

Substituent Effects in the Fischer Indolization of (2-Sulfonyloxyphenyl)-hydrazones (Fischer Indolization and Related Compounds. XXX¹⁾)

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The effects of a variety of additional substituents of ethyl pyruvate 2-(2-methanesulfonyloxy)phenylhydrazone (**7**) in Fischer indolization were examined. When the substituent was a methyl group at the 3-, 4-, or 5-position, the yields of normal 7-methanesulfonyloxyindoles depended upon the position. The hydrazones having a methyl group at the position nearer to the methanesulfonyloxy group tended to give normal 7-methanesulfonyloxyindole in a higher percentage to total indolic products. In a series of 4-substituted phenylhydrazones (**7d**, **e**, **f**), more electron-withdrawing substituents tended to give normal 7-methanesulfonyloxyindole in a higher percentage to total indolic products than electron-donating ones. A hydrazone with a strong electron-withdrawing substituent at the 4-position (**7f**) underwent intramolecular aromatic nucleophilic substitution by the enehydrazine moiety to give the cinnoline derivative.

Key words Fischer indolization; mechanism; sulfonyloxy; substituent effect; cinnoline

In our previous paper²⁾ we reported that Fischer indolization of (2-sulfonyloxyphenyl)hydrazones (**1**, Chart 1) proceeded mainly toward the unsubstituted *ortho*-position to give 7-sulfonyloxyindole (**2**), in contrast to the (2-methoxyphenyl)hydrazone³⁾ (**3**) which formed the normal 7-methoxyindole (**4**) as a minor product and abnormal 6-chloroindole (**5**) as a main one. Thus, the Fischer indolization of **1** has provided a practical synthetic method for 7-oxygenated indoles. In order to extend its application, we examined the electronic and steric effects of an additional substituent on the (2-sulfonyloxyphenyl)hydrazones. In this paper we report our detailed results.

We selected a methanesulfonyloxy (mesyloxy) group as the substituent on the phenylhydrazones to minimize the steric effect. In order to examine the steric effects of additional substituents, phenylhydrazones with a methyl group at its 3, 4, or 5-positions (**7a–c**) were prepared first. Next, phenylhydrazones with a methoxy, a bromo, or a methoxycarbonyl group at its 4-position (**7d–f**) were prepared, in order to examine the electronic effect of the additional substituent (Chart 2).

The hydrazones (**7**) were prepared a) by Japp–Klingemann⁴⁾ reaction, which involved diazotization of the corresponding aniline (from **8** to **9**), followed by coupling with ethyl α -methyl acetoacetate, or b) by coupling of the hydrazine (**10**) prepared by reduction of the diazonium salt (**9**) with ethyl pyruvate. When 2-aminophenol (**8**, R=H) was used as a starting material, the order of the synthetic steps was reversed: first phenylhydrazone formation, then mesylation. The hydrazones (**7**) existed as (*E*)- and (*Z*)- isomers, which were separated and then used for Fischer indolization. Both isomers gave the same result, as *E–Z* isomerization occurred during the Fischer indolization.

Fischer Indolization The Effect of the Position of an Additional Substituent: The Fischer indolization reaction was carried out with *p*-toluenesulfonic acid (TsOH) in benzene and the results are summarized in Chart 3. All three methyl-substituted hydrazones (**7a–c**) gave the normal 7-mesyloxyindoles (**11a**, **12a**, and **13a**) as the main products. How-

ever, the ratio of the normal product to total indolic products varied, depending on the position of the methyl group. The Fischer indolization of the (3- and 4-methylphenyl)hydrazones (**7a** and **7b**) gave a higher percentage (88 and 96%, see Table 1) of normal 7-mesyloxyindoles (**11a** and **12a**) to total indolic products, whereas the reaction of (5-methylphenyl)hydrazone (**7c**) formed a low percentage (58%, see Table 1) of the normal one to total indolic products. This fact concerning **7c** is consistent with the result⁵⁾ that Fischer indolization of a 3-substituted phenylhydrazone gave more 6-substituted indole than 4-substituted one. The abnormal product was the one in which the sulfonyloxy group was rearranged or was substituted at the 5-position (corresponding to the 4-position of phenylhydrazone) of the resulting indolic product. In the case of **7b** where the 4-position was already occupied with a methyl group, the sulfonyloxy group was removed during the reaction. Various 2-substituents of phenylhydrazones were often reductively removed in our Fischer indolization procedure,^{2,6)} but the mechanism has been unknown. The structures of the indolic products in the Fischer indolization, especially the position of substituent, were determined by ¹H-NMR including the nuclear Overhauser enhancement (NOE) technique, in which C₄-H or C₄-methyl group was identified by correlation with C₃-H. The C₃-H of indoles is easily identified, because it appears independently in the higher aromatic region, apart from other aromatic protons, and its coupling with indolic NH (*J*=1–2 Hz) changed from doublet (sometimes multiplet) to singlet by addition of D₂O. The mechanism for the abnormal product is shown in Chart 4, which is essentially based on our previous work.^{2,6)}

In the Fischer indolization of **7a**, the cyclization towards the C₂-position bearing a mesyloxy group formed the intermediate **B** via **A**. The 1,3-rearrangement of the mesyloxy group gave the 5-mesyloxy product (**11b**) via intermediate **D** and **E**, whereas the substitution at C₅-position in the intermediate **F**(=**D**) gave the 5-tosyloxy product (**11c**) via the intermediate **G**. In the case of (2-methoxyphenyl)hydrazone (**3**) the nucleophile (Cl[–]) attacked the C₆-position in the intermediate **M**, while rearrangement or substitution occurred at the

