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STEREOSELECTIVE GENERATION OF Z-KETENE S,N-ACETAL FROM S-ALKYL ONIUM SALT OF THIOAMIDE AND ITS APPLICATION TO DIASTEREOSELECTIVE α-ALLYLATION OF THIOAMIDE

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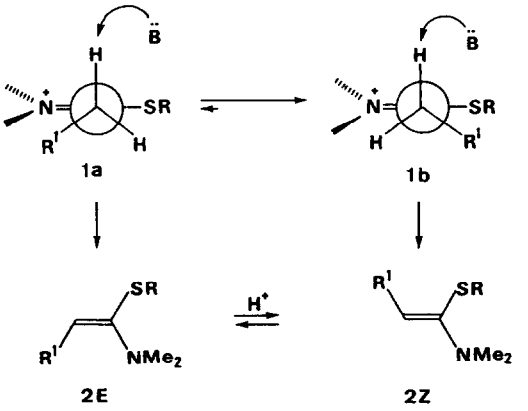
Summary: Highly diastereoselective α-allylation of thioamides has been achieved via S-allylation of thioamide, dehydrohalogenation, and thio-Claisen rearrangement sequences in one pot.

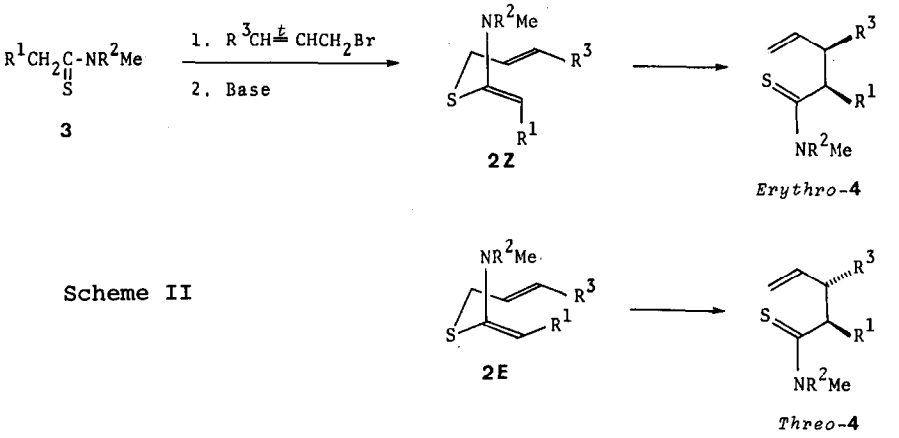
In sharp contrast to the E-configuration of kinetic enolates of ordinary carbonyl compounds,[1] both the kinetic and thermodynamic enolates of secondary[2] and tertiary thioamides[3] possess the Z-configuration[4] in very high geometric purity. The similar and higher Z-selectivity is expected in the formation of ketene S,N-acetal 2 by a dehydrohalogenation of S-alkyl onium salt 1, because between two conformers only the conformer 1b seems to be responsible for a dehydrohalogenation (Scheme I): the conformer 1a might experience a substantial A(1,3)-strain[5] between R^1 and the substituent on nitrogen atom, amplified by an increased bouble bond character of the C_{sp^2}-N bond in 1 compared with that in thioamide.[6] This argues against the results reported previously,[7] where the structure of ketene S,N-acetals, generated by the dehydrohalogenation of 1 with potassium t-butoxide, was assigned to E by a systematic investigation of the chemical shifts of vinylic protons of 2 in ^{1}H NMR spectra. The apparent inconsistency needs to be investigated further and we examined the stereochemical nature of 2 by making use of the thio-Claisen rearrangement,[8] because the diastereoselectivity of this rearrangement is well correlated to the structure of 2 through a six-membered chair-like transition state[9] (Scheme II).

Generally the reaction was performed as follows: A mixture of thioamide (2 mmol) and allyl bromide (3 ∿ 6 mmol) in 2 ml of anhydrous t-butanol was stirred

Scheme I



overnight at room temperature under argon. After evaporation of an excess allyl bromide and the solvent in vacuo (below 40 °C), a solution of a base (2.3 mmol) in 2 ∿ 5 ml of t-butanol was added and stirred under the conditions indicated in Table I (method A). In some cases, the process of evaporation of allyl bromide and the solvent was omitted and an excess amount of base (1.1 equiv to allyl bromide) was employed (method B). After usual extractive work up and purification by means of column chromatography (silica gel, hexane-benzene) were isolated the products 4, whose diastereoselectivity was determined by VPC, HPLC, ^{1}H and/or ^{13}C NMR spectra.



Scheme II

Taking it into consideration that protic solvents and the conjugate acids of bases serve as proton donors and isomerize the ketene S,N-acetals 2,[7] the use of aprtic solvents and strong bases seem to be a reasonable choice in order to minimize the isomerization of 2. However, in the aprotic solvents (such as THF), the S-alkylation was not completed and the use of strong bases (such as t-BuOK in t-BuOH or LDA in THF) generally resulted in the suppressed yields and in some instances caused epimerization of products (entry 7, Table I). From a practical point of view, especially for conducting the reaction in one pot, we selected t-butanol as a solvent and DBU or triethylamine as a base,[10] because this system was found to catalyze the isomerization of 2 very slowly at an ambient temperature.

