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THREO SELECTIVE CROSS ALDOL CONDENSATION WITH THIOAMIDE ENOLATES GENERATED BY A MICHAEL ADDITION OF ORGANOMETALLICS TO UNSATURATED THIOAMIDES

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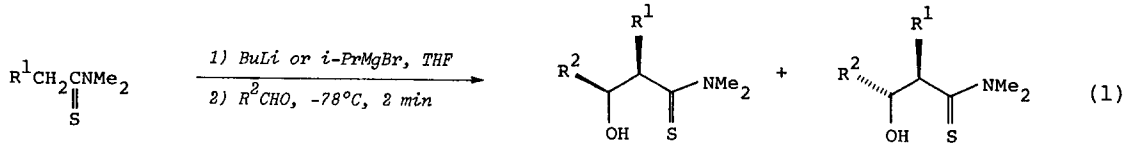
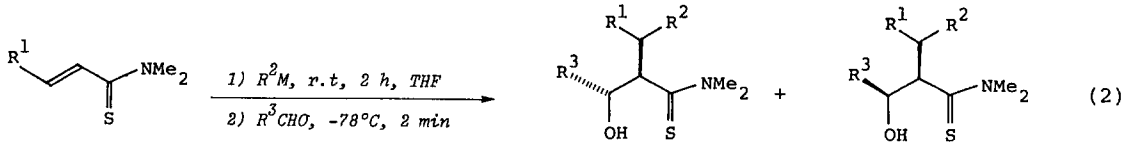
Summary: Crotonothioamide, sorbothioamide, and cinnamothioamide undergo a threo selective aldol condensation via their enolates generated by a Michael addition of organometallics.

Previously we have reported a highly erythro selective aldol condensation of tertiary thioamides 1 (R^1= Me and Ph, equation 1).[1] However, a further examination has revealed an interesting fact that N,N-dimethylisovalerothioamide 1 (R^1 = i-Pr) provides the aldol products in a reversed selectivity, predominating the threo adducts: the enolate, generated by treatment of 1 (R^1 = i-Pr) with i-PrMgBr (2 equiv) at room temperature in THF for 2 hours, reacted with benzaldehyde (-78°C, 2 min) to provide a mixture of erythro 2 and threo 3 (R^1= i-Pr, R^2= Ph) in a ratio of 34:66 (equation 1). Similarly the corresponding lithium enolate reacted with dihydrocinnamaldehyde to furnish a mixture of erythro 2 and threo 3 (R^1= i-Pr, R^2= CH_2CH_2-Ph) in 25 and 54% isolated yields, respectively.



(1)

1 2 3



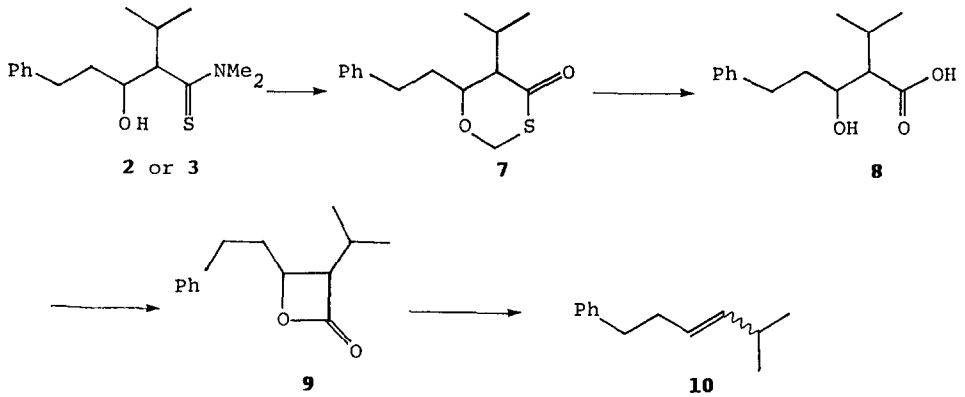
(2)

