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

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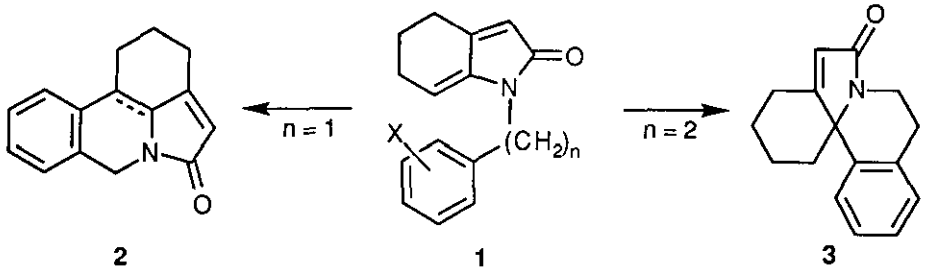
Abstract —— A new method for the synthesis of 1,4,5,6-tetrahydro-2*H*-indol-2-ones by means of 5-*endo-trigonal* cyclization of α-thiocarbocations generated from sulfoxide (**12**) and α-chlorosulfide (**17**) is described. The sulfoxide (**12**), upon heating with TsOH, gave **14**, which eliminated benzenethiol to give tetrahydroindolone (**15**). By contrast, the chlorosulfide (**17**), upon treatment with $TiCl_4$, gave the desulfurized tetrahydroindolone (**18**). The mechanism for the formation of **18** is also discussed.

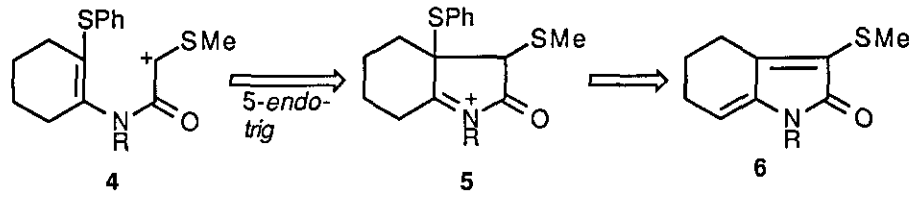
1,4,5,6-Tetrahydro-2*H*-indol-2-ones are useful intermediates for the synthesis of several types of *Amaryllidaceae* alkaloids. For examples, the *N*-(arylmethyl) derivatives (**1**: n = 1) having a bromine or iodine atom on the *ortho* position of the aromatic ring, when subjected to the Heck reaction conditions or to the Bu_3SnH-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-2*H*-indol-2-ones using a 5-*endo-trigonal* cyclization of α-thiocarbocations[3] as a key step.



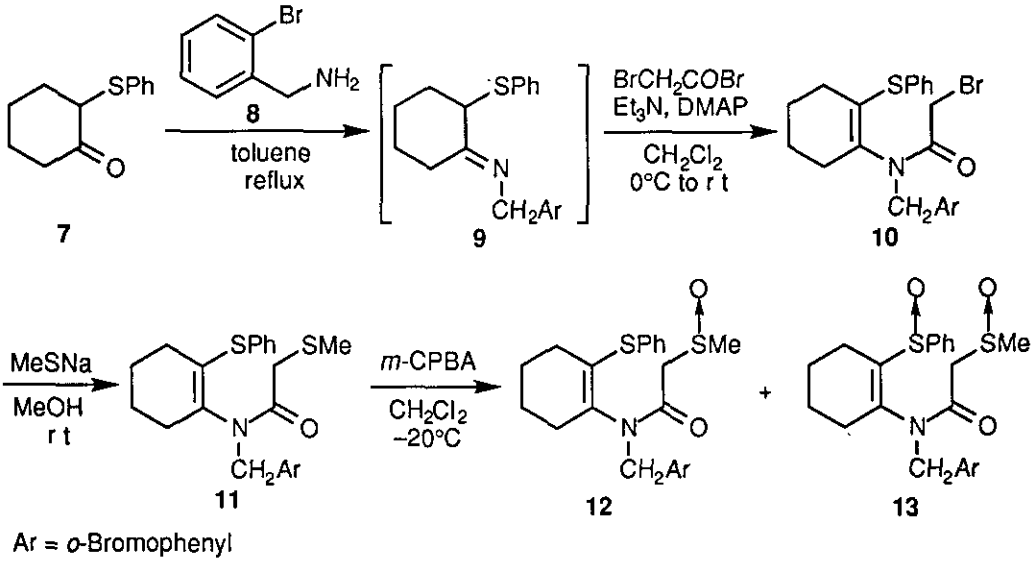
2 **1** **3**

† This paper is dedicated to the memory of Professor Emeritus Shun-ichi Yamada (Univeristy 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.