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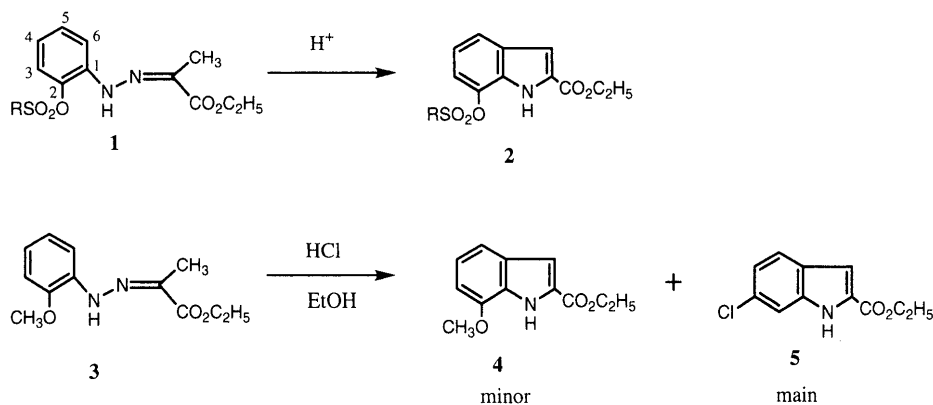


Chart 1

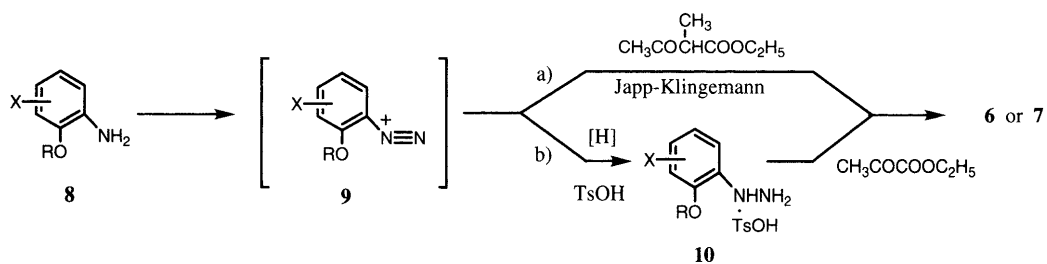
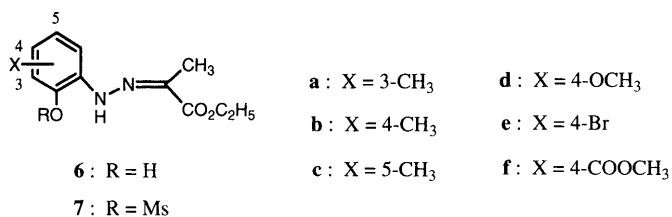


Chart 2

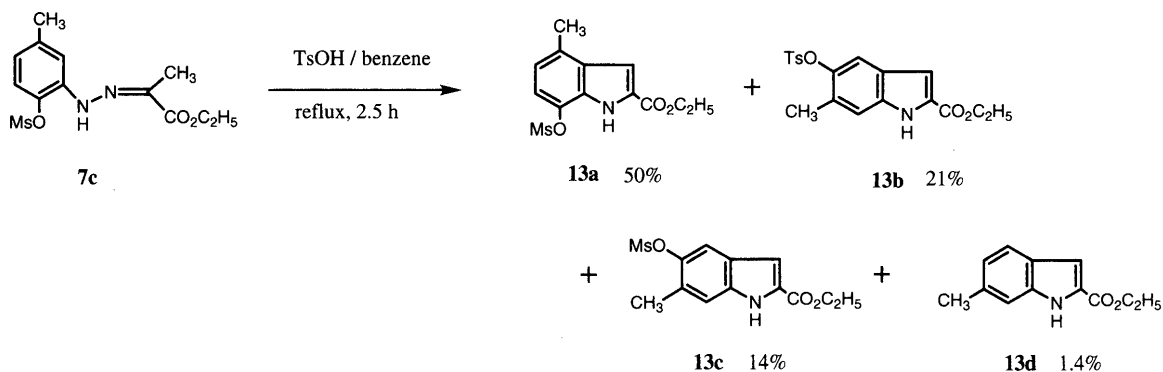
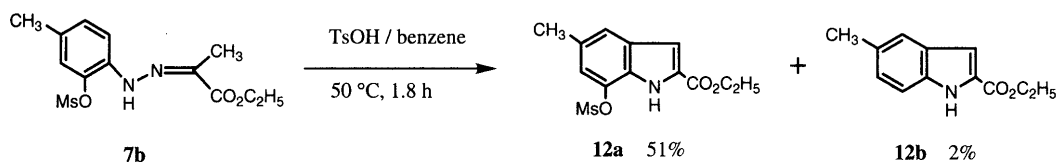
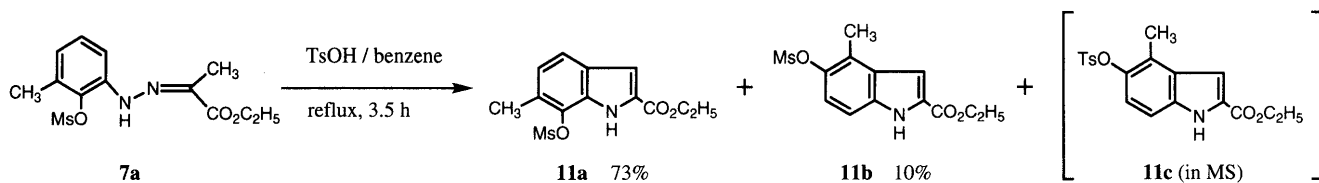


Chart 3