4 5 6

4a; R^1= CH_3, **4b**; R^1= $CH{=}CHCH_3$, **4c**; R^1= Ph

The vicinal coupling constants of these diastereomers do not show a correlation of $J_{erythro} < J_{threo}$ any longer in the ^1H NMR spectra probably owing to an inhibition of an intramolecular hydrogen bonding caused by a repulsion between NMe_2 and R^1 groups (e.g., 2: $J_{C(2)HC(3)H}$ = 3.5 Hz; 3: $J_{C(2)HC(3)H}$ = 3.0 Hz for R^1= i-Pr, R^2= CH_2CH_2Ph).[2] The structures of 2 and 3 were therefore determined by means of a stereospecific chemical transformation to cis and trans 2-methyl-6-phenyl-3-hexenes 10, respectively. In scheme I is outlined the sequence, which consists of a thiolactonization with formaldehyde (excess formalin, 1.5 equiv of TsOH in DME at 70-80 °C),[3] an alkaline hydrolysis (1.5 equiv of KOH in aq THF at room temperature), and a lactonization (1.3 equiv of TsCl in anhydrous pyridine at room temperature), followed by a thermal decarboxylation (160 °C in DMF).[4] All these reactions were established to proceed with complete retention of configurations. cis 10: ^{13}C NMR ($CDCl_3$) 26.4 (C_2) and 29.2 (C_5). IR (neat film) 730 cm^{-1} (s). trans 10: ^{13}C NMR ($CDCl_3$) 30.9 (C_2) and 34.3 (C_5). IR (neat film) 966 (s) and 740 cm^{-1} (s).

SCHEME I



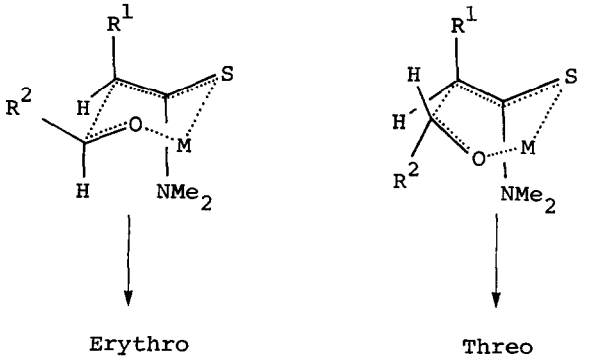
In marked contrast to the enolate generated from 1 (R^1= i-Pr), the enolate, generated by a Michael addition of MeLi or MeMgBr to N,N-dimethylcrotonothioamide 4a,[5] provided the threo aldols in very high selectivities (equation 2). Results of the tandem 1,4-addition-aldol condensation[6] for 4a-4c are summarized in Table I. With respect to 4a, the slight lowering of selectivity is observed with an increase in the steric bulk of organometallics (cf. entries 1 and 7 and 4 and 5). Interestingly, 9-borabicyclo[3.3.1]nonane (9-BBN) and diisobutylaluminium hydride (DIBAH) added to 4a selectively in a 1,4-fassion. In these cases, however, the erythro aldols turned out to be the main products (entries 9 and 10). trans N,N-Dimethylcinnamothioamide (4c) showed the results similar to 4a. N,N-Dimethylsorbothioamide (4b) underwent the selective 1,4-addition of organometallics and furnished the threo aldols 5 selectively (entries 11-13).

Table I. Cross Aldol of Enolates Generated by 1,4-Addition of Organometallics to 4a-4c[a]

Entry	Thioamide[b] 4	Organometallics R^2-Metal	Aldehyde R^3CHO	Product Distribution 5 : 6[b,c]	% Isolated Yield[d]
1	4a	Me-MgI	Me	96 : 4	88
2	4a	Me-Li	Me	90 : 10	88
3	4a	Me-MgI	i-Pr	>99 : 1	78
4	4a	Me-MgI	Ph	94 : 6	85
5	4a	Et-MgBr	Ph	85 : 15	84
6	4a	n-Bu-Li	Ph	87 : 13	82
7	4a	i-Pr-MgBr	Me	74 : 26	80
8	4a	i-Pr-MgBr	i-Pr	>99 : 1	70
9	4a	H-B	Ph	13 : 87	80
10	4a	H-Al(i-Bu)$_2$	Ph	36 : 64	80
11	4b	Me-MgI	i-Pr	>99 : 1	85
12	4b	i-Pr-MgBr	Me	89 : 11	80
13	4b	i-Pr-MgBr	i-Pr	>99 : 1	85
14	4c	i-Pr-MgBr	Me	82 : 18	74

