AN EASY SYNTHESIS OF 4-ALKYLTHIOINDOLES

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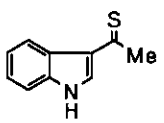
Abstract —— 4-Alkylthio-indoles 7 and 9 were synthesized from 4-thioxo-4,5,6,7-tetrahydroindole (5) in one pot reaction.

Recently, we found that the alkylation of 3-thioacetylindole (1) afforded sulfur substituted 3-vinylindole 2, and the resulted compound 2 undergoes cycloaddition reaction with various dienophiles to give functionallized carbazoles.[1] We also found that such behavior is common in thioenaminones.[2] This paper describes an application of such character of thioenaminone for the synthesis of 4-alkylthio-indoles in connection with construction of biological active substances chuangxinmycin (3)[3] and N,N-dimethyl-4-methylthiotryptamine.[4]



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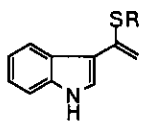

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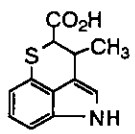

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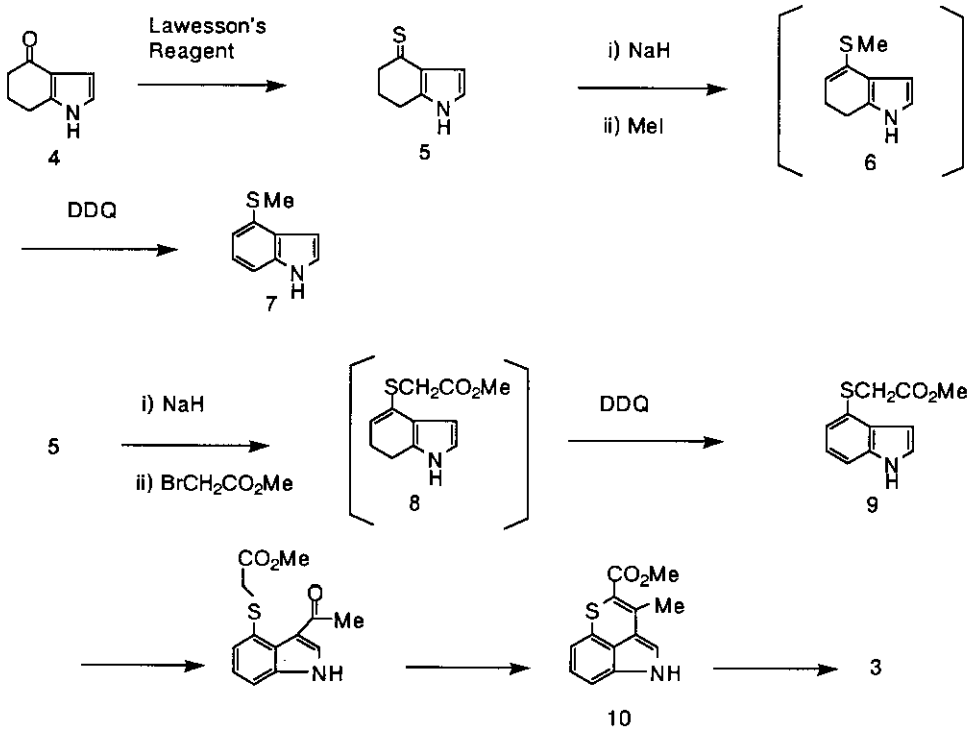
Starting material 5 was synthesized by the reaction of 4-oxo-4,5,6,7-tetrahydroindole (4), prepared from 1,3-cyclohexadione and aminoacetaldehyde dimethyl acetal,[5] with the Lawesson's reagent, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, in 98% yield. Reaction of the sodium salt of 5 with methyl iodide followed by dehydrogenation reaction of an intermediate 6 with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) afforded 4-(methylthio)-indole (7)[6] in 67% yield, successfully.

Dedicated to late Prof. Tetsuji Kametani for his memories.

Similarly, reaction of the sodium salt of 5 with methyl bromoacetate followed by treatment of an intermediate 8 with DDQ afforded methyl (4-indolylthio)-acetate (9)[7] in 57% yield. According to Kozikowski's method[7] and Matsumoto's method[6], the ester 9 can be easily transformed to chuangxinmycin (3) through dehydrochuangxinmycin (10). Although several methods for the synthesis of 4-mercaptoindoles have been reported,[8] this procedure may provide an easy method for the synthesis 4-alkylthioindoles.



EXPERIMENTAL

All melting points are uncorrected. Infrared (ir) spectra were recorded with a Hitachi 260-10 spectrophotometer, proton nuclear magnetic resonance spectra (^{1}H-nmr) with a Varian T-60 spectrometer (with tetramethylsilane as an internal standard in $CDCl_3$) and mass spectra (ms) with a JEOL JMS-d 300 spectrometer. Wako Silica Gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254} were used for column chromatography and thin layer chromatography, respectively.

