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THIO-CLAISEN AND COPE REARRANGEMENTS

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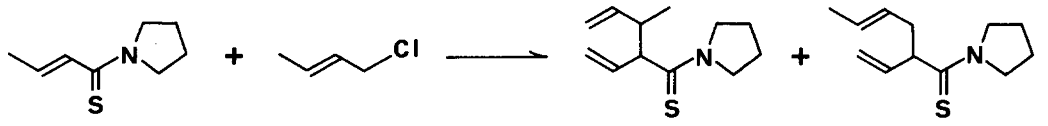
The various modifications of the Cope and Claisen rearrangements have been developed in recent years and these methods have proved very useful for the natural product synthesis owing to their high stereoselectivities.[1] Although Nozaki et al.[2] found the stereoselective trisubstituted olefin synthesis via a thio-Claisen rearrangement in 1973, only a few reports have appeared on this rearrangement so far.[3] Takano et al. reported an α-allylation of thioamides via a thio-Claisen rearrangement[4a] and its successful application to the indole alkaloid synthesis.[4b] In this communication we wish to report the first example of the double thio-Claisen and Cope rearrangements, which furnish α,β-ε,ζ-unsaturated thioamides possessing the fundamental terpene skeleton. The total profile of this reaction is illustrated in Scheme I. The S-alkylation of α,β-unsaturated thioamides 1 with allylic halides 2 and subsequent dehydrohalogenation with a base afforded thioamides 4, which appeared to be derived from ketene S,N-ketal intermediates (3E and/or 3Z) via a thio-Claisen rearrangement. This transformation could be undertaken most satisfactorily by the S-allylation in t-BuOH followed by dehydrohalogenation with DBU (1,5-diazabicyclo[5.2.0]undecene-5). For example, α-allylation of thiocrotonoylpyrrolidine 1c with crotyl chloride 2b in t-BuOH gave 3-methyl-2-vinylthiopent-4-enoylpyrrolidine 4 ($R^1 = R^2 =$ H, $R^3 =$ Me) exclusively in 72% yield (entry 5),[5] while in THF a mixture of 4 and 2-vinylthiohex-4-enoylpyrrolidine 7 were obtained in 30 and 20% yields, respectively, as a result of S-alkylations at both termini of unsymmetrical allylic halide (eq 1). When KO^tBu was used instead of DBU, the first formed β,γ-unsaturated thioamide 4 was completely isomerized to α,β-unsaturated thioamide, i.e., in entry 3, 2-isopropylidenethiopent-4-enoylpyrrolidine was obtained in 45% yield as the only isolable product.



(1)

