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A new synthesis of 4-oxygenated β-carboline derivatives by Fischer indolization☆

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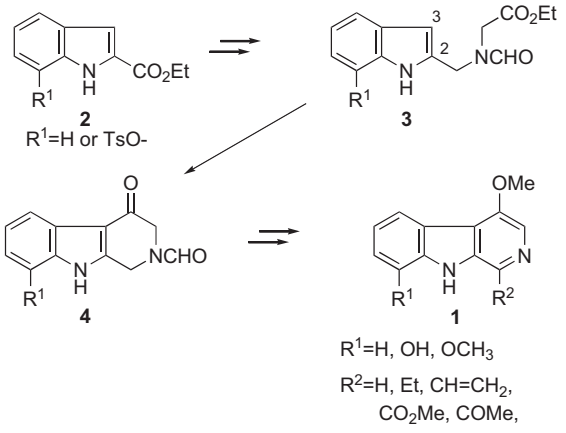
Abstract—A new and short synthetic route to the 4-methoxy-β-carboline skeleton is described. The route involves Fischer indolization of enehydrazine of 1-tosylpiperidine-3,5-dione and successive acetalization–elimination for aromatization of 1,2,3,4-tetrahydro-2-tosyl-9*H*-β-carbolin-4-one. This method is efficiently applicable to synthesis of the benzene-part substituted 4-oxygenated β-carboline derivatives.

Recently, many 4-methoxy-β-carboline alkaloids (**1**) have been isolated[3] and some of them have been found to be biologically active[4] (cytotoxicity,[4a] anti-HIV,[4b] anti-malaria,[4c] suppression of iNOS,[4d] antimicrobial activity[4e]). We have developed[5–8] a general synthetic method of **1**, starting from ethyl indole-2-carboxylates (**2**) as shown in Scheme 1. On the other hand, synthesis of 4-oxygenated β-carboline from a 3-substituted indole derivative via Pictet–Spengler and Bischler–Napieralski reactions has so far been unsuccessful.[5]

Now, we are interested in a variety of benzene-part substituted 4-methoxy-β-carbolines (**10**) (Table 3) from the viewpoint of their biological activities. Therefore, a new convenient synthetic method for the benzene-part substituted 4-methoxy-β-carbolines is required. To this end, we envisaged that the Fischer indolization starting from a variety of substituted phenylhydrazines (**5**) was feasible. On the other hand, Chen et al. reported[9] the synthesis of 1,2,3,4-tetrahydro-β-carbolin-4-ones from 1-benzylpiperidine-3,5-dione (**6a**)[10] with aniline derivatives via Pd-mediated C–C bond formation under stoichiometric conditions,[9a] followed by a catalytic reaction.[9b] We believe that our method is a more convenient and general synthetic method for benzene-part substituted 4-methoxy-β-carbolines (**10**).



Scheme 1.

First, we tried to prepare the phenylhydrazone of 1-benzylpiperidine-3,5-dione (**6a**), but the reaction gave only tarry products, probably owing to the basic property of **6a** (Table 1). A tosyl group was chosen as an *N*-protecting group for the substrate (**6b**)[10] because the sulfonyl group stabilizes the amino group with a stronger electron-withdrawing property. Thus, the hydrochlorides of phenylhydrazines (**5a**–**e**) were reacted with 1-tosylpiperidine-3,5-dione (**6b**, 1 mol equiv) in the presence of sodium acetate (2 mol equiv) in acetic acid.

Keywords: Fischer indolization; β-carboline; Indole; Acetalization; Aromatization.
☆ See Ref. 1.
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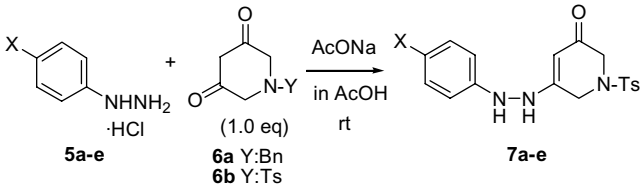
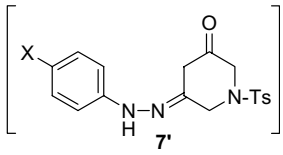
Table 1. Synthesis of enehydrazine (**7**)



X	Y	Yield of **7** (%)
5a[a] H	**6a** Bn	Many spots
5a[a] H	**6b** Ts	72
5b Me	**6b** Ts	70
5c Cl	**6b** Ts	69
5d OMe	**6b** Ts	73
5e NO_2	**6b** Ts	61

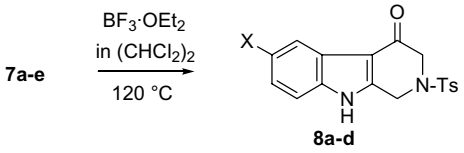
[a] TsOH salt of **5a** was used.



