A NOVEL SYNTHESIS OF 3-[(METHYLAMINO)METHYL]-6-OXO-3,4,5,6-TETRAHYDRO-1*H*-AZEPINO[5,4,3-*cd*]INDOLE

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Abstract: The title compound has been synthesized previously at Solvay Pharmaceuticals, Inc. and shown to be a potent CNS agent. Starting with the same substrate a new, greatly improved synthetic route to this product is described.

The ergot alkaloides are comprised of an indole subunit that is bridged at positions 3 and 4 by a functionalized chain. This class of compounds exhibits a broad spectrum of biological properties. The hallucinogen activity of lysergic acid diethylamide (LSD) is well known, and many ergots are currently in clinical use (1). These include ergonovine and methylergonovine (postpartum hemorrhage), nicergoline (hypertension), bromocriptine (prolactin disorders), and methylsergide (migraine). In addition, the synthetic compound **9** (Scheme 1) shows promise for development as an antimigraine drug (2). Starting with methyl indole-4-carboxylate (**4**) the racemic compound **9** was synthesized in an overall yield of 7%, and the biologically active 3R(+)-enantiomer was obtained by using crystallization of diastereomeric salts.

In this paper we report a new synthetic route which, starting with the same substrate **4**, furnishes racemic compound **9** in an overall yield of 21% (Scheme 1). The key step is a conjugate addition reaction of the apparent organometallic reagent **3** with a nitrovinyl function of the intermediate indole derivative **5**. The generation of **3** in solution is summarized as follows. The substrate **1** is a known compound (3) that can efficiently be prepared by the reaction of di-*tert*-butyl dicarbonate with dimethylamine or dimethylammonium chloride in the presence of triethylamine. We found that the latter method is experimentally simpler and produces the desired product **1** in a greater yield. Compound **1** may also be prepared from commercially available dimethylcarbamoyl chloride (4) Me_2NCOCl or phenyl chloroformate (3) ClCOOPh. The conversion of **1** into a tin derivative **2**, a new compound, was accomplished by lithiation of **1** followed by treatment of the resultant lithium derivative with tributyltin chloride. Analogous transformations have been reported for tert-butoxycarbonyl (BOC) derivatives for cyclic secondary amines (5-7). The organotin compound **2** was efficiently purified by a simple flash chromatography on silica gel eluting with hexanes, and the resulting colorless oil was used to generate the apparent reagent **3** as shown in Scheme 1. This generation of **3** in solution was based on the analyses of several transmetallation reactions reported in the literature (7-10). In comparison to the conjugate addition reactions of other organometallic reagents derived from **1**, the reaction of **3** with **5** can be conducted under experimentally acceptable conditions at –70 °C and is more efficient. For example, the treatment of **1** with *s*-BuLi followed by a reaction of the resultant lithium reagent with **5** at –100 °C gave the conjugate addition product **6** in a low yield, and the efficiency was even lower at –78 °C. An indirect generation of this lithium reagent by a sequence of the lithiation of **1**, preparation and

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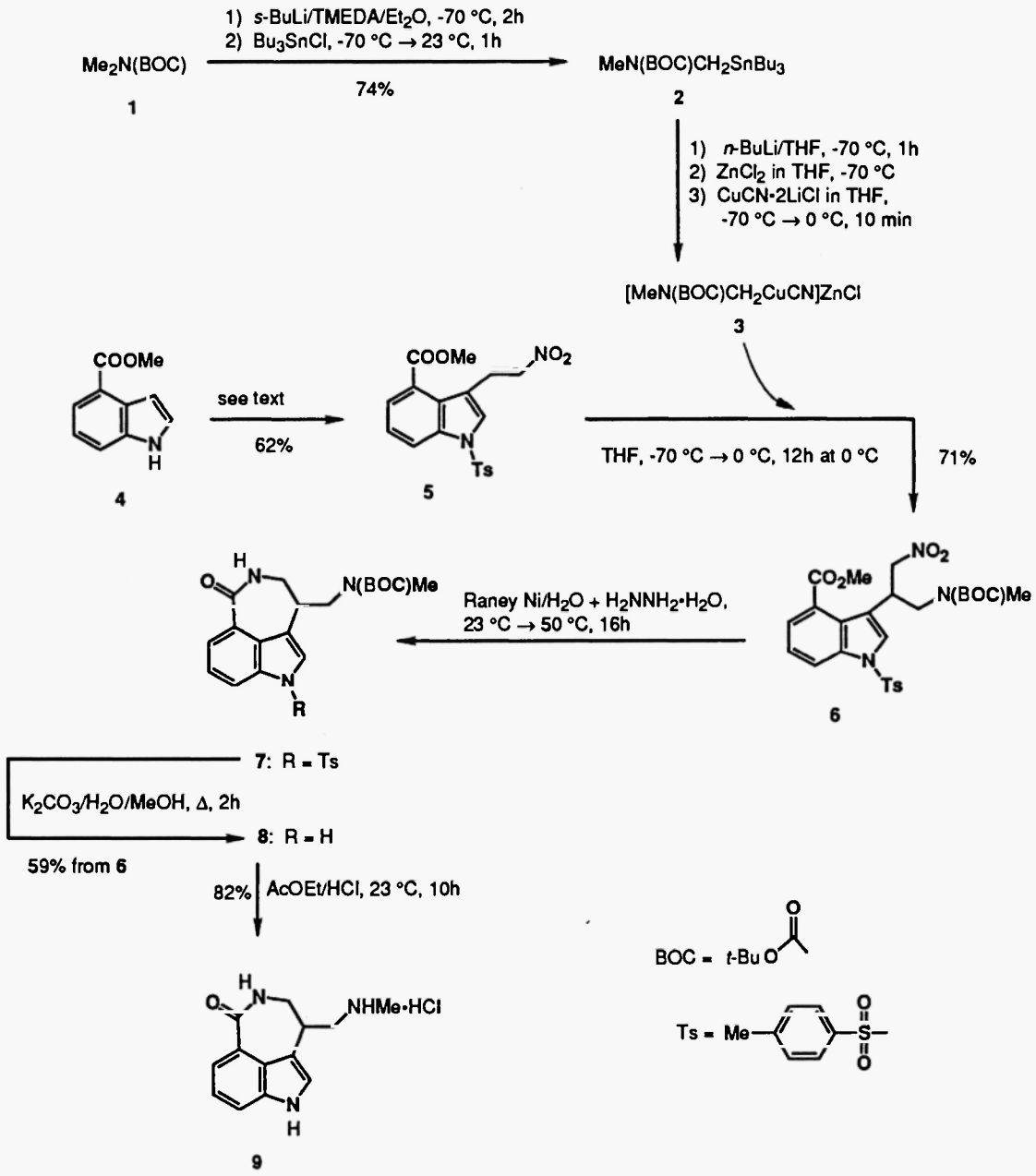
Scheme 1


