SYNTHESIS OF 4-(4-INDOLYL)-3-OXOBUTANOIC ACID DERIVATIVES FROM 5-HALO-4-OXO-4,5,6,7-TETRAHYDROINDOLES

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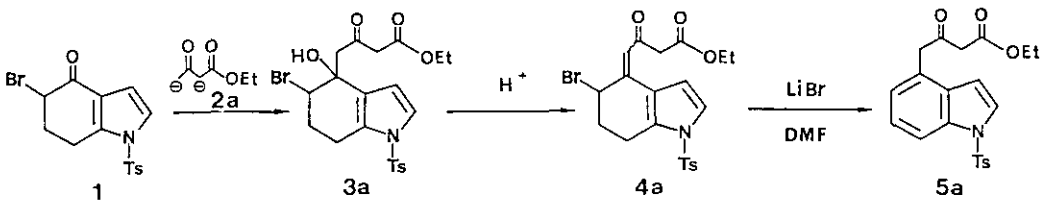
Abstract——The reaction of 5-halo-4-oxo-4,5,6,7-tetrahydroindoles with dianion of acetoacetic acid esters or N,N-dimethylamide followed by dehydration and dehydrohalogenation gave 4-(4-indolyl)-3-oxobutanoic acid derivatives. 4-Acetonylindoles with benzoyl and p-toluenesulfonyl at γ-position of the side chain were also synthesized.

Ergot alkaloids and their related compounds hold important parts in the family of biologically active alkaloids. Their common structure is characterized by the indole skeleton bearing an isoprene C_5 unit at 4-position.[1] In the synthesis of these indoles, there have so far been used indoles with C_1 or C_2 unit at 4-position, such as 4-formylindole, 4-indoleacetaldehyde, and 4-indoleacetonitrile as a starting material.[2]

Acetoacetic acid esters and their derivatives are well known as an important C_4 building block with wide utilities in organic synthesis, because all the four carbons have different reactivities from each other toward electrophiles and nucleophiles.[3] Indoles possessing acetoacetate functionalities at 4-position should become a new versatile intermediate for the synthesis of ergot and its related alkaloids. We wish to report here a facile synthesis of 4-(4-indolyl)-3-oxobutanoic acid esters from 5-halo-4-oxo-4,5,6,7-tetrahydroindoles and acetoacetates. The synthesis of 4-acetonylindoles with N,N-dimethylaminocarbonyl, benzoyl, and p-toluenesulfonyl group is also described together with some preliminary investigations on reactivities of these 4-acetonylindoles.

The reaction of 5-bromo-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (1)[4] with the dianion of ethyl acetoacetate (2a) prepared with NaH and BuLi

proceeded smoothly to afford an unstable alcohol 3a, which was immediately dehydrated to an olefin 4a by the catalysis of acid such as p-toluenesulfonic acid and phosphoric acid. Aromatization of the olefin 4a to 4-(4-ethoxycarbonyl-2-oxopropyl)indole (5a) required the dehydrobromination and was attained by the use of LiBr in dimethylformamide (DMF).

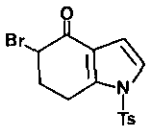
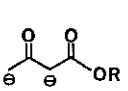
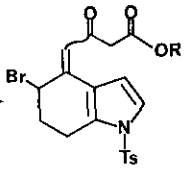
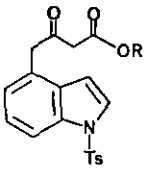
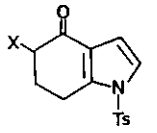
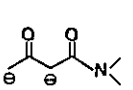
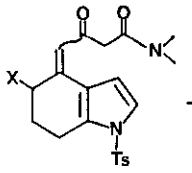
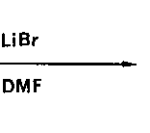
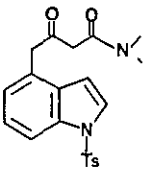
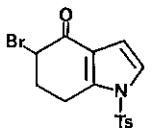
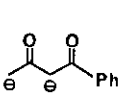
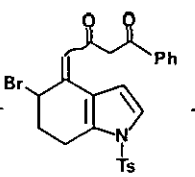
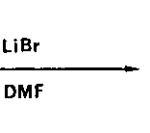
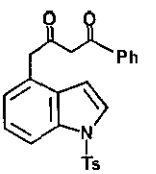
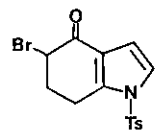
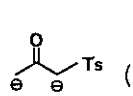
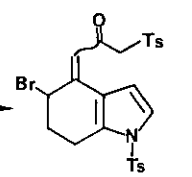
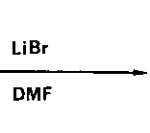
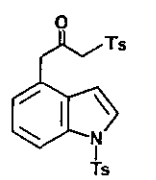