The reaction proceeded at room temperature to give the product in good yields as shown in Table 1.[23,27] The structures of the product were found to be the enehydrazines **7a**–**e**, tautomers of the corresponding phenylhydrazone (**7′**). The enehydrazine structure was known to be the first intermediate in the Fischer indolization of phenylhydrazones.[11]

The Fischer indolization of the enehydrazines **7a**–**e** was carried out under various conditions. The classical conditions for Fischer indolization (HCl–MeOH, TsOH in benzene, etc.) gave poor results, whereas the reaction with excess of $BF_3{\cdot}OEt_2$ in 1,1,2,2-tetrachloroethane at 120 °C gave a better result as shown in Table 2.[24,28]

Table 2. Fischer indolization of enehydrazine (**7**)



X	$BF_3{\cdot}OEt_2$ (mol equiv)	Time (h)	Yield (%)	
			8	**9**
7a H	27	1.5	**84**	19
7b Me	20	0.3	**64**	32
7c Cl	20	2	**66**	12
7d OMe	20	0.3	28 (X=OMe) 11 (X=OH)	—
7d OMe	None[a]	0.4	**43**	—
7e NO_2	20		Decomp.	

[a] Reflux in $(CHCl_2)_2$.

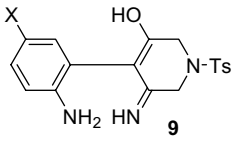
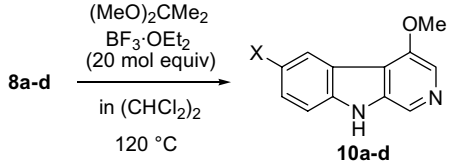


Table 3. Synthesis of 4-methoxy-β-carboline (**10**)



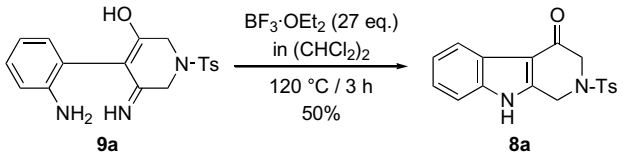
X	Time (h)	Yield of **10** (%)
8a H	0.2	92
8b Me	0.7	84
8c Cl	0.3	86
8d OMe	0.8	94

The reactions of these enehydrazines (**7a**–**c**) gave the target 1,2,3,4-tetrahydro-β-carbolin-4-ones (**8a**–**c**) in good yields with the second intermediate[11] (**9**) of the Fischer indolization as a by-product. For the methoxy derivative **7d**, yield of the target product (**8d**) was only 28% and a de-methylated compound (**8**, X=OH) was obtained in 11% yield as well. However, the thermal Fischer indolization condition[12] of **7d** gave a reasonable 43% yield of **8d**. The nitro derivative (**7e**) was not cyclized under any examined conditions, due to the inactiveness of the aromatic ring by the electron-withdrawing effect of the nitro group.

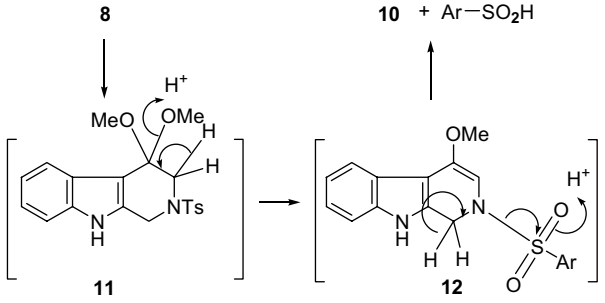
As compound (**9**) should be the second intermediate in the Fischer indole synthesis, compound (**9a**) was treated under the same conditions as the Fischer indolization. The target 1,2,3,4-tetrahydro-β-carbolin-4-one (**8a**) was obtained in 50% yield (Scheme 2). Compound (**8**) thus obtained was treated with dimethoxypropane and excess of $BF_3{\cdot}OEt_2$ in 1,1,2,2-tetrachloroethane to give 4-methoxy- β-carboline (**10**) directly with unexpected removal of the *N*-tosyl group in good yield as shown in Table 3.[25,29] In this reaction, we obtained *p*-toluenesulfinic acid from the reaction mixture and identified it as the methyl ester in the NMR spectrum.

