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# ASYMMETRIC INDUCTION IN THE [2,3] SIGMATROPIC REARRANGEMENT VIA CHIRAL AMMONIUM YLIDES

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The asymmetric [2,3] sigmatropic rearrangements of the chiral ammonium chlorides (E)-(3a,b) were achieved upon treatment with t-BuOK followed by acidic hydrolysis of the aminonitriles (5a,b) obtained to give (R)-(+)-2-methyl-2-phenyl-3-butenal (6). The rearrangement of (E)-(3a) at -78° resulted in the highest optical yield (90%) of (R)-(+)-(6). The geometrical isomer (Z)-(3a) underwent the same [2,3] shift under the same conditions to afford (S)-(-)-(6). The mechanism of this asymmetric induction is discussed based on these results.

An asymmetric induction reaction in C-C bond formation is of great importance for the preparation of pharmacologically active compounds such as sesquiterpenes and steroids. In recent years there has been an increased interest in exploiting sigmatropic rearrangements[1] for the performance of chiral synthesis with enantiomerically high selectivity.

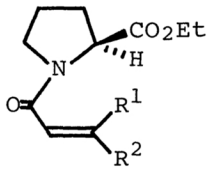
Hitherto many investigators have reported various examples of asymmetric [3,3] sigmatropic rearrangements[2] such as Cope[3] and Claisen rearrangements.[4]

In the last few years attention has been devoted to asymmetric [2,3] sigmatropic rearrangements using various chiral sources such as optically active allyl alcohols,[5] sulfenates,[6] sulfoxides,[7] sulfur ylides,[8] and amine oxides.[9]

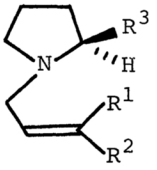
We wish to communicate herein our first example of the asymmetric [2,3] sigmatropic rearrangements via chiral ammonium ylides.

An optically active allylamine (S)-(E)-(2b) was prepared by amidation (90%) of (S)-proline ethyl ester, according to the usual mixed anhydride method, with (E)-β-methylcinnamic acid followed by reduction with $LiAlH_4$ (at 0° 1 h and at room temp. 2-3 h, 99%) and benzylation (NaH, $C_6H_5CH_2Br$, toluene-DMSO (20:1), reflux 6 h, 67%).

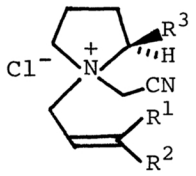
Quaternization of (S)-(E)-(2b) with cyanomethyl chloride (40-45°, 3-4 h)[10] followed by treatment with t-BuOK at 0°∿-10° for 6 h in THF-DMSO (2 : 1) underwent a [2,3] sigmatropic rearrangement via a chiral ammonium ylide (E)-(4a) to give an aminonitrile (E)-(5a). This aminonitrile was hydrolyzed by refluxing for 2.5 h with 30% oxalic acid in THF-$H_2O$ (1 : 1) to give (+)-2-methyl-2-phenyl-3-butenal (6).



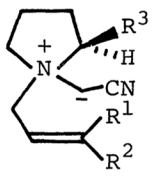
(1)



(2a) $R^3$=$CH_2OH$
(2b) =$CH_2OCH_2C_6H_5$
(2c) =$CH_3$

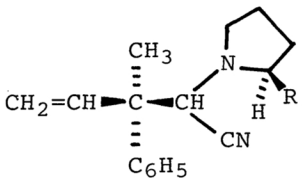


(3a) $R^3$=$CH_2OCH_2C_6H_5$
(3b) =$CH_3$

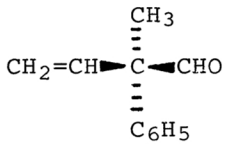


(4a) $R^3$=$CH_2OCH_2C_6H_5$
(4b) =$CH_3$

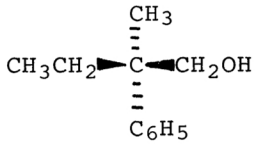
(E)- : $R^1$=$CH_3$, $R^2$=$C_6H_5$; (Z)- : $R^1$=$C_6H_5$, $R^2$=$CH_3$



(5a) R=$CH_2OCH_2C_6H_5$
(5b) =$CH_3$



(R)-(+)-(6)



(R)-(-)-(7)

In order to establish the absolute cofiguration and the enantiomeric purity of the newly created asymmetric center, (+)-(6) ($[\alpha]_D^{21}$ +7.5° (c 12.1, MeOH)) obtained above was transformed by hydrogenation with Raney Ni into (-)-2-methyl-2-phenyl-1-butanol (7) ($[\alpha]_{546}^{24}$ -5.4° (c 12.2, $CHCl_3$)). Since optically pure (R)-(-)-(7) was reported to have a rotation $[\alpha]_{546}^{25}$ -9.7° ($CHCl_3$),[11] the optical rotation of optically pure (+)-(6) is calculated to be $[\alpha]_D^{21}$ +13.5° (MeOH) and its absolute configuration is determined to be (R)-(+)-(6). Thus the optical yield in the above [2,3] sigmatropic rearrangement is estimated to be 56%.