1) s-BuLi/TMEDA/Et2O, -70 °C, 2h
2) Bu3SnCl, -70 °C → 23 °C, 1h
Me2N(BOC)
1
74%
MeN(BOC)CH2SnBu3
2
1) n-BuLi/THF, -70 °C, 1h
2) ZnCl2 in THF, -70 °C
3) CuCN·2LiCl in THF,
-70 °C → 0 °C, 10 min
[MeN(BOC)CH2CuCN]ZnCl
3
COOMe
see text
62%
COOMe
NO2
Ts
4
5
THF, -70 °C → 0 °C, 12h at 0 °C
71%
CO2Me
NO2
N(BOC)Me
Ts
6
Raney Ni/H2O + H2NNH2·H2O,
23 °C → 50 °C, 16h
N(BOC)Me
R
7: R = Ts
K2CO3/H2O/MeOH, Δ, 2h
8: R = H
59% from 6
82%
AcOEt/HCl, 23 °C, 10h
NHMe·HCl
9
BOC = t-Bu O
Ts = Me

purification of a tin derivative **2**, transmetallation of **2**, followed by the addition reaction of the resultant lithium reagent with **5** at –100 °C gave the adduct **6** in a respectable yield of 60%. Again, increasing the temperature to –78 °C resulted in a sharp decrease of the efficiency of the last addition step. The addition reactions of Grignard reagents generated indirectly from **1** (11) were also relatively inefficient.

We wish also to comment on the preparation of the known indole derivative **5** which is a substrate for the conjugate addition reaction. The treatment of **4** with 1-dimethylamino-2-nitroethylene (12) followed by tosylation (13) gave **5** in an overall yield of 62%. However, the preparation of 1-dimethylamino-2-nitroethylene is difficult (14) and the commercially available reagent (Lancaster) is quite expensive. A useful modification of the synthesis of **5** involves formylation (15) of **4** followed by condensation of the resultant aldehyde with nitromethane in the presence of ammonium acetate (16) and then tosylation of the product. In this work the two approaches to **5** were examined and found to give similar results.

Copper-zinc reagents that are analogous to **3** have been shown to undergo conjugate addition with nitroalkenes (10). In our hands the conjugate addition reaction of **3** with **5** furnished the desired product **6** in a 71% yield after purification by flash chromatography (silica gel; hexanes/AcOEt, 7:3). The final compound 9 was obtained by reductive cyclization of **6** followed by detosylation and removal of the BOC group from the resulting intermediate products.

Many methods for reduction of nitroalkanes to alkylamines are known (17), and some of them have been successfully used in reductive cyclizations (2, 18, 19) that are similar to the conversion of **6** into **7**. On the other hand, the high sensitivity of the BOC group to hydrolysis limited the choice of reducing agents to those which work under neutral or mildly basic conditions. Hydrogenation of **6** in the presence of PtO_2 (19, 20) was slow at 23 °C under an atmospheric pressure of hydrogen, and it always gave **7** in a mixture with the starting material **6**. An attempted reduction of **6** with $NaBH_4$ in the presence of 10% Pd/C as a catalyst (21) was unsuccessful. Finally, it was found that the treatment of **6** with hydrazine hydrate in the presence of Raney nickel (2, 22) provides an excellent synthetic route to **7**. This reaction was accomplished by partial detosylation to give a mixture of **7** and **8**. This mixture was then subjected to a classical detosylation of indole derivatives under basic conditions (23, 24). The BOC group of the resultant compound 8 can easily be removed under a variety of conditions (25). In this work a hydrochloride salt 9•HCl was obtained directly by treatment (26) of 8 with HCl. The product 9•HCl was crystallized from EtOH/MeOH (1:1). The ^{1}H NMR and IR spectra of 9•HCl thus prepared and the spectra of the hydrochloride obtained by the previous method (2) were virtually identical. The purity of 9 was found to be greater than 99.9% by using an HPLC analysis on a C-18 column with various solvent systems (27).

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(27) Compound, mp: **2**, an oil; **6**, 61-64 °C; **8**, 139-142 °C; 9•HCl, >300 °C. Full experimental details will be published in due course.

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