The mechanism of this successive acetalization and elimination for aromatization of **8** is proposed in Scheme 3. The key step should be the reductive β-elimination of the tosyl group as *p*-toluenesulfinic acid with the intramolecular oxidative–reductive aromatization under acidic condition.

There are some reports[13,14] for aromatization toward the pyridine ring by β-elimination of the tosyl group under basic conditions. However, the reductive elimination of the tosyl group to sulfinic acid is not described in their papers. We previously reported[6] that the aromati-



Scheme 2.



Scheme 3.

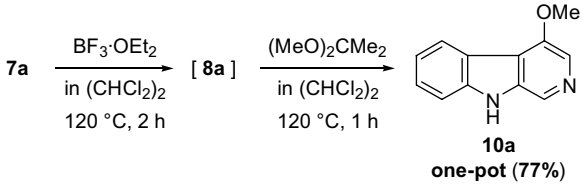
zation of the *N*-formyl derivative (**4**) to 4-methoxy-β-carboline (**10a**), required chloranil as an oxidative agent. In the present route, the intermediate (**12**) was inevitably aromatized with reductive elimination of sulfonic acid without an oxidative agent or air oxidation under acidic condition.[15]

The condition for this acetalization–elimination reaction was similar to the Fischer indolization condition. Thus, the one-pot reaction of **7a** to **10a** was carried out. Dimethoxypropane was added to the reaction mixture after the Fischer indolization of the enehydrazine (**7a**) was conducted, and then the mixture was heated at 120 °C for 1 h (Scheme 4).[26]

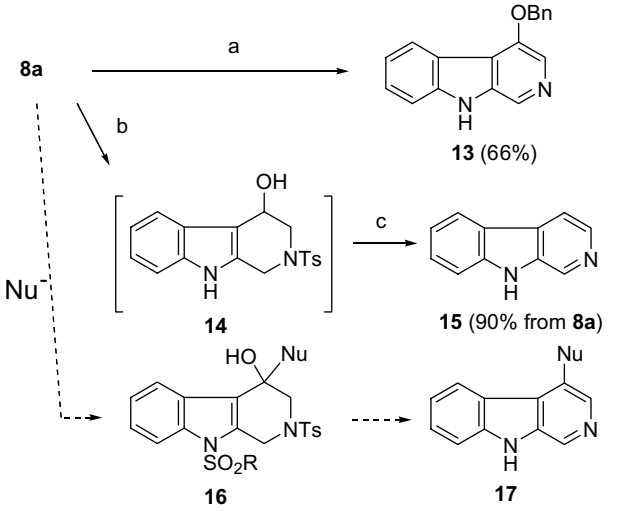
The reaction gave the target 4-methoxy-β-carboline (**10a**) in good yield (77%) as the two separate operations. The conversion of 4-methoxy-β-carboline (**10a**) to the natural products (**1**) was already reported[6] by us.

Cook and co-workers[15c] reported the synthesis of 4-benzyloxy-β-carboline (**13**), but their yield was 36% starting from 2-benzoyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (corresponding to **8a**). By applying this acetalization–elimination reaction to compound **8a**, we succeeded in the synthesis of compound **13** in good yield (66%) using dibenzyloxypropane[15c] instead of dimethoxypropane. This compound (**13**) should be an important synthetic intermediate to 4-hydroxy-β-carboline alkaloids.[16] Furthermore, the Fischer product (**8a**) was converted to unsubstituted β-carboline (**15**) in 90% yield by the reduction of the C^4-carbonyl group using $NaBH_4$, followed by reductive elimination on treatment with HCl/MeOH at room temperature for 1 h (Scheme 5).

From these experiments, it is expected that the Fischer product (**8**) becomes the key intermediate for the general synthesis of various 4-substituted β-carbolines. The 4-carbonyl group of **8** must be modified variously by



Scheme 4.



Scheme 5. Reagents and conditions: (a) $(BnO)_2CMe_2$, $BF_3{\cdot}OEt_2$ (20 mol equiv) in $(CHCl_2)_2$, 120 °C; (b) $NaBH_4$ in $CHCl_3$–MeOH, rt, 16 h; (c) HCl in MeOH, rt, 1 h.

nucleophilic addition, leading to the synthesis of 4-substituted β-carbolines such as 4-amino (**17**, Nu = NHR),[15a,17,18] 4-aralkyl (**17**, Nu = alkyl or aryl),[19–22] and 4-thio (**17**, Nu = SR) derivatives. These synthetic applications and a precise study of the desulfination mechanism of the *N*-tosyl group of this reaction are now in progress.