Effects of the reaction temperature on asymmetric induction in this rearrangement were studied and the results are listed in Table.

It should be noted, as shown in the Table, that the [2,3] sigmatropic rearrangement of (E)-ylide (4a) at -78° produced (R)-(+)-(6) in the highest optical yield (90%).

The rearrangement of (R)-(E)-ammonium chloride (3b), prepared in the same sequence starting with (R)-(-)-2-methylpyrrolidine[12] derived from (S)-proline ethyl

Table Effect of Reaction Temperature on Asymmetric Induction in the Rearrangement of (E)-(4a)

| Reaction Conditions for Rearrangement | | Product (R)-(+)-(6) | | |
|---|---|---|---|---|
| Reaction Temp. (°C) | Reaction Time (h) | Yield of (6)[a] (%) | $[\alpha]_D$(MeOH)[b] | Optical Yield (%) |
| 0∼-10 | 6 | 39 | +7.5° (c 12.1) | 56 |
| -20 | 8 | 40 | +8.8° (c 11.3) | 65 |
| -40 | 10.5 | 40 | +9.8° (c 11.5) | 73 |
| -78 | 12 | 44 | +12.1° (c 13.9) | 90 |

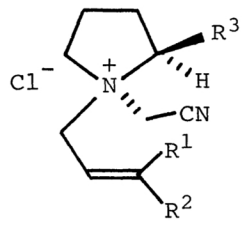
a) Based on (E)-(2b) used. b) Measured at 20.5°-21°

ester, was carried out in the same way by treating with t-BuOK in THF-DMSO (2 : 1) at 0° for 7 h followed by acidic hydrolysis to afford (R)-(+)-(6) in 30% yield based on the allylamine (E)-(2c) used with 16% enantiomeric excess.

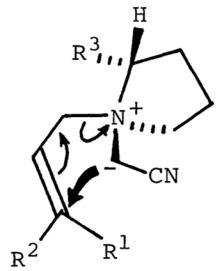
The other geometrical isomer (Z)-(2b) of the allylamine was prepared from (Z)-β-methylcinnamic acid in the same sequence in order to study the effect of the substituents attaching to the double bond on this asymmetric induction.

Treatment of (Z)-ammonium chloride (3a) with t-BuOK in THF-DMSO (2 : 1) at 0°--10° for 6 h followed by acidic hydrolysis gave (S)-(-)-(6) in 35% yield from the allylamine (Z)-(2b) used with 36% enantiomeric excess.

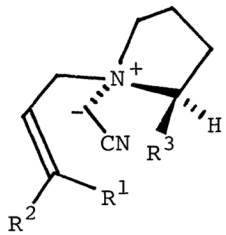
In a consideration of the absolute configuration of the product (6) obtained from (E)- or (Z)-(4), the most plausible mechanistic pathway for this asymmetric induction would be presented as follows.



(8)



(9a)



(9b)

In quaternization of (E)-(2), the cyanomethyl group attacks to the nitrogen atom mainly from the opposite side of the substituent $R^3$ at the asymmetric carbon to form (8). Inspection of Dreiding models of the ylide (9) derived from (8) suggests that approach of the ylide anion to the bottom side of the double bond is substantially encumbered, as shown in (9b), by the great steric interaction between $R^1$ group at the trigonal carbon and the substituent $R^3$, while the conformation (9a) is strongly favored over (9b) due to the orientation of the substituent $R^3$ to the less hindered side in (9a). Therefore the rearrangement of (E)-(3a,b)

is assumed to occur preferentially from the top side of the double bond, as indicated by the black arrow in (9a), followed by hydrolysis to give (R)-(+)-(6). The stereochemical outcome in the rearrangement of (Z)-(3a) can also be explained in the same manner by the transformation via (9a) into the enantiomer (S)-(-)-(6).

Thus a readily available chiral allylamine affording consistently high enantioselectivity would represent a valuable synthetic tool for optically active α-substituted aldehydes.

Improvement and further development by variation of the chiral auxiliary as well as other substituted allylamines are in progress.

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