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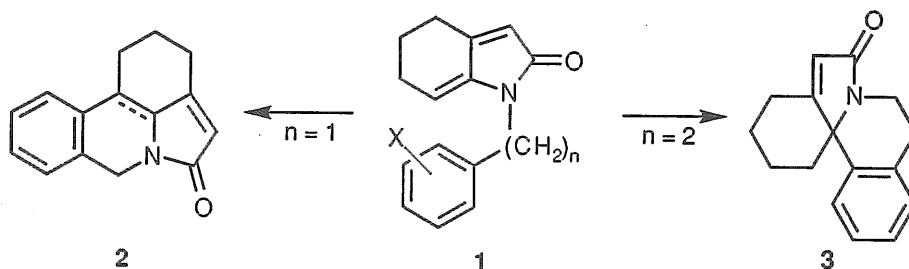
NEW ENTRY TO 1,4,5,6-TETRAHYDRO-2H-INDOL-2-ONES USING A CATIONIC 5-ENDO-TRIGONAL CYCLIZATION ONTO ENAMIDES[†]

Hiroyuki Ishibashi,^{1*} Masahiro Higuchi,¹ Hiromi Masuko,² Kazuya Kodama,² and Masazumi Ikeda²

¹Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan and ²Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

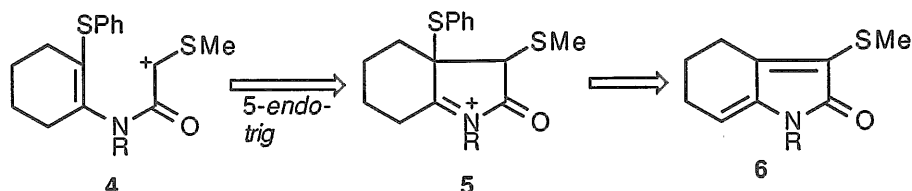
Abstract — A new method for the synthesis of 1,4,5,6-tetrahydro-2H-indol-2-ones by means of 5-endo-trigonal cyclization of α -thiocarbocations generated from sulfoxide (12) and α -chlorosulfide (17) is described. The sulfoxide (12), upon heating with TsOH, gave 14, which eliminated benzenethiol to give tetrahydroindolone (15). By contrast, the chlorosulfide (17), upon treatment with TiCl₄, gave the desulfurized tetrahydroindolone (18). The mechanism for the formation of 18 is also discussed.

1,4,5,6-Tetrahydro-2H-indol-2-ones are useful intermediates for the synthesis of several types of *Amaryllidaceae* alkaloids. For examples, the *N*-(arylmethyl) derivatives (1: $n = 1$) having a bromine or iodine atom on the *ortho* position of the aromatic ring, when subjected to the Heck reaction conditions or to the Bu₃SnH-mediated radical cyclization conditions, give the lycorine skeletons (2),¹ and the *N*-(2-arylethyl) congeners (1: $n = 2$) having electron-donating 3,4-dimethoxy groups on the aromatic ring, when treated with organic acids, provide the erythrinan skeletons (3).^{1a, 2} Herein we report a new entry to 1,4,5,6-tetrahydro-2H-indol-2-ones using a 5-endo-trigonal cyclization of α -thiocarbocations³ as a key step.

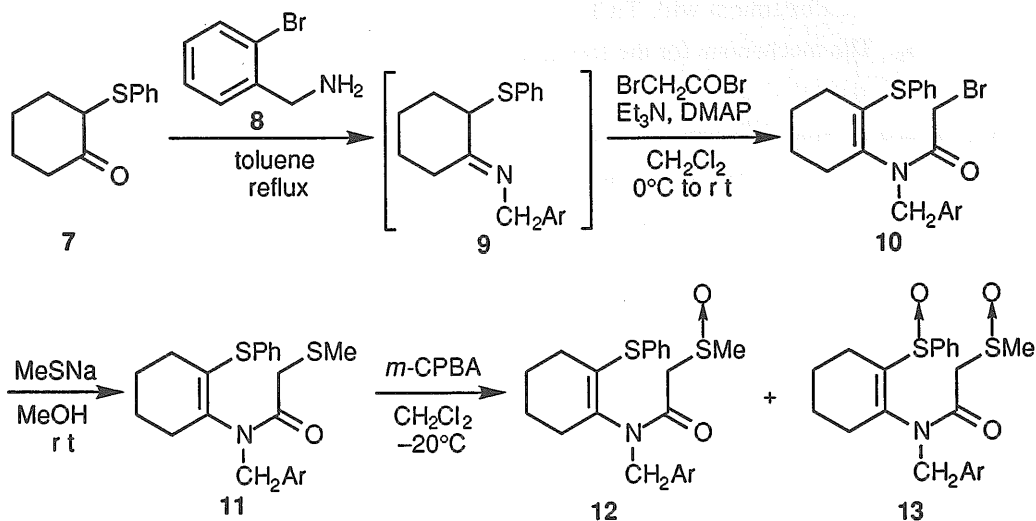


[†] This paper is dedicated to the memory of Professor Emeritus Shun-ichi Yamada (University of Tokyo).