The rate of rearrangement seems to depend mainly on the steric bulk of R^1 group. When R^1 is methyl, rearrangement proceeds smoothly at an ambient temperature, irrespective of the bulk of R^3. With an increase in the steric bulk of R^1, the rearrangement becomes slow and requires external heating to obtain 4 in reasonable yields. In these cases, however, the diastereoselectivities were considerably diminished probably owing to the isomerization of 2. Although most of the products in Table I showed no appreciable epimerization by the catalysis of DBU or triethylamine, the products derived from δ-thiovalerolactam were exceptionally prone to epimerize. This unfavorable isomerization could be minimized by the use of triethylamide as a base (cf. entries 11 and 12).

Table I. Diastereoselective α-Allylation of Thioamides via Thio-Claisen Rearrangement[a)]

Entry	Thioamide 3		Allyl Bromide	Method[b)]	Base	Conditions[b,c)]	% Yield of 4[d)]	Ratio[e)] 4-*Erythro*: 4-*Threo*
	R^1	R^2	R^3					
1	Me	Me	Me	A	DBU	r.t., 6 h	67	24 : 1
2	Me	Me	Me	A	DBU	70 °C, 4 h	82	6.7 : 1
3	Me	Me	Ph	B	DBU	r.t.. 6 h	65	13 : 1
4	Me_2CH	Me	Me	A	DBU	85 °C, 5 h	97	1.2 : 1[f)]
5	N,N-Dimethylthio-crotonamide		Me	B	DBU	r.t., 9 h	35	24 : 1
6	"		Me	B	DBU	85 °C, 4 h	69	2.9 : 1
7	Ph	Me	Me	A	^{t}BuOK	70 °C, 4 h	60	1 : 1
8	Ph	Me	Me	A	DBU	70 °C, 4 h	79	4.0 : 1
9	Ph	Me	Me	B	Et_3N	r.t., 43 h	53	13 : 1
10	$-(CH_2)_3-$		Me	A	Et_3N	85 °C, 2 h	82	1 : 9.0
11	$-(CH_2)_3-$		Ph	B	DBU	85 °C, 4 h	89	1 : 1.1
12	$-(CH_2)_3-$		Ph	B	Et_3N	85 °C, 4 h	88	1 : 99
13	$-(CH_2)_4-$		Ph	B	Et_3N	83 °C, 4 h	74	1 : 99

a) See Scheme II for the structures of 3 and 4. b) See text for experimental conditions. c) Conditions applied for the thio-Claisen rearrangement process. d) Combined isolated yield for spectroscopically pure products. e) Determined by HPLC (μ-porasil, 95 : 5 hexane-EtOAc), ^1H, and/or ^{13}C NMR spectra. f) Tentative structural assignment.

All the results in Table I, except for entry 4, clearly indicate that the acyclic thioamides provide the kinetic ketene S,N-acetal 2-Z in more than 95% purity. The low selectivity in entry 4[11] might be explained as a result of a destabilization of a chair-like transition state in the thio-Claisen rearrangement due to a pseudo gauche interaction between olefinic methyl and iso-propyl groups (2-Z: R^1= iso-Pr, R^3= Me, Scheme II).[12] Interestingly, the α-allylation of N,N-dimethylthiocrotonamide provided *erythro*-N,N,3-trimethyl-2-vinylthiopent-4-enamide[8h] (4, R^1= $CH=CH_2$, R^2= R^3= Me, entry 5) selectively, indicating the selective formation of 2-Z even in the γ-proton abstraction, probably through a conformer similar to 1b.[13]

The structure of *erythro*- and *threo*-4 (R^1= R^2= R^3= Me; R^1= Ph, R^2= R^3= Me) was determined by the selective transformation to cis- and trans-2,3-disubstituted-δ-valerolactones, respectively, via a hydroboration (9-BBN then NaOH-H_2O_2) followed by a lactonization (10 equiv MeI, 2N HCl in aq THF). The selective

Cope rearrangement giving N,N-dimethyl-trans,trans-thioocta-2,6-dienamide (DMF, 153 °C, 0.5 h) established the structure of *erythro*-4 (R^1= $CH=CH_2$, R^2=R^3= Me).[14]

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(10) N,N-Dimethyl-4-aminopyridine and N,N,N',N'-tetramethyl-1,3-diaminopropane were also effective, though providing 4 in somewhat lower yields. Pyridine or N,N,N',N'-tetramethyl-1,2-diaminoethane was ineffective, providing no or a trace of 4.

(11) The similar result is obtained even in the low conversion (*erythro*-4:*threo*-4 = 62:38 in 3% conversion, ambient temperature, 8 h).

(12) At present could not be ruled out another possibility of the low selectivity in the formation of 2, due to repulsion between iso-Pr and SR groups in the conformer 1b.

(13) The maximum overlap of pπ-pπ in a N=C-C=C system is assumed.

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