldol product (75% yield; 4:1 *anti:syn*) as reported: Hirama, M.; Noda, T.; Takeshi, S.; Ito, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2645-2646; Majewski, M.; Gleave, D. M. *Tetrahedron Lett.* **1989**, *30*, 5681-5684. Addition of TMSCl instead of **3** gave **2c** (88% yield). Using PhCHO instead of **3** gave a mixture of aldol diastereomers (30-50%, 4-6:1 *anti:syn*), a result inferior to that reported[1] (98%, 9:1 *anti:syn*). Both **4a** and **4b** were recovered unchanged (>95% yield) after addition to LDA (1.2 equiv.) at -78 °C (cf. reported[1] retroaldol).
5. Seebach, D. *Angew. Chem., Int. Ed. Eng.* **1988**, *27*, 1624-1654.
6. Procedure: **2c** & MeLi (0°C, 30 min); addition of **3** at -78°C (5 min); HOAc quench; then aqueous work up.
7. (a) δ_H 5.00 (d, J = 9 Hz, C*H*OH). (b) For intramolecularly H-bonded aldols, the $^3J_{HH}$ for O=CC*H*C*H*OH in the *anti* isomer typically is larger (7-10 Hz) than that in the *syn* isomer (2-6 Hz). Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985, vol. 3, pp 111-212.
8. Procedure: **2c** (1.5 equiv.) added to **3** and $TiCl_4$ (1 equiv.) in CH_2Cl_2 at -78 °C; 1 h; H_2O added; work up.
9. Mukaiyama type reactions of cyclohexanone enol silyl ethers with aldehydes typically give poor *syn:anti* diastereoselectivity (3:1 to 1:3), see: Raju, S. V. N.; Ponrathnam, S.; Rajan, C. R; Srinivasan, K. V. *Synlett* **1996**, 239-240 and cited references.
10. Assignments could not be made unambiguously by ^{1}H NMR (cf. assignment of **4a** in ref 1) because the apparent $^3J_{H\text{-}3,H\text{-}4}$ for **4a** (6.5 Hz) and for **4b** (8.5 Hz) were too similar[7b] and the validity of those J's was questionable because of possible second order effects due to the similar δ's for H-3, H-7a, and H-7b.
11. H-4 for **4a**: δ 4.50 (dd, J = 4.5, 6.5 Hz); for **4b**: 4.79 (dd, J = 3, 8.5 Hz). The J for **4a** was not reported.[1]
12. The reactions were highly diastereoselective and, in each case, only one diastereomer was isolated. The diol product from **4a** was clearly a *trans* cyclic alcohol (H-2, ddd, J = 4, 9.5, 9.5 Hz) and that from **4b** was a *cis* cyclic alcohol (H-2, narrow m, J's < 3 Hz). For the DIBAL reduction of aldols to give *syn* 1,3-diols selectively, see: Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009-3012.
13. Ketal hydrolyses were shown to occur without epimerization by isolating products without deuterium from reactions using $DClO_4$. Both **7a** and **7b** were ca. 1.3:1 mixtures of *trans:cis* alcohols: H-2 for **7a** δ 4.19 (narrow m) and 3.77 (ddd, J =4, 10.5, 10.5 Hz); for **7b** δ 4.08 (narrow m) and 3.62 (ddd, J =3, 8, 8 Hz).
14. If the 4,5 relative stereochemistry was *anti*, then one of triols (i.e. from *trans* **7a**) would be symmetrical.

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