Our approach to the synthesis of tetrahydroindolones is outlined in the following Scheme. The key step is the *5-endo-trigonal* cyclization of the α -thiocarbocations (4) which provides the acyliminium ion intermediates (5). This step is then followed by an elimination of benzenethiol to give 1,4,5,6-tetrahydro-3-methylthio-2*H*-indol-2-ones (6). The α -thiocarbocations (4) can be easily derived from the corresponding sulfoxides or α -chlorosulfides.



We initiated our investigation by examining the cyclization of the sulfoxide (12) under the Pummerer rearrangement conditions. The synthesis of 12 was begun by condensation of 2-(phenylthio)cyclohexanone (7) with *o*-bromobenzylamine (8) followed by *N*-acylation of the resulting imine (9) with bromoacetyl bromide to give the bromoacetamide (10) in 70% yield (based on 7). Treatment of 10 with sodium methylmercaptide gave, in 80% yield, the sulfide (11), which was oxidized by slow addition of *m*-CPBA to give the sulfoxide (12) in 60% yield along with the disulfoxide (13) (21% yield).

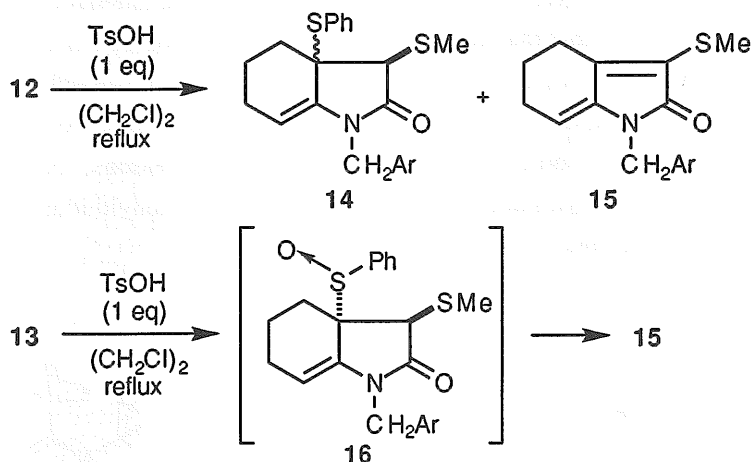


Ar = *o*-Bromophenyl

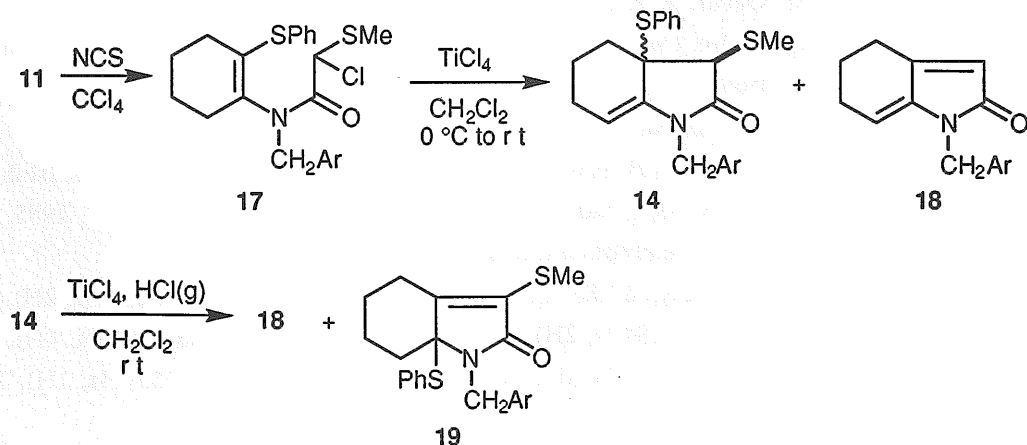
Heating the sulfoxide (12) in boiling 1,2-dichloroethane in the presence of a stoichiometric amount of TsOH for 5 min gave the hexahydroindolone (14) and the tetrahydroindolone (15)⁴ in 42 and 36% yields, respectively. The ¹H-NMR spectrum of 14 showed it to be a mixture of two diastereoisomers (*cis* and *trans* relationships between the phenylthio and the methylthio groups) in a ratio of *ca.* 2:1. The formation of 15 appears to be the result of an acid-catalyzed elimination of benzenethiol from the initial cyclization

product (14). Indeed, when the period of heating of 12 was extended up to 30 min, the tetrahydroindolone (15) was obtained as a sole product in 65% yield.