a) Reaction conditions: Except for entries 9-11, 1,4-addition (room temperature, 2 h in THF) and aldol (-78°C, 2 min). Entry 9: 1,4-addition (0°C, 3 h in THF) and aldol (0°C, 2.5 h). Entry 10: 1,4-addition (0°C, 1.5 h in THF) and aldol (-78°C, 2 min). Entry 11: 1,4-addition (room temperature, 2 h in ether) and aldol (-78°C, 2 min). b) For the structures of 4, 5, and 6, see equation 2. c) The ratio was determined on the basis of HPLC, ^1H, and/or ^{13}C NMR spectra. d) Combined isolated yield of 5 and 6 for the spectroscopically pure materials.

Scheme II



Erythro Threo

The erythro selective reaction in the cases of 1 (R^1= Me and Ph, equation 1) is based both on the Z-structure of enolate and on a cyclic six-membered chair-like transition state (Scheme II). The threo selective reaction as observed in entries 1-8 and 11-14 suggests that, when the steric bulk of R^1 is more than i-Pr group, a transition state might take a skew boat conformation in order to avoid a pseudo gauche interaction between R^1 and R^2 in a chair-like transition state (Scheme II).[7,8] The low aldol selectivity for R^1= i-Pr (equation 1) might be attributed to a low stereochemical purity of the enolate, which might stem from a repulsion between i-Pr and thiocabonyl groups in a transition state leading to the Z enolate.[11]

In conclusion, in this paper were dealt with the following two findings. The first is that the stereochemically homogeneous thioamide enolates (probably Z)[8] could be generated by the Michael addition of organometallics to 4 (equation 2). The same enolate was generated in poor stereochemical purity (Z:E = 2:1) by the proton abstraction method (equation 1). The second is that the enolate generated by the Michael addition method selectively provides the threo aldols (equation 2). This makes sharp contrast to the erythro selective aldols (equation 1, R^1 = Me, Ph).[12]

References and Notes

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(2) (a) C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, J. Org. Chem., 44, 4294 (1979). (b) K. K. Heng, J. Simpson, R. A. J. Smith, W. T. Robinson, Ibid., 46, 2932 (1981).

(3) See accompanying communication.

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(6) For tandem addition-alkylation of unsaturated amides, see (a) J. E. Baldwin and W. A. Dupont, Tetrahedron Lett., 21, 1881 (1980). (b) G. B. Mpango, K. K. Mahalanabis, Z. Mahdavi-Damghani, and V. Snieckus, Ibid, 21, 4823 (1980). For unsaturated ketones, see ref 2b.

(7) The similar prohibition of a chair-like transition state has been noted for a thio-Claisen rearrangement: Y. Tamaru, Y. Furukawa, M. Mizutani, O. Kitao, and Z. Yoshida, J. Org. Chem., 48, 3631(1983).

(8) Although presently we are unable to determine the structure of the enolate,[9] the Z-structure is most likely, because many precedents[10] indicate that Michael addition of organometallics proceed through a coordination of their metal cations to the thioamide sulfur atom to form a cyclic 6π-electron transition state.

(9) For structure determination of thioamide enolates, see ref 7a.

(10) (a) Y. Tamaru, T. Harada, S. Nishi, and Z. Yoshida, Tetrahedron Lett., 23, 2383 (1982). (b) Y. Tamaru, T. Hioki, S. Kawamura, H. Satomi, and Z. Yoshida, J. Am. Chem. Soc., 106, 3876 (1984).

(11) See footnote 12 in ref. 1a.

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