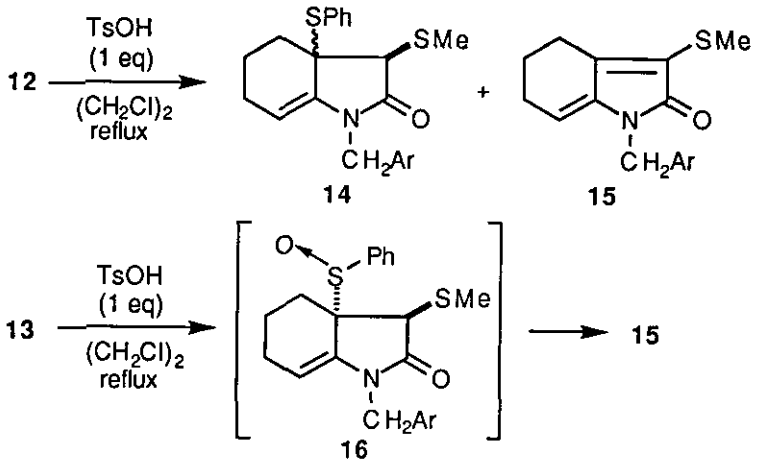
We initiated our investigation by examining the cyclization of the sulfoxide (**12**) under the Pummerer rearrangement conditions. The synthesis of **12** was begun by condensation of 2-(phenylthio)-cyclohexanone (**7**) with *o*-bromobenzylamine (**8**) followed by *N*-acylation of the resulting imine (**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).



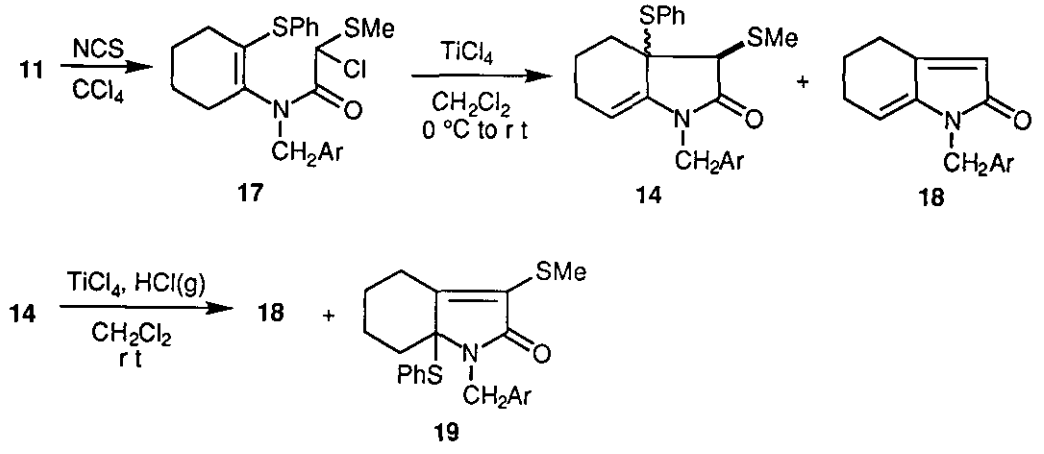
Heating the sulfoxide (**12**) in boiling 1,2-dichloroethane in the presence of a stoichiometric amount of TsOH for 5 min gave the hexahydroindolone (**14**) and the tetrahydroindolone (**15**)[4] in 42 and 36% yields, respectively. The ^{1}H-NMR spectrum of **14** showed it to be a mixture of two diastereoisomers (*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.

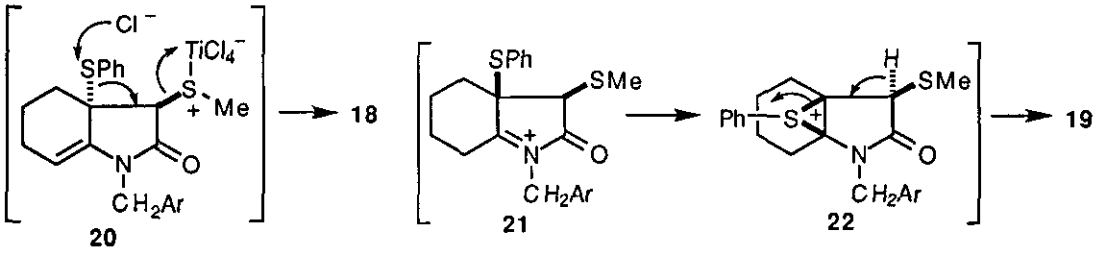
On the other hand, heating the disulfoxide (**13**) in the presence of TsOH (1 equiv.) in boiling 1,2-dichloroethane for 5 min gave only the tetrahydroindolone (**15**) in 60% yield. A bulky phenylsulfinyl group of the initial cyclization product (**16**) might be in positions *trans* to the adjacent 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}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}H-NMR spectrum[4] 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.

REFERENCES AND NOTES

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4. ^{1}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).
5. 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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