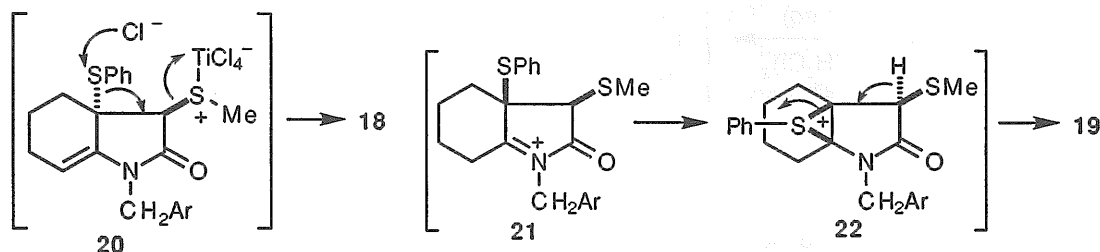
On the other hand, heating the disulfoxide (13) in the presence of TsOH (1 equiv.) in boiling 1,2-dichloroethane for 5 min gave only the tetrahydroindolone (15) in 60% yield. A bulky phenylsulfinyl group of the initial cyclization product (16) might be in positions *trans* to the adjacent methylthio group, and hence a thermal elimination of benzenesulfenic acid appeared to occur rapidly to give 15.



Our attention was next turned to the Lewis acid-promoted cyclization of the chlorosulfide (17), which was prepared (quant.) from the corresponding sulfide (11) by treating with NCS. When the chlorosulfide (17) was exposed to a stoichiometric amount of TiCl_4 in CH_2Cl_2 at room temperature for 1 h, two indolone derivatives were obtained. One of them was the compound (14) (30% yield: a *ca.* 5:1 mixture of two diastereoisomers) which was identical to that obtained from 12. Interestingly, another one was proven to be an unexpected product (18) (34% yield). The $^1\text{H-NMR}$ spectrum of 18 exhibited the signals at δ 5.51 (dt, $J = 1.7, 4.7$ Hz) and δ 5.85 (br s) due to the olefinic protons at the C7 and C3 positions, respectively.



In order to see the mechanism for the formation of **18** (probably from **14**), several experimentations were carried out with TiCl_4 and HCl gas, the latter of which might arise during the formation of **14** from **17**. When compound (**14**) was treated either with a stoichiometric amount of TiCl_4 or with HCl gas in CH_2Cl_2 at room temperature, only the starting material was recovered unchanged. However, treatment of **14** with TiCl_4 in the presence of HCl gas gave **18** in 29% yield together with an additional product (**19**) (30% yield). The structure of **19** was deduced from its $^1\text{H-NMR}$ spectrum⁴ and its chemical transformation: heating **19** with TsOH in benzene afforded **15** in 60% yield. One possible rationalization for the formation of **18** is based on the assumption that the methylthio group at the C3 position of the *trans*-isomer of **14** coordinates to TiCl_4 to give the sulfonium ion intermediate (**20**), and then the *anti*-elimination occurs by an attack of the chloride ion (derived from HCl) on the phenylthio group to give **18**. This type of reaction, however, is inapplicable to the *cis*-isomer of **14** for the stereoelectronic reasons, and hence the *cis*-isomer is merely protonated to give the acyliminium intermediate (**21**). The phenylthio group of **21** undergoes 1,2-migration through the episulfonium salt **22** to give the observed **19**.⁵



Thus we revealed that the 5-*endo-trigonal* cyclization of α -thiocarbocations generated from the sulfoxide (**12**) and the chlorosulfide (**17**) provided a new method for the synthesis of a different type of 1,4,5,6-tetrahydro-2*H*-indol-2-ones such as **15** and **18**. An application of the method to the synthesis of lycorine and erythrina alkaloids will be reported in due course.

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- $^1\text{H-NMR}$ for **15** (300 MHz, CDCl_3): δ 1.83 (quint, $J = 6.1$ Hz, 2H), 2.28 (q, $J = 6.1$ Hz, 2H), 2.55 (s, 3H), 2.66 (t, $J = 6.5$ Hz, 2H), 4.84 (s, 2H), 6.46 (t, $J = 4.7$ Hz, 2H), 6.95-7.55 (m, 4H). For **19**: δ 1.2-3.0 (m, 8H), 2.53 (s, 3H), 4.71 (d, $J = 15.6$ Hz, 1H), 4.98 (d, $J = 15.6$ Hz, 1H), 7.05-7.60 (m, 9H).
- It seems reasonable to assume that the reaction of **17** giving **14** and **18** provides also the compound **19**, but no corroborating evidence for this assumption is offered at the moment.

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