

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

著者	Saito Miho, Matsuo Jun-ichi, Uchiyama Masahiko, Ishibashi Hiroyuki
journal or publication title	Heterocycles
volume	69
number	1
page range	69-72
year	2006-12-01
URL	http://hdl.handle.net/2297/3864

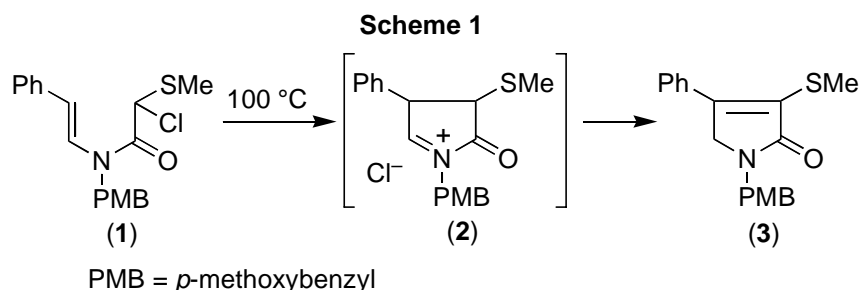
STEREOSELECTIVE SYNTHESIS OF *TRANS*-3a-ARYLOCTAHYDRO-INDOLES USING CYCLIZATION OF *N*-VINYLIC α -(METHYLTHIO)-ACETAMIDES[†]

Miho Saito, Jun-ichi Matsuo, Masahiko Uchiyama, and Hiroyuki Ishibashi*

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kanazawa 920-1192, Japan. E-mail: isibasi@p.kanazawa-u.ac.jp

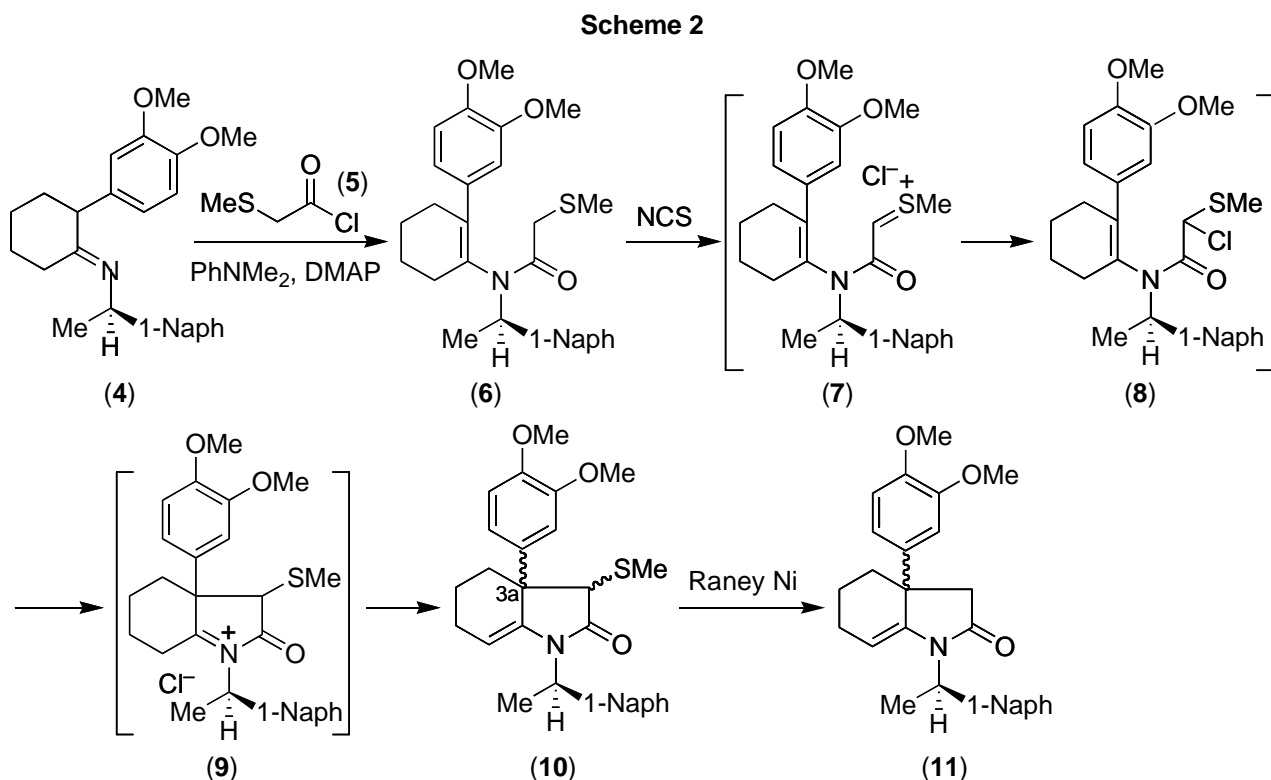
Abstract – Treatment of *N*-(2-arylcylohex-1-enyl)- α -(methylthio)acetamide with NCS underwent cyclization to give 3a-arylhexahydroindol-2-one, which was stereoselectively converted into *trans*-3a-aryloctahydroindole.

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*-vinyllic 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**).



