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A New, General Entry to 4-Substituted Indoles. Synthesis of (*S*)-(-)-Pindolol and (±)-Chuangxinmycin

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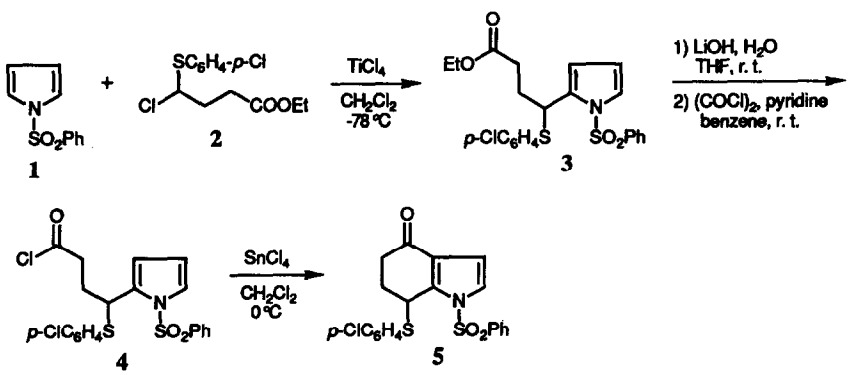
Summary: A new method for synthesis of 4-substituted indoles has been developed by using the 7-arylthio-6,7-dihydroindol-4(5*H*)one **5** as a common intermediate. The method was applied to the synthesis of (*S*)-(-)-pindolol (**11**) and (±)-chuangxinmycin (**16**).

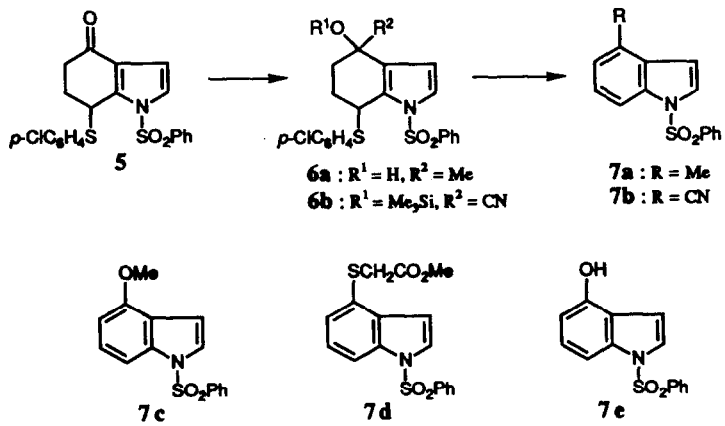
The synthesis of 4-substituted indoles has attracted considerable attention due largely to their importance as building blocks for many therapeutically usuful materials.[1] Herein we report a new, general entry to this class of compounds by using the 7-arylthio-6,7-dihydroindol-4(5*H*)one **5** as a common intermediate. Applications of the method to the synthesis of (*S*)-(-)-pindolol (**11**) and (±)-chuangxinmycin (**16**) are also presented.

The key indolone **5** was prepared as follows. A mixture of equimolar amounts of *N*-phenylsulfonylpyrrole (**1**) and the α-chlorosulfide **2**[2] was treated with 4 equiv of $TiCl_4$ in CH_2Cl_2 at -78 °C to give the alkylation product **3** (an oil) in 65% yield. The ester group was then selectively hydrolyzed with LiOH in aqueous tetrahydrofuran at room temperature and the resulting carboxylic acid was treated with oxalyl chloride to afford the acid chloride **4** in quantitative yield. The cyclization of **4** was effected with $SnCl_4$ in CH_2Cl_2 at 0 °C to give the indolone **5** (mp 108-110 °C) in 86% yield.