1c 2b 4 7

Table I Thio-Claisen and Cope Rearrangements

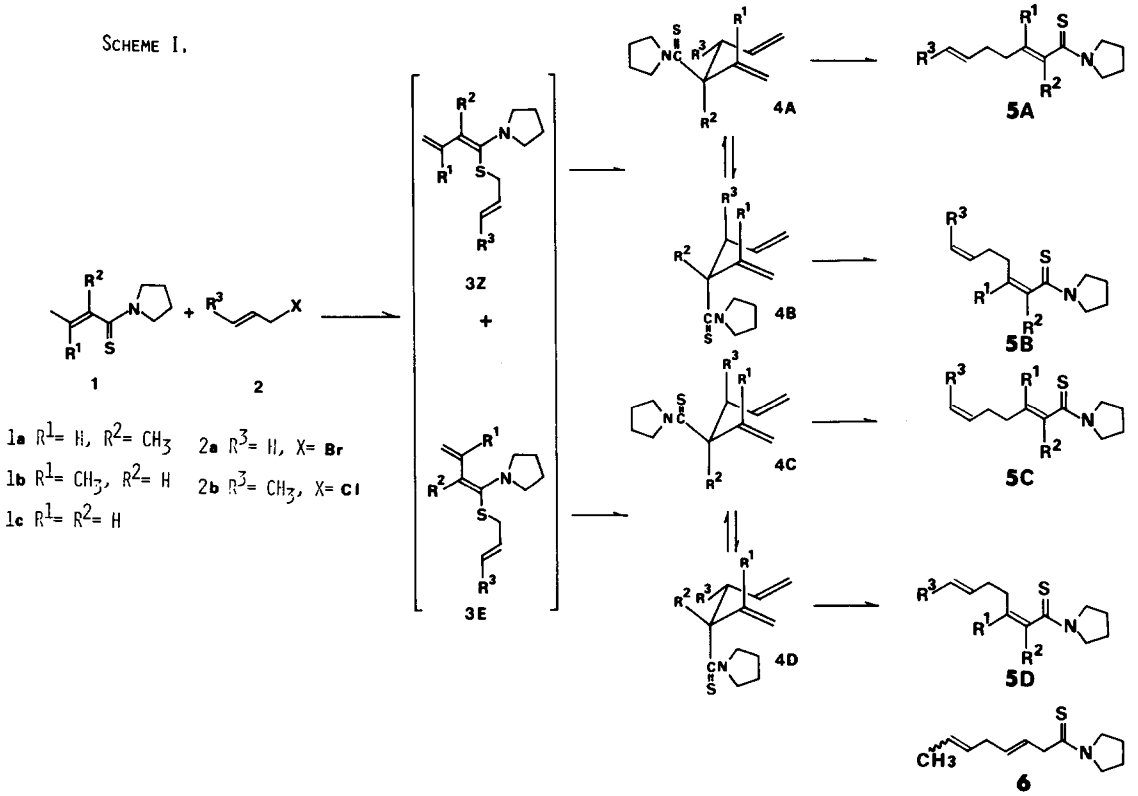
Entry	Thio-amide	Allylic Halide	Thio-Claisen Rearrangement		Cope Rearrangement	
			Reaction Conditions[a]	Product 4[b] % yield	hr[c]	Product 5 and/or 6[d]
1	1a	2a	1) ^{t}BuOH, r.t., 17h 2) DBU, 75°, 2h	78	2	5A, 5B (44:56) [90]
2	1a	2b	1) ^{t}BuOH, 70°, 4h 2) DBU, 70°, 2h	52	0.75	[95][e]
3	1b	2a	1) ^{t}BuOH, r.t., 20h 2) DBU, r.t., 2h	96	9	5A, 5B (67:33) [80]
4	1b	2b	1) ^{t}BuOH, 75°, 2.3h 2) DBU, 75°, 0.75h	93	0.5	5A, 5D (78:22) [95]
5	1c	2b	1) ^{t}BuOH, NaBPh$_4$,[f] r.t., 48h 2) DBU, r.t., 5h	72	1.8	5A, 6 (77:23) [88]

a) See the text for details. b) Isolated yield. c) Heated at 200° in tetralin under argon over a period of time indicated (hour). d) The values in parentheses refer to the product distributions determined by VPC. The values in blackets refer to the isolated yields. All products showed the satisfactory spectral (IR, NMR and mass) and analytical results. e) The VPC analysis of the products showed the poorly separated four peaks of equal heights probably ascribable to the four configurational isomers. f) In order to attain the completion of reaction, an equimolar amount of sodium tetraphenylborate was added.

The present method permits the allylation of the tertiary carbons α to the thiocarbonyl groups in reasonable yields (entries 1 and 2), while the allylation by the previously reported method[4a] is limited only to the primary or secondary carbons α to the thiocarbonyl groups. It should also be pointed out that the thio-Claisen rearrangement proceeds at much lower temperatures (ranging from ambient temperature to 75°C as opposed to ∿200°C) even for the reactions to form the C-C bonds between the highly substituted termini, than is required to isomerize the allyl vinyl sulfides[6] (substitute NR$_2$ by alkyl or H).

