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

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

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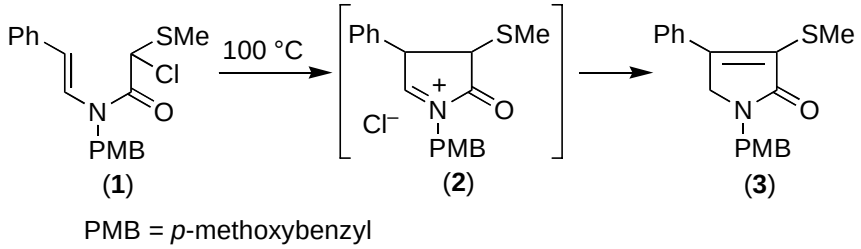
Abstract – Treatment of *N*-(2-arylcyclohex-1-enyl)-α-(methylthio)acetamide with NCS underwent cyclization to give 3a-arylhexahydroindol-2-one, which was stereoselectively converted into *trans*-3a-aryloctahydroindole.

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*-vinylic 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

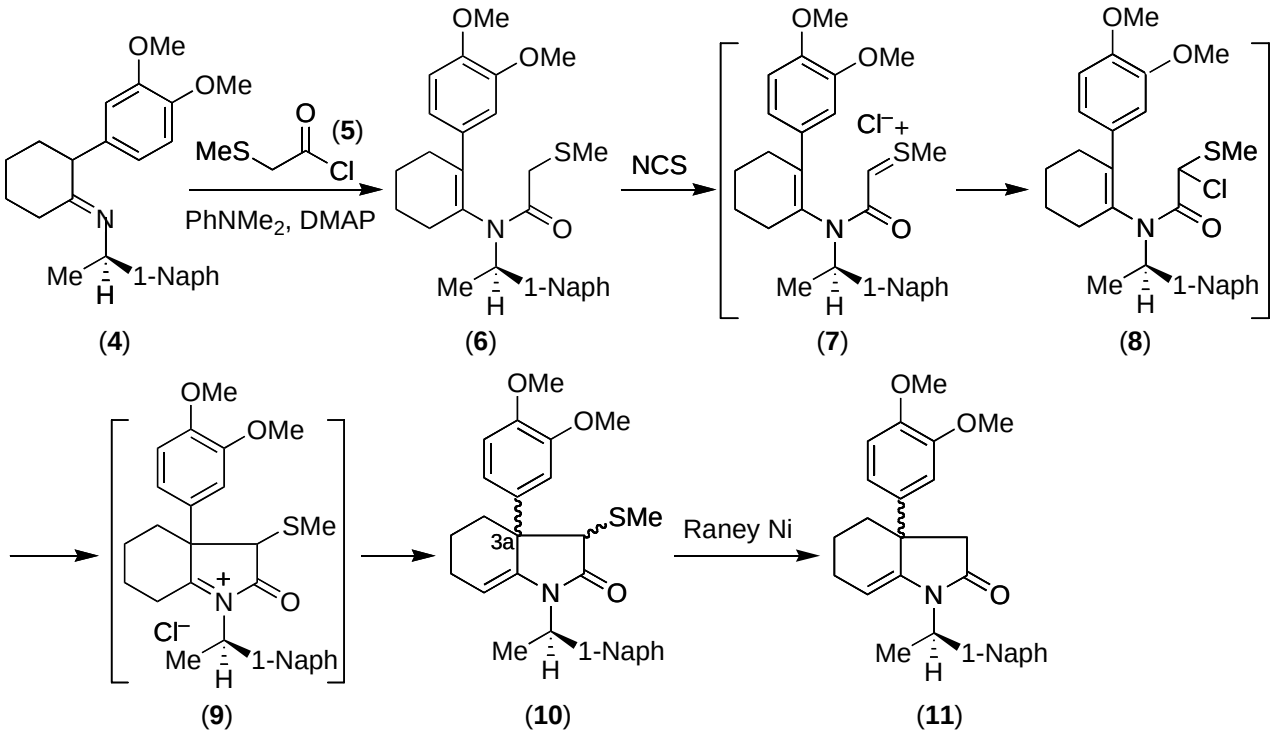


PMB = *p*-methoxybenzyl

† 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)-α-(methylthio)acetamide (**6**) with NCS at room temperature gives no α-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.