[†] 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-arylcylohex-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.

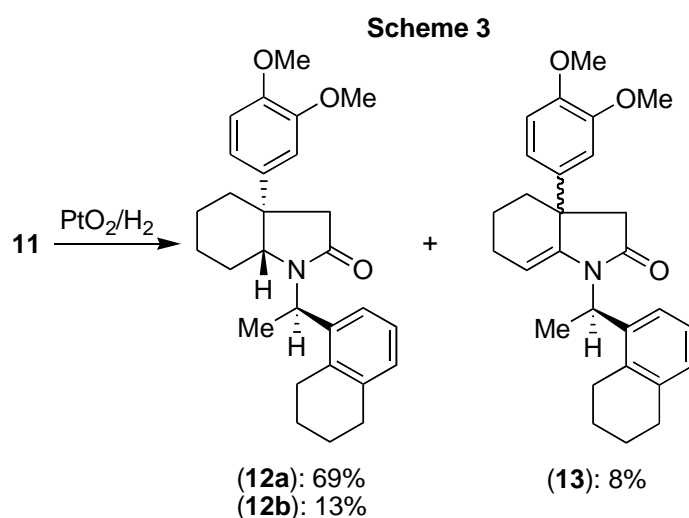


Condensation of 2-(3,4-dimethoxyphenyl)cyclohexanone and (*R*)-1-(1-naphyl)ethylamine followed by acylation of the resulting imine (**4**) with (methylthio)acetyl chloride (**5**)³ at room temperature in the presence of *N,N*-dimethylaniline and 4-dimethaminopyridine (DMAP) gave α -(methylthio)acetamide (**6**) having a chiral auxiliary on the nitrogen atom in 45% yield

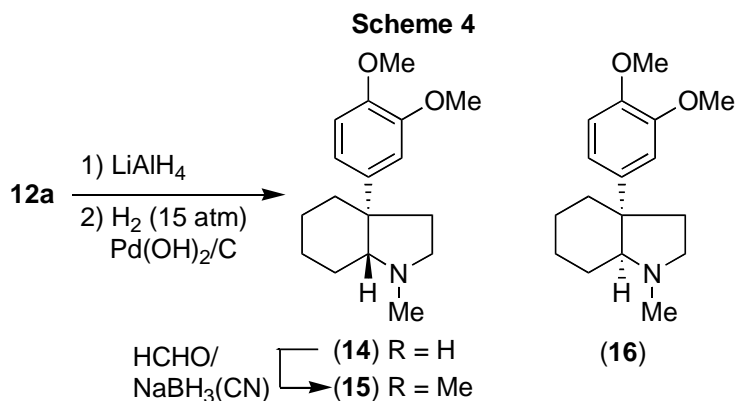
When compound (**6**) was treated with *N*-chlorosuccinimide (NCS) in CCl₄ at room temperature, cyclization occurred smoothly within 30 min to give two diastereoisomeric products (**10**) in a ratio of 74:26 and in 59% yield: no α -chlorosulfide (**8**) was obtained. Easy access of **10** from **6** 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 substitution 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)**.

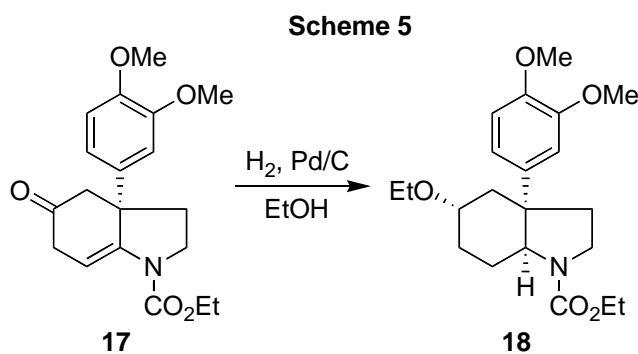
The catalytic hydrogenation of **(11)** in the presence of PtO₂ in acetic acid gave two stereoisomers **(12a)** and **(12b)** bearing 1-(5,6,7,8-tetrahydro-1-naphtyl)ethyl group on the nitrogen atom in 69 and 13% yields, respectively, together with compound **(13)** (8%) (Scheme 3). Stereochemistries 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)**)⁴ 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).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

1. For reviews, see: (a) H. Ishibashi and M. Ikeda, *J. Synth. Org. Chem. Jpn.*, 1989, 47, 330. (b) H. Ishibashi and M. Ikeda, *Rev. Heteroatom Chem.*, 1992, 7, 191.
2. H. Ishibashi, T. Nakaharu, M. Nishimura, A. Nishikawa, C. Kameoka, and M. Ikeda, *Tetrahedron*, 1995, 51, 2929.
3. A. Mooradian, C. J. Cavallito, A. J. Bergman, E. J. Lawson, and C. M. Suter, *J. Am. Chem. Soc.*, 1949, 71, 3372.
4. W. H. Pearson, D. P. Szura, and M. J. Postich, *J. Am. Chem. Soc.*, 1992, 114, 1329.
5. A. Padwa, M. A. Brodney, M. Dimitroff, B. Liu, and T. Wu, *J. Org. Chem.*, 2001, 66, 3119.