The Cope rearrangement, attempted in tetralin under argon, was brought to the completion within 2h at 200°C, except for entry 3, which required an exceptionally long reaction time. As illustrated in Scheme I, the Cope rearrangement of 4 obtained by the reaction of 1a-1c and allyl bromide 2a, is expected to provide two types of products 5A and 5B, derived from two conformational isomers 4A and 4B, respectively. The reaction of 1a-1c with crotyl chloride 2b gives a mixture of diastereomers 4A and 4C (via 3E and 3Z, respectively) and hence four kinds of products 5A-5D are possible.[7] The results in

SCHEME I.



entry 1 suggests that methyl and thioamide groups favor the equatorial position in a similar order of magnitude, though depending on the solvents. The ratio (44:56) obtained in tetralin altered to 61:39 in ethylene glycol, probably owing to the favorable hydrogen bonding between a solvent and the equatorial thioamide groups.[8] In entry 4, only two (5A and 5D) of the four possible isomers are obtained, which suggests that 4A and 4D are the much preferable conformers over 4B and 4C, respectively, because the latters experience the nonbonded interaction between pseudo-1,3-diaxial methyl groups.

The present thio-Claisen and Cope rearrangements seem to have some advantages over the method of the trans-etherification of allylic alcohols[10] with dienyl ethers: (a) the easy availability of starting materials; (b) especially for the point that 4, possessing the α-proton to thiocarbonyl group, undergoes the Cope rearrangement completely without any interference of hydrogen migration[10] to give α,β-unsaturated thioamide.

Experiments typified with entry 4 are as follows. A solution of 1b (3 mmol) and 2b (6 mmol) in 3 ml of anhydrous t-BuOH was stirred and heated at 75° over a 2.3 h period under argon. After addition of 6 mmol of DBU at r.t., the reaction mixture was allowed to warm to 75° and stirred for 45 min. Extraction with EtOAc, drying over $MgSO_4$, evaporation of the solvent, and column purification (Silica gel, hexane-PhH) gave 4 (R^1= R^3= Me, R^2= H, a mixture of two diastereomers); mp 51-53° (EtOH-hexane). $\delta^{TMS}_{CCl_4}$ 0.93 (d, 6Hz, 3H), 1.75 (s, 3H), 2.0 (m, 4H), 3.18 (m, 1H), 3.75 (m, 5H), 4.83, 5.05 (m, 4H), 5.65 (m, 1H). ν_{neat}^{max} 3080(w), 1640(m), 1490,1470, 1440(s), 980(w), 900(m). Found: m/e 223.1367, Calcd for $C_{13}H_{21}NS$: M, 223.1394. A solution of 4 (2 mmol, R^1= R^3= Me, R^2= H) in 2 ml of tetralin was stirred and heated at 200° for 30 min. The products, not separated well by VPC (SiDC 550, He), were directly treated with an excess of CH_3I, followed by the hydrolysis with aq. NaOH[9b] to give a mixture of amides in a ratio of 78:22 in 95% yield (Kugelrohr 120°/2 mmHg), which were separated by preparative VPC. 3-Methyl-2,6-trans, trans-octadienoylpyrrolidine (amide of 5A, R^1= R^3= Me, R^2= H): $\delta_{CCl_4}^{TMS}$ 2.03 (s, 3H, $CH_3C{=}CCO$),[11] 5.66 (br.s, 1H, CHCO); ν_{neat}^{max} 1610(vs), 1430(vs), 960(m), 850(w); Found: 207.1602, Calcd for $C_{13}H_{21}NO$: M, 207.1622. 3-Methyl-2,6-cis, trans-octadienoylpyrrolidine (amide of 5D), R^1= R^3= Me, R^2= H): $\delta_{CCl_4}^{TMS}$ 1.80 (s, 3H, $CH_3C{=}CCO$),[11] 5.66 (br. s, 1H, CHCO); ν_{neat}^{max} 1620(vs), 1440(vs), 970(m); Found: m/e 207.1684, Calcd for $C_{13}H_{21}NO$: M, 207.1622.

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