4-Thioxo-4,5,6,7-tetrahydroindole (5) To a solution of 4-oxo-4,5,6,7-tetrahydroindole (4)[5] (338 mg; 2.5 mmol) in THF (30 ml), the Lawesson's reagent (1.01 g; 2.5 mmol) was added slowly with stirring at room temperature. After 15

min, the reaction mixture was poured into saturated aqueous $NaHCO_3$, and then the whole was extracted with ether. The organic layer was washed with brine, then dried over Na_2SO_4 and concentrated. The residue was recrystallized with ether-hexane to yield 369 mg (98%) of 5 as red needles. mp 135-136°C. Ir ($CHCl_3$) cm^{-1}: 3450. ^{1}H-Nmr ($CDCl_3$) δ: 2.0-2.3 (2H, m, $-CH_2-$), 2.7-3.1 (4H, m, $-CH_2-$ and $-CH_2-C=S$), 6.6-6.8 (2H, m, C-2H and C-3H), 8.7 (1H, br, NH). MS m/z: Calcd for $C_8H_9NS(M^+)$: 151.0453. Found: 151.0442.

4-(Methylthio)indole (7) To a suspension of NaH (60% in oil; 69 mg; 1.73 mmol) in dry THF (10 ml), a solution of 5 (217 mg; 1.44 mmol) in THF (1 ml) was added with stirring at -20°C under a nitrogen atmosphere. After 15 min, a solution of methyl iodide (409 mg; 2.88 mmol) in THF (1 ml) was added to the mixture and the whole was stirred for 20 min under the same temperature and atmosphere. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and then extracted with benzene (30 ml). The organic layer was washed with brine, and then dried over Na_2SO_4. To this organic layer, DDQ (327 mg; 1.44 mmol) was added, and the mixture was stirred at room temperature for 30 min. The solvent was removed under the reduced pressure. Chloroform was added to the residue, the insoluble material was filtered off, and then the mother liquor was concentrated. The residue was subjected to silica gel column chromatography to give 156 mg (67%) of 7 as colorless needles (petroleum ether), mp 44-45°C,[4] from the chloroform-hexane (1:1) eluate.

Methyl (4-Indolylthio)acetate (9) To a suspension of NaH (60% in oil; 96 mg; 2.4 mmol) in THF (13 ml), a solution of 5 (302 mg; 2 mmol) in THF (1 ml) was added with stirring at -20°C under a nitrogen atmosphere for 15 min. To the mixture, a solution of methyl bromoacetate (367 mg; 2.4 mmol) in THF (1 ml) was added and the whole was stirred at the same temperature and atmosphere for 1 h. Resulted mixture was poured into saturated aqueous $NaHCO_3$, and then extracted with benzene (40 ml). The organic layer was washed with brine, and then dried over Na_2SO_4. To the organic layer, DDQ (454 mg; 2 mmol) was added and the mixture was stirred at room temperature for 30 min. The solvent was removed under the reduced pressure. The residue was treated with chloroform, and the insoluble matereial was filtered off. The chloroform solution was concentrated and the residue was subjected to silica gel column chromatography to give 250 mg (57%) of 9 as colorless crystals (benzene-petroleum ether), mp 83-85°C,[6] from the chloroform eluate.

REFERENCES

1) M. Murase, T. Hosaka, T. Koike, and S. Tobinaga, Chem. Pharm. Bull., 1989, 37, 1999.

2) M. Murase, T. Hosaka, S. Yoshida, and S. Tobinaga, unpublished results.

3) H. -T. Liang, H. -D, Hsu, C. -P. Chang, H. -E. Ku, and W. -S Wang, Hua Hsueh Hsueh Pao, 1976, 34, 129 (Chem. Abstr., 1977, 87, 165948z); L. Wang and T. Qi, Kangshengsu, 1986, 11, 338 (Chem. Abstr., 1986, 105, 168773q).

4) T. B. Kline, F. Benington, R. D. Morin, and M. Beaton, J. Med. Chem., 1982, 25, 908.

5) J. M. Bobbitt, C. L. Kulkarni, C. P. Dutta, H. Kofod, and K. N. Chiong, J. Org. Chem., 1978, 43, 3541.

6) A. P. Kozikowski, M. N. Greco, and J. P. Springer, J. Am. Chem. Soc., 1982, 104, 7622.

7) M. Matsumoto and N. Watanabe, Heterocycles, 1987, 26, 913.

8) E. Piers, V. B. Haarstad, R. J. Cushley, and R. K. Brown, Can. J. Chem., 1962, 40, 511; M. Murase, T. Koike, Y. Moriya, and S. Tobinaga, Chem. Pharm. Bull., 1987, 35, 2656; M. Somei, Yuki Gosei Kagaku Kyokai Shi, 1982, 40, 387.

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