Stereoselective synthesis of trans-3α-aryloctahydroindoles using cyclization of N-vinylic 3α-(methylthio)acetamides

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STEREOSELECTIVE SYNTHESIS OF TRANS-3a-ARYLOCTAHYDROINDOLES USING CYCLIZATION OF N-VINYLIC α-(METHYLTHIO)-ACETAMIDES†

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Abstract – Treatment of N-(2-arylcyclohex-1-enyl)-α-(methylthio)acetamide with NCS underwent cyclization to give 3a-arylhexahydroindol-2-one, which was stereoselectively converted into trans-3a-aryloctahydroindole.

Lewis acid promoted inter- and intramolecular carbon-carbon bond forming reactions of α-chlorosulfides with alkenic bonds have emerged as valuable tool in organic synthesis.1 We previously reported that N-vinyl α-chloro-α-(methylthio)acetamide (1) underwent cyclization at 100 °C in the absence of Lewis acid to give product (3) in 30% yield (Scheme 1).2 This cyclization can be explained in terms of a high nucleophilic nature of the C=C bond of enamide and a high electrophilic nature of α-chlorosulfide, giving the acyliminium ion intermediate (2).

Scheme 1

† This paper is dedicated to Prof. Dr. Satoshi Omura (The Kitasato Institute) with respect and admiration on the occasion of his 70th birthday.
We have now found that treatment of $N$-(2-arylcyclohex-1-enyl)-$\alpha$-(methylthio)acetamide (6) with NCS at room temperature gives no $\alpha$-chlorosulfide (8) but affords cyclization product, 3a-aryhexahydroindol-2-one (10) in good yield (Scheme 2). Subsequent reductions of 10 gives no expected mesembrane (16) but affords stereoselectively trans-mesembrane (15). Herein, we report the preliminary result of the works in this area.

Condensation of 2-(3,4-dimethoxyphenyl)cyclohexanone and (R)-1-(1-naphyl)ethylamine followed by acylation of the resulting imine (4) with (methylthio)acetyl chloride (5) at room temperature in the presence of $N,N$-dimethylaniline and 4-dimethaminopyridine (DMAP) gave $\alpha$-(methylthio)acetamide (6) having a chiral auxiliary on the nitrogen atom in 45% yield. When compound (6) was treated with $N$-chlorosuccinimide (NCS) in $CCl_4$ at room temperature, cyclization occurred smoothly within 30 min to give two diastereoisomeric products (10) in a ratio of 74:26 and in 59% yield: no $\alpha$-chlorosulfide (8) was obtained. Easy access of 10 from 6 without the formation of $\alpha$-chlorosulfide can be explained by an attack of an electron rich olefinic bond of enamide (7) on its thionium ion, which is an intermediate for the formation of $\alpha$-chlorosulfide (8) from 6 and NCS, followed by deprotonation of the resulting iminium ion (9). An alternative mechanism for the formation of 10 may involve an intramolecular $S_N2$ type nucleophilic substituion of $\alpha$-chlorosulfide (8).
Desulfurization of compound (10) with Raney Ni gave a 73:27 diastereoisomeric mixture of compound (11) in 94% yield. This result indicated that the chiral induction by a 1-(1-naphtyl)ethyl group on the nitrogen atom was estimated to be 74:26 on the basis of the diastereoisomeric ratio of compound (10).

The catalytic hydrogenation of 11 in the presence of PtO₂ in acetic acid gave two stereoisomers (12a) and (12b) bearing 1-(5,6,7,8-tetrahydro-1-naphtyl)ethyl group on the nitrogen atom in 69 and 13% yields, respectively, together with compound (13) (8%) (Scheme 3). Stereochemistry of the ring junctures of 12a and 12b were found to be trans by transforming 12a into trans-mesembrane (15) (vide infra) (the relative trans-stereochemistry of the ring junctures of 12a and 12b are depicted in Scheme 3).

Reduction of the major stereoisomer (12a) with LiAlH₄ followed by hydrogenolysis of the resulting amine in the presence of Pd(OH)₂/C gave compound (14) in 60% yield from 12a. N-Methylation of amine (14) with HCHO/NaBH₃(CN) gave trans-mesembrane (15) in 88% yield (Scheme 4).

Unfortunately, mesembrane (16) was not obtained by a sequence of reductions of compound (11).
Hydrogenation of 11 to trans-fused compounds (12) was in sharp contrast to that of enamide (17) which gave exclusively cis-fused compound (18) (Scheme 5).\textsuperscript{5} We assumed that the size of substituents on the nitrogen atom might play an important role in controlling stereochemistry of the products.

Elucidation of the absolute configuration of trans-mesembrane (15) and mechanistic problems for the stereochemistry of the hydrogenation of enamides of the type (11) are currently underway.

REFERENCES AND NOTES