Scheme 2



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**)[3] at room temperature in the presence of *N*,*N*-dimethylaniline and 4-dimethaminopyridine (DMAP) gave α-(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 α-chlorosulfide (**8**) was obtained. Easy access of **10** from **6** without the formation of α-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 α-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 α-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 PtO_2 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). Stereochemistris 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).

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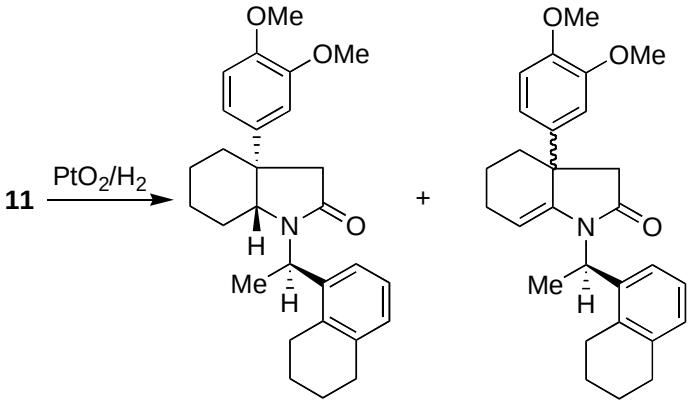
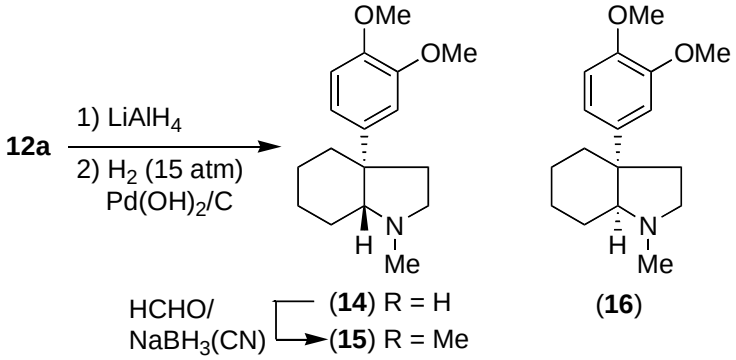
Scheme 3



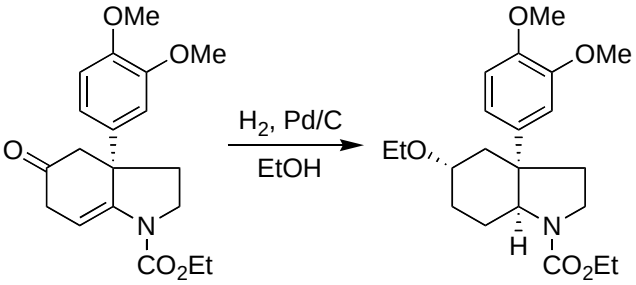
Reduction of the major stereoisomer (**12a**) with $LiAlH_4$ followed by hydrogenolysis of the resulting amine in the presence of $Pd(OH)_2/C$ gave compound (**14**) in 60% yield from **12a**. *N*-Methylation of amine (**14**) with $HCHO/NaBH_3(CN)$ gave *trans*-mesembrane (**15**)[4] in 88% yield (Scheme 4). Unfortunately, mesembrane (**16**) was not obtained by a sequence of reductions of compound (**11**).

Scheme 4



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).[5] We assumed that the size of substituents on the nitrogen atom might play an important role in controlling stereochemistry of the products.

Scheme 5



17 **18**

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

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