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ASYMMETRIC INDUCTION IN THE [2,3] SIGMATROPIC REARRANGEMENT VIA SULFUR YLIDES DERIVED FROM CHIRAL KETENIMINES

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The asymmetric [2,3] sigmatropic rearrangement of 2-alkylamino-3-phenyl-2-pentenylmethylsulfonium methylide (4) was accomplished by reaction of ethylphenylketenimines 2, having chiral carbons next to the nitrogen atoms, with trimethylsulfonium ylide (3) and acidic hydrolysis of the imines 5 obtained led to optically active 3-methylthiomethyl-3-phenyl-2-pentanone (6). The reaction of ethylphenylketene (-)-menthylimine (2f) with 3 at -78 °C resulted in the highest optical yield (55.6%) of (R)-(-)-6 in the same sequence.

A number of new synthetic methodologies for creation of new asymmetric centers[1] have been devised in recent years for efficient chiral synthesis of biologically active compounds mainly due to pharmaceutical use.

Among them, one of the most useful and efficient methods is intramolecular transfer of chirality utilizing usually [3,3][2] and [2,3] sigmatropic rearrangements,[3] and intramolecular substitution reactions.[4]

There have been published only a few reports on asymmetric [2,3] sigmatropic rearrangements of sulfur ylides[3d] involving chirality at the sulfur atoms. Apparently, these chiral sulfonium salts were not accessible with ease, and therefore these methods could not be general and practically not useful for introduction of asymmetry into a molecule.

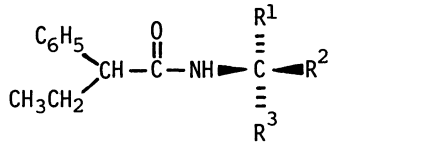
We wish to disclose herein a potentially useful method for creation of a new asymmetric carbon by [2,3] sigmatropic rearrangements via sulfur ylides which were easily derived from readily obtainable ketenimines,[5] having chirality next to the nitrogen atoms, and a sulfur ylide. To our knowledge no report has been published hitherto on asymmetric induction with chiral ketenimines. A quite recent paper on asymmetric cycloaddition to chiral ketene iminium salts[6] stimulates us to communicate

our current results on asymmetric induction with chiral ketenimines.

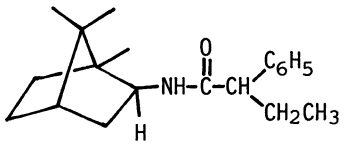
The ketenimines 2 having an asymmetric carbon next to the nitrogen atom were prepared without racemization by heating amides 1 and an equivalent amount of phosphorus pentachloride in benzene followed by dehydrochlorination of the imino chlorides upon treatment with triethylamine in refluxing benzene. Complete maintenance of chirality during these procedures was clearly confirmed with optical properties of the corresponding recovered starting amides obtained by hydrolysis of ketenimines 2 with 4N-hydrochloric acid-acetone (1 : 7).

Distillation of 2a gave an analytically pure sample (2a: bp 85-95 °C (1 mmHg); ν_{max}^{film}: 2020 cm^{-1} (C=C=N); $[\alpha]_D^{26}$ +33.0° (c=4.33, THF)). Other ketenimines 2b-f having higher boiling points, however, were thermally decomposed partially or wholly to the nitriles[7] during distillation under high vacuum and therefore they were subjected directly to the next rearrangement without distillation.

Nucleophilic addition of trimethyl sulfonium ylide (3)[8] to a carbon-nitrogen double bond in chiral ketenimines 2, followed by [2,3] sigmatropic rearrangements of sulfur ylides 4B generated by proton-transfer from the C_1 carbon to the nitrogen atom in 4A, produced imines 5, which were smoothly converted into optically active



	R^1	R^2	R^3
1a	CH_3	CH_2CH_3	H
b	$CH_2C_6H_5$	CH_2OCH_3	H
c	$CH_2(CH_3)_2$	CH_2OCH_3	H
d	CH_3	CH_2OCH_3	H



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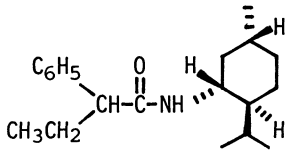

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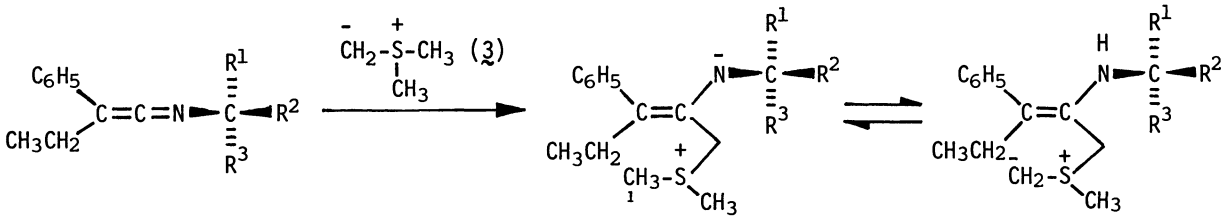
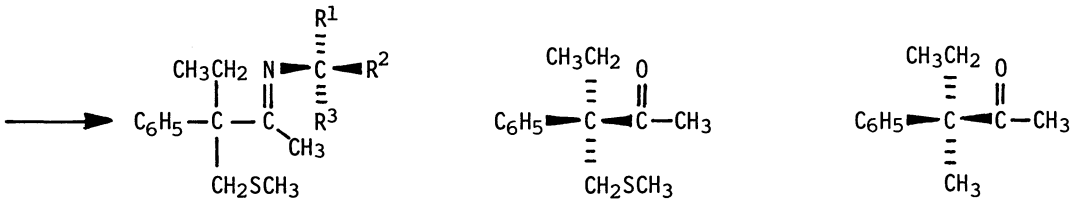