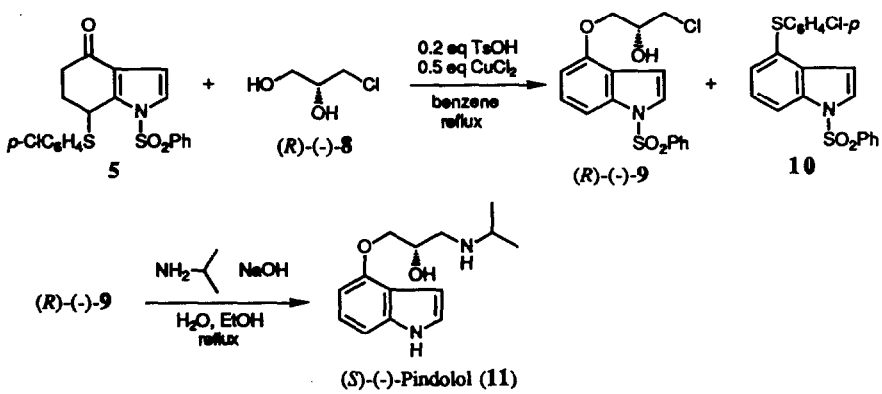


Transformation of **5** to the 4-substituted indoles was readily accomplished as follows. Thus, Grignard coupling of **5** with methylmagnesium iodide in refluxing tetrahydrofuran followed by treatment of the resulting carbinol **6a** with *p*-toluenesulfonic acid (TsOH) afforded the 4-methylindole **7a** (mp 92-92.5 °C) in 86% yield (based on **5**). Reaction of **5** with cyanotrimethylsilane in the presence of ZnI_2 gave quantitatively the *O*-TMS cyanohydrin **6b**, which was then treated with $POCl_3$ in pyridine[3] at 60 °C to give the 4-cyanoindole **7b** (mp

175-176 °C) in 63% yield. A simple heating of a methanol solution of **5** in the presence of TsOH gave the 4-methoxyindole **7c** (mp 79-80 °C) in 87% yield. Treatment of **5** with methyl thioglycolate (3 equiv) in benzene in the presence of boron trifluoride etherate afforded the sulfur substituted indole **7d** (mp 135-136 °C) in 89% yield. On the other hand, oxidation of **5** with *m*-CPBA followed by heating of the resultant sulfoxide in benzene gave the 4-hydroxyindole **7e** (mp 130-131 °C) in 84% yield (based on **5**). Thus, a variety of indoles substituted at the 4-position with carbon, oxygen, and sulfur atoms were obtained in high yields from the indolone **5**.



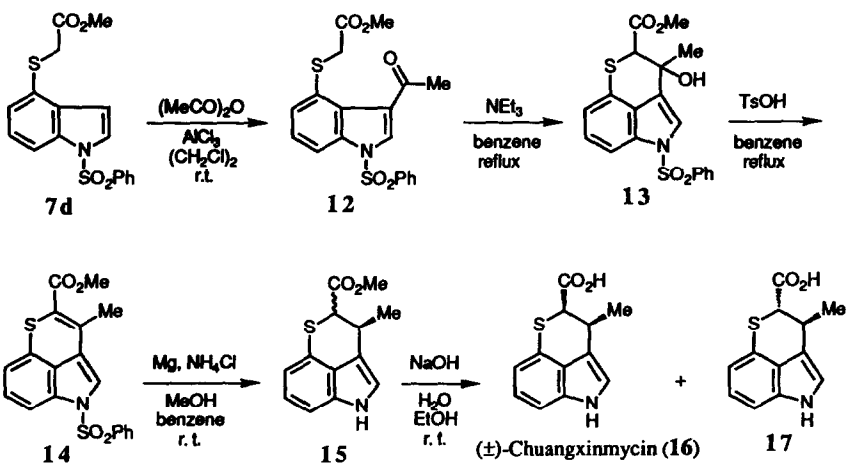
(±)-Pindolol is one of the most effective β-adrenergic agents, widely used for the treatment of tachycardia and hypertension. As an application of the above method, we first examined a synthesis of (*S*)-(-)-pindolol (**11**) which was shown to be pharmacologically more active than the racemic mixture of pindolol.[4] Treatment of **5** with (*R*)-(-)-3-chloro-1,2-propanediol (**8**) (3 equiv) in boiling benzene in the presence of TsOH (0.2