References and notes

1. This paper is "Synthetic Studies on Indoles and Related Compounds 54": Part 53: "A Total Synthesis of 1-Methoxycanthin-6-one: An Efficient One-Pot Synthesis of the Canthin-6-one Skeleton from β-Carboline-1-carbaldehyde" Suzuki, H.; Adachi, M.; Ebihara, Y.; Gyoutoku, H.; Furuya, H.; Murakami, Y.; Okuno, H. *Synthesis* **2005**, 28–32.
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23. General procedure for preparation of **7** from **5**: To a suspended solution of 1-(*p*-toluenesulfonyl)-piperidine-3,5-dione (**6b**) (4.0 mmol) and NaOAc (8.0 mmol) in AcOH (10 mL) was added a solution of phenylhydrazine hydrochloride (**5**) (2.0 mmol) in AcOH (10 mL) at 0 °C. Then the mixture was stirred at rt for 0.3–2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residual solid was purified by column chromatography on silica gel using CH_2Cl_2–EtOAc (1:1) as a solvent system to afford the product (**7**) shown in Table 1.
24. General procedure for preparation of **8** from **7**: To a stirred solution of phenylhydrazone (**7**) (0.20 mmol) in 1,1,2,2-tetrachloroethane (4.0 mL), borontrifluoride etherate (4.0 mmol) was added at 0 °C under argon atmosphere, and then the reaction mixture was heated to 120 °C for 0.2–3 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residual solid was purified by column-chromatography on silica gel using CH_2Cl_2–EtOAc (1:1) as a solvent system to afford the product (**8**) shown in Table 2.
25. General procedure for preparation of **10** from **8**: To a stirred solution of 1,2,3,4-tetrahydro-β-carbolin-4-one (**8**) (0.050 mmol) in 1,1,2,2-tetrachloroethane (1.0 mL), dimethoxypropane (0.40 mmol), and borontrifluoride etherate (1.0 mmol) were added at 0 °C under argon atmosphere, and then the reaction mixture was heated to 120 °C for 0.2–0.8 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residual solid was purified by column-chromatography on silica gel using CH_2Cl_2–MeOH (10:1) as a solvent system to afford the product (**10**) shown in Table 3.
26. One-pot procedure for **10a** from **7a**: To a stirred solution of compound (**7a**) (38.6 mg, 0.108 mmol) in 1,1,2,2-tetrachloroethane (2.0 mL), borontrifluoride etherate (0.36 mL, 2.9 mmol) was added at 0 °C under argon atmosphere, and then the reaction mixture was heated to 120 °C for 2 h. To the reaction mixture, dimethoxypropane (0.2 mL, 1.6 mmol) was added at 120 °C, and heated at 120 °C for 1 h. The reaction mixture was worked up as described above to afford the product (**10a**, 16.5 mg) in 77% yield.
27. Data for selected compounds: 5-[(4-chloro-phenyl)-hydrazono]-1-(*p*-toluenesulfonyl)-piperidin-3-one (**7c**): mp 190–191 °C. ^{1}H NMR (DMSO-d_6) δ: 2.39 (3H, s), 3.62 (2H, s), 4.10 (2H, s), 4.83 (1H, s), 6.59 (2H, d, J = 8.8), 7.17 (2H, d, J = 8.8), 7.45 (2H, d, J = 8.3), 7.62 (2H, d, J = 8.3), 8.04 (1H, br s), 9.14 (1H, br s). IR max (KBr) cm^{-1}: 3345, 3255, 1595.
28. 6-Chloro-1,2,3,4-tetrahydro-2-(*p*-toluenesulfonyl)-9*H*-β-carbolin-4-one (**8c**): mp 248–250 °C. ^{1}H NMR (DMSO-d_6) δ: 2.15 (3H, s), 3.98 (2H, s), 4.78 (2H, s), 7.18 (2H, d, J = 8.3), 7.22 (1H, dd, J = 8.8 and 2.0), 7.50 (1H, d, J = 8.8), 7.54 (2H, d, J = 8.3), 7.66 (1H, d, J = 2.0), 12.16 (1H, br s). IR max (KBr) cm^{-1}: 3388, 1660.
29. 6-Chloro-4-methoxy-β-carboline (**10c**): mp 265–267 °C. ^{1}H NMR (DMSO-d_6) δ: 4.17 (3H, s), 7.54 (1H, dd, J = 8.8 and 2.0), 7.63 (1H, d, J = 8.8), 8.14 (1H, d, J = 2.0), 8.14 (1H, br s), 8.63 (1H, br s), 11.86 (1H, br s). IR max (KBr) cm^{-1}: 3447.