Similarly, the combination of the ketone 1 with acetoacetic acid methyl (2b), benzyl (2c), and t-butyl (2d) esters gave the corresponding indolylacetoacetates 5b, 5c, and 5d. Other dianions prepared from N,N-dimethylacetoacetamide (6), benzoylacetone (7), and p-toluenesulfonylacetone (8) were reactive enough toward 1 to yield olefins 9, 10, and 11 after dehydration. The dehydrobromination of the olefins gave the corresponding acetonylindoles 12, 13, and 14. These results were summarized in the Table I.[5]

In place of the bromoketone 1,5-chloro-4-oxo-4,5,6,7-tetrahydroindole (15) was also useful for the present purpose. For example, the ketone 15 and the acetoacetamide (6) gave the corresponding adduct 16 as stable crystals in a 90% yield (see experimental). The dehydration of 16 with phosphoric acid in hot benzene afforded an olefin 17 (90% yield), whose dehydrochlorination gave the indole 12 in a 71% yield.

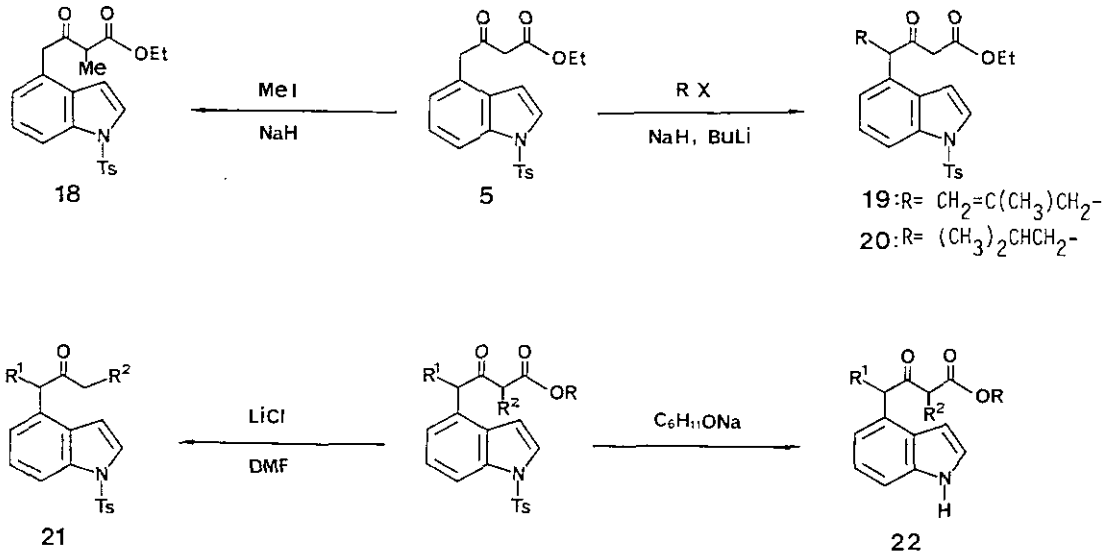
The indolylacetoacetate 5 has two active methylene groups capable of undergoing electrophilic substitution. The regioselective alkylation was easily attained by the standard method as illustrated below. When the indole 5a was treated with methyl iodide and NaH, methyl group was selectively introduced at α-position of the side chain to afford an indole 18. On the other hand, the dianion of 5a prepared by the action of NaH and BuLi reacted with an electrophile such as 2-methyl-2-propenyl iodide, 2-methyl-2-propenyl tosylate, and isobutyl iodide to give the corresponding indole 19 and 20 having 2-methyl-2-propenyl or isobutyl at γ-position of the side chain.

Table I. Synthesis of 4-Acetonylindole.