equiv) for 24 h gave the 4-alkoxyindole **9** (an oil) in only 15% yield, along with several by-products including the 4-arylthioindole **10**. The undesired **10** might arise from the reaction of **5** with 4-chlorobenzenethiol eliminated during the course of the formation of **9**. We found, however, that a similar reaction carried out by adding $CuCl_2$ to remove the thiol thus formed, took place smoothly within 1 h to give the desired compound **9** in 81% yield, along with **10** (6%). These results, together with the fact that $CuCl_2$ alone gave no compound **9**, suggest that $CuCl_2$ acts not only as a thiol scavenger, but also as a catalyst for the reaction. The product **9** was then heated with a large excess of isopropylamine in the presence of NaOH in aqueous ethanol to give, with concomitant deprotection of the *N*-sulfonyl group, (*S*)-(-)-pindolol (**11**) in 85% yield: mp 94-95 °C (from benzene), $[\alpha]_D^{23}$ -4.9° (c 1, MeOH) [lit.[5] mp 95-97 °C, $[\alpha]_D^{16}$ -5.1° (c 1, MeOH)].

Pindolol has been usually prepared *via* the reaction of 4-hydroxyindole with epichlorohydrin. Application of the method to the synthesis of (*S*)-(-)-pindolol by using chiral (-)-epichlorohydrin, however, brings about decrease in optical purity as a result of a partial attack of the aryloxy anion on the carbon α to the chlorine atom of epichlorohydrin in competition with epoxide ring-opening.[6] In the present method, the alcohol **8** attacks on the carbonyl group of **5** with complete retention of its optical activity, and hence gives optically pure (*S*)-(-)-pindolol (**11**).

Chuangxinmycin (**16**), an antibiotic isolated from *Actinoplanes tsinanensis*, is a unique indole derivative bearing a sulfur substituent at the 4-position.[7] This compound has been known to be active against a number of Gram-negative and Gram-positive bacteria, and particularly effective for the treatment of *Escherichia coli* infections.[7] Our attention was next turned to the synthesis of chuangxinmycin starting from the indole **7d**.



Friedel-Crafts acylation of **7d** with acetic anhydride in the presence of $AlCl_3$ gave the 3-acetyl derivative **12** (an oil) in 93% yield. Treatment of **12** with piperidine and acetic acid in boiling benzene afforded the Knoevenagel condensation product **14** (mp 172-173 °C) in 54% yield. Alternatively, the compound **14** was obtained in excellent yield by the following two steps procedure. Thus, treatment of **12** with triethylamine in boiling benzene afforded, in 97% yield, the addition product **13** as a mixture of two stereoisomers (*ca.* 4:3), which was then heated with TsOH to give **14** in 98% yield. With **14** in hand, we next examined a deprotection

of the *N*-sulfonyl group with Mg / methanol in the presence of NH_4Cl.[8] This, fortunately, brought about also a reduction of the olefinic bond of the vinyl sulfide moiety to give, in 48% yield, a mixture of chuangxinmycin methyl ester **15a**[9, 10] and its *trans*-isomer **15b**[10], whose ratio was estimated to be *ca.* 2:3 by ^{1}H-NMR spectroscopy. The mixture of **15a,b** was then hydrolyzed with NaOH to give a mixture of chuangxinmycin (**16**) and its *trans*-isomer **17** (2:3) in quantitative yield. As reported,[9] the isolation of **16** was easily accomplished by fractional crystallization of the mixture from CH_2Cl_2/petroleum ether to give pure (±)-chuangxinmycin: mp 186-187 °C (lit. mp 181-184,[11] 145-145.5,[9] and 190-191[12] °C).

In conclusion, the results described herein offer a general procedure for the synthesis of indoles substituted at the 4-position with carbon, oxygen as well as sulfur atoms. Thus, the method provides an efficient synthesis of (*S*)-(-)-pindolol and (±)-chuangxinmycin.

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References and Notes

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