2a-f 4A 4B



5 (S)-(+)-6 (R)-(-)-7

3-methylthiomethyl-3-phenyl-2-pentanone (6) by hydrolysis with 10% hydrochloric acid. The absolute configuration of 6 was determined as (S)-(+)-configuration by its hydrogenetic conversion with Raney Ni into 3-methyl-3-phenyl-2-pentanone (7) of known configuration.[9]

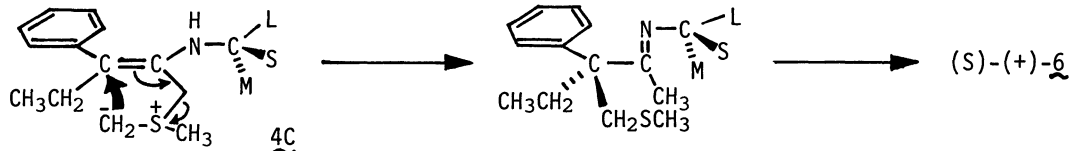
A typical experimental procedure is as follows; a solution of 3, prepared by treating trimethyl sulfonium iodide (1.5 equiv) with butyllithium (1.5M hexane solution,1.5equiv) at -20 °C for 45min,in tetrahydrofuran(THF) was allowed to react with (S)-(+)-2a at -20 °C for 21 h to give 5a, which was hydrolyzed under reflux in 10% hydrochloric acid-benzene for 3 h, affording finally (S)-(+)-6 in 40% yield based on the starting amide 1a used and corrected by the recovered amide 1a (22%).

Effects of other amino components and reaction temperature on this asymmetric induction were studied in the same way by employing readily available optically active primary amines and the results were summarized in Table.

The enantiomeric purity of the newly created asymmetric carbon of 6 was determined, as shown in the Table, by nmr analysis using a shift reagent [$Eu(hfc)_3$].

As indicated in the Table, reaction of the ketenimine 2f, prepared in the same sequence as described above with a readily obtainable amide 1f starting from (-)-menthylamine, with 3 at -78 °C resulted in the highest optical yield of (R)-(-)-6.

In a consideration of the absolute configuration of the product, the most plausible mechanistic pathway for this asymmetric induction would be presented as follows. Initial addition of 3 to the carbon-nitrogen double bond in ketenimines would be preferred from the less hindered side, namely in the same direction to ethyl group in this case. After proton-transfer from the C_1 carbon to the nitrogen atom in 4A, approach of the sulfur ylide group to the π-bond in 4B would be occurred from the less hindered upside, as indicated with the black arrow in 4C, because of energetic difference due to steric interference between the small (S) or medium (M) groups and the sulfur ylide moiety in the most preferred conformation (4C) of 4B, in which the large group (L) might be oriented on the same extending plane as the carbon-carbon double bond-nitrogen line in anti conformation to the functionality.



Thus a readily obtainable ketenimine 2f affording consistently high enantioselectivity would represent a valuable synthetic tool for preparation of optically active α'-substituted methyl ketones which have a wide utility in organic synthesis.

Table Asymmetric Induction in [2,3] Sigmatropic Rearrangement via Sulfur Ylide by Reaction of Ketenimines 2a-f with 3

Ketenimines 2[a] (Absolute Confign.)	Reaction Conditions for Rearrangement[b] Reaction Temp. (°C)	Reaction Time (h)	Yield of 6[c] (%)	Product 6 $[\alpha]_D$ (EtOH)[d] (Absolute Confign.)	e.e.(%)[e]
a (S)	-20	21	40	+10.2° (S)	14.1
a (S)	-78	11	33	+9.3° (S)	13.0
b (S)	-20	24	37	-3.2° (R)	4.4
c (S)	-20	18.5	20	-11.0° (R)	15.3
d (S)	-20	21.5	21	+4.0° (S)	5.6
e (S)	-20	22	46	+10.3° (S)	14.3
e (S)	-78	11	6	+28.1° (S)	39.0
f (R)	-20	23.5	47	-27.3° (R)	37.8
f (R)	-78	12.5	36	-40.0° (R)	55.6

a. Ketenimines 2a-f were prepared by refluxing the corresponding amides 1a-f with an equivalent amount of phosphorus pentachloride in benzene for 3 h followed by treatment with triethylamine (10 equiv) in refluxing benzene over night. b. Ketenimines 2a-f reacted with 3 (1.5 equiv) in THF under the reaction conditions given in this Table followed by refluxing in 10% HCl-benzene for 3 h. c. Based on 1a-f used and corrected by the recovered starting materials (1a-f). d. Measured at 15-25°C. e. Calculated by nmr analysis with a shift reagent [Eu(hfc)$_3$].

Improvement and further developement by variation of the chiral auxiliary as well as other substituted ketenimines, in order to reveal more evidently a detailed mechanism of this asymmetric induction, are now in progress.

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