5-halo-4-oxo-4,5,6,7-tetrahydroindole	dianion	alkylidene-tetrahydroindole	yield [a] (%)	acetonylindole yield(%) [b]
	 (2)			
R=Me (2b)		(4b): 81%		(5b): 94%
R=CH_2Ph (2c)		(4c): 41%		(5c): 91%
R=t-Bu (2d)		(4d): 56%		(5d): 49%
	 (6)			
(1): X=Br		(9) : 76%		(12): 84% [d]
(15): X=Cl		(17): 81% [c]		71% [e]
	 (7)			
		(10): 67%		(13): 89%
	 (8)			
		(11): 42%		(14): 91%

a) Based on 5-halo-4-oxo-4,5,6,7-tetrahydroindoles. b) Based on 4-alkylidene-5-halo-4,5,6,7-tetrahydroindoles. c) The intermediary alcohol 16 was obtained as stable crystals in a 90% yield (see experimental). d) Yield from the bromide 9. e) Yield from the chloride 17.

The 4-indolylacetoacetates obtained in the present work were, of course, able to be decarboxylated into 4-acetonylindoles 21 by means of the standard procedure (LiCl/DMF)[6], and was also able to be converted to N-free indoles 22 without missing the ester functions. The N-tosyl group of these indolylacetoacetates was effectively removed by sodium salt of cyclohexanol.



Further use of the indoles represented by 4-indolylacetoacetates is now investigated and will be reported in near future.

EXPERIMENTAL

5-Bromo-4-(3-ethoxycarbonyl-2-oxopropylidene)-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (4a). A solution of 5-bromo-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (1)(1.5 g, 4.1 mmol) in tetrahydrofuran (THF, 30 ml) was added drop by drop into a THF solution (20 ml) of dianion of ethyl acetoacetate prepared by the use of NaH (50%, 247 mg, 5.1 mmol) and butyllithium (15% hexane solution, 3.6 ml) under an argon atmosphere at -78 °C in 20 min. After stirring for 2 h, the reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel and eluted with dichloromethane-ethyl acetate (100:1) to give an oily 5-bromo-4-(3-ethoxycabonyl-2-oxopropyl)-4-hydroxy-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (3a) (1.92 g, 95%), which was contaminated with a slight amount

of 4a.

The unstable alcohol 3a was stirred together with a catalytic amount (ca. 10 mg) of p-toluenesulfonic acid in chloroform (20 ml) at room temperature for 20 min and then at 50°C for 40 min. The mixture was washed with water and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed by SiO_2/dichloromethane-ethyl acetate (100:1) to afford the olefin 4a as pale yellow crystals (from ethyl acetate-hexane) melted at 108.0-109.5°C(dec.) in a yield of 94%.

NMR(in $CDCl_3$)δ1.25(t,J=7.0Hz,3H), 1.72-2.50(m,2H), 2.40(s,3H), 2.86-3.10(m,2H),3.51(s,2H), 4.16(q,J=7.0Hz,2H), 6.24(s,1H), 6.30(t,J=3.0Hz,1H), 6.41(d,J=3.6Hz,1H), 7.14-7.44(m,3H), 7.56-7.80(m,2H) ppm. IR(KBr) 1740, 1675, 1584, 1500, 1343, 1178 cm^{-1}. Mass(m/z,%) 481(M^+,1.5), 479(M^+,1.7), 399(36), 284(96), 130(41), 91(57), 82(96), 81(51), 80(100), 79(39). Anal. Calcd.($C_{21}H_{22}NSO_5Br$,%): C,52.51; H,4.62; N,2.92; S,6.67; Br,16.63. Found: C,52.34; H,4.57; N,2.87; S,6.45; Br,16.57.

4-(3-Ethoxycarbonyl-2-oxopropyl)-1-(p-toluenesulfonyl)indole (5a). 5-Bromo-4-(3-ethoxycarbonyl-2-oxopropylidene)-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (4a, 4.0g, 8.3 mmol) and anhydrous LiBr (2.17g, 25 mmol) was stirred in DMF (20 ml) under an argon atmosphere at 85°C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed four times with water, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel and eluted with dichloromethane-ethyl acetate (100:1) to give the indole 5a as colorless prisms (from ethyl acetate-hexane) melted at 75.0-76.5°C in a 99% yield (3.3g).

NMR($CDCl_3$)δ1.18(t,J=7.0Hz,3H), 2.29(s,3H), 3.35(s,2H), 3.97(s,2H), 4.07(q,J=7.0Hz,2H), 6.63(d,J=3.6Hz,1H), 6.94-7.36(m,4H), 7.54(d,J=3.6Hz,1H), 7.62-7.98(m,3H) ppm. IR(KBr) 1750, 1725, 1600, 1357, 1176 cm^{-1}. Mass(m/z,%) 399(M^+,57), 311(31), 284(100), 130(52), 129(30), 91(75). Anal. Calcd.($C_{21}H_{21}NSO_5$,%): C,63.14; H,5.30; N,3.51; S,8.03. Found: C,63.09; H,5.17; N,3.37; S,7.83.

5-Chloro-4-[3-(N,N-dimethylaminocarbonyl)-2-oxopropyl]-4-hydroxy-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (16). 5-Chloro-4-oxo-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (15)(1.5 g, 4.6 mmol) was added to a

solution of dianion of N,N-dimethylacetoacetamide (6)(780 mg, 6.0 mmol) prepared by the use of NaH (5.0 mmol) and butyllithium (15% hexane solution, 3.8 ml) in THF (20 ml) under an argon atmosphere at -78°C. The reaction mixture was stirred at room temperature for 3.5 h, then was poured into saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The extract was washed with water, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel and eluted with dichloromethane-ethyl acetate (4:1) to give the alcohol 16 (1.89 g, 90%) as colorless granules (from ethyl acetate) melted at 116-117°C.

NMR($CDCl_3$)δ 2.00-2.50(m,2H), 2.42(s,3H), 2.64-3.22(m,2H), 2.94(s,3H), 2.95(s,3H), 3.13(s,2H), 3.59(s,2H), 4.46-4.70(m,1H), 6.26-6.48(m,1H), 7.14-7.42(m,3H), 7.56-7.80(m,2H) ppm. IR(KBr) 3425, 1717, 1643, 1600, 1497, 1365, 1179 cm^{-1}. Mass(m/z,%) 398(M^+-H_2O, HCl, 27), 284(30), 130(36), 114(43), 91(86), 87(50), 72(100), 44(65). Anal. Calcd.($C_{21}H_{25}N_2SO_5Cl$,%): C,55.69; H,5.56; N,6.18; S,7.08. Found: C,55.46; H,5.53; N,6.08; S,7.26.

5-Chloro-4-[3-(N,N-dimethylaminocarbonyl)-2-oxopropylidene]-1-(p-toluenesulfonyl)-4,5,6,7-tetrahydroindole (17). The alcohol 16 (452 mg, 1 mmol) and phosphoric acid (70%, 0.3 ml) were stirred in benzene (10 ml) at refluxing temperature for 20 min. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel and elutiuon with dichloromethane-ethyl acetate-ethanol (100:10:1) gave the olefin 17 (390 mg, 90%) as colorless granules (from ethyl acetate) melted at 151-152°C.

NMR($CDCl_3$)(a 1:1 enol-keto form mixture) δ 1.70-2.48(m,2H), 2.42(s,3H), 2.80-3.16(m,2H), 2.98(s,6H), 3.61(broads, 1H), 5.33(broads, 0.5H), 5.83(broad s, 0.5H), 6.17(t,J=3.0Hz,1H), 6.26-6.52(m,1.5H), 7.10-7.40(m,3H), 7.55-7.76(m,2H) ppm. IR(KBr) 1636, 1597, 1560, 1504, 1377, 1180 cm^{-1}. Mass(m/z,%) 436(M^+,1.2), 434(M^+,1.9), 398(47), 354(63), 114(38), 91(67), 87(43), 72(93), 44(100). Anal. Calcd.($C_{21}H_{23}N_2SO_4Cl$,%): C,57.99; H,5.33; N,6.44; S,7.37; Cl,8.15. Found: C;57.75, H;5.26, N;6.29, S;7.42, Cl;8.03.

4-[3-(N,N-Dimethylaminocarbonyl)-2-oxopropyl]-1-(p-toluenesulfonyl)indole (12). The olefin 17 (351 mg, 0.81 mmol) and LiBr (210 mg, 2.4 mmol) were stirred under

a nitrogen atmosphere at 80°C for 24 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel and eluted with dichloromethane-ethyl acetate-ethanol (100:10:1) to afford the indole derivative 18 (230 mg, 71%) as colorless granules (from ethyl acetate) melted at 135-138.5°C.

NMR($CDCl_3$)δ2.31(s,3H), 2.69(s,3H), 2.85(s,3H), 3.42(s,2H), 4.00(s,2H), 6.71(d,J=3.6Hz,1H), 6.96-7.34(m,4H), 7.53(d,J=3.6Hz,1H), 7.60-7.96(m,3H) ppm. IR(KBr) 1635, 1606, 1504, 1421, 1373, 1190 cm^{-1}. Mass(m/z,%) 398(M^+,4), 284(34), 114(88), 91(63), 87(100), 72(97). Anal. Calcd.($C_{21}H_{22}N_2SO_4$,%): C,63.30; H,5.56; N,7.03; S,8.05. Found: C,63.17; H,5.58; N,6.95; S,8.22.

4-(6-Ethoxycarbonyl-2-methyl-5-oxohex-1-en-4-yl)-1-(p-toluenesulfonyl)indole (19). A solution of dianion of the indole 5a (1.0 g, 2.5 mmol) in THF (15 ml) was prepared by the use of NaH (50%, 128 mg, 2.67 mmol) and BuLi (15% hexane solution, 1.75 ml) under an argon atmosphere. To the solution, 2-methyl-2-propenyl tosylate (623 mg, 2.76 mmol) was added and stirred under an argon atmosphere at 0 C for 20 min. The mixture was poured into NH_4Cl aq. solution and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel and eluted with dichloromethane to yield the indole derivative 19 (941 mg, 85% yield) as a viscous oil.

NMR($CDCl_3$) δ1.10(t,J=7.0Hz,3H), 1.61(s,3H), 2.32(s,3H), 2.43(dd,J=14.4 and 7.2Hz,1H), 2.95(dd,J=14.4 and 7.2Hz,1H), 3.15(d,J=15.6Hz,1H), 3.37(d,J=15.6Hz,1H), 4.02(q,J=7.0Hz,2H), 4.39(t,J=7.2Hz,1H), 4.57(broad s,1H), 4.64(broad s,1H), 6.80(d,J=3.6Hz,1H), 7.02-7.42(m,4H), 7.65(d,J=3.6Hz,1H), and 7.70-8.06(m,3H) ppm. IR(liquid film) 1745, 1720, and 1650 cm^{-1}. Mass(m/z,%) 453(M^+,19), 338(74), 183(42), 182(100), 168(33), 167(44), 155(45), and 91(94). High Mass (m/z) 453.1592 (er= -1.5mmu)(M^+, $C_{25}H_{27}NSO_5$).

4-(3-Ethoxycarbonyl-2-oxopropyl)indole 22 (R=Et, R^1,R^2=H). Cyclohexanol (400 mg, 4 mmol) and NaH (50%, 150 mg, 3.13 mmol) were stirred in THF (10 ml) under an argon atmosphere at room temperature for 2 h. To the solution, the indole 5a (500 mg, 1.25 mmol) was added and stirred for 3 h. The mixture was poured into NH_4Cl aq. solution and extracted with ethyl acetate. The extract was washed

with water, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel and eluted with dichloromethane to afford the N-free indole 22 (R=Et, R^1, R^2=H) (77% yield) as a colorless oil.

NMR($CDCl_3$) δ1.20(t,J=7.2Hz,3H), 3.41(s,2H), 4.09(s,2H), 4.15(q,J=7.2Hz,2H), 6.47-6.64(m,1H), 6.90-7.44(m,4H), and 8.26-8.66(m,1H) ppm. IR(liquid film) 3430, 1743, and 1717 cm^{-1}. Mass(m/z,%) 245(M^+,17) and 130(100). High Mass(m/z) 245.1043 (er= -0.7mmu) (M^+, $C_{14}H_{15}NO_3$).

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5. 4b: colorless prisms (from ethyl acetate-hexane) melted at 115.0-117.0°C. 4c: colorless prisms (from ethyl acetate-hexane) melted at 95.5-97.0 °C. 4d:viscous oil. 5b: viscous oil. 5c: viscous oil. 5d: viscous oil. 10: pale yellow prisms (from ethyl acetate) melted at 150°C(dec). 11: colorless needles (from ethyl acetate-hexane) melted at 160-162 C. 13: colorless prisms (from ethyl acetate) melted at 142.5-143.5°C. 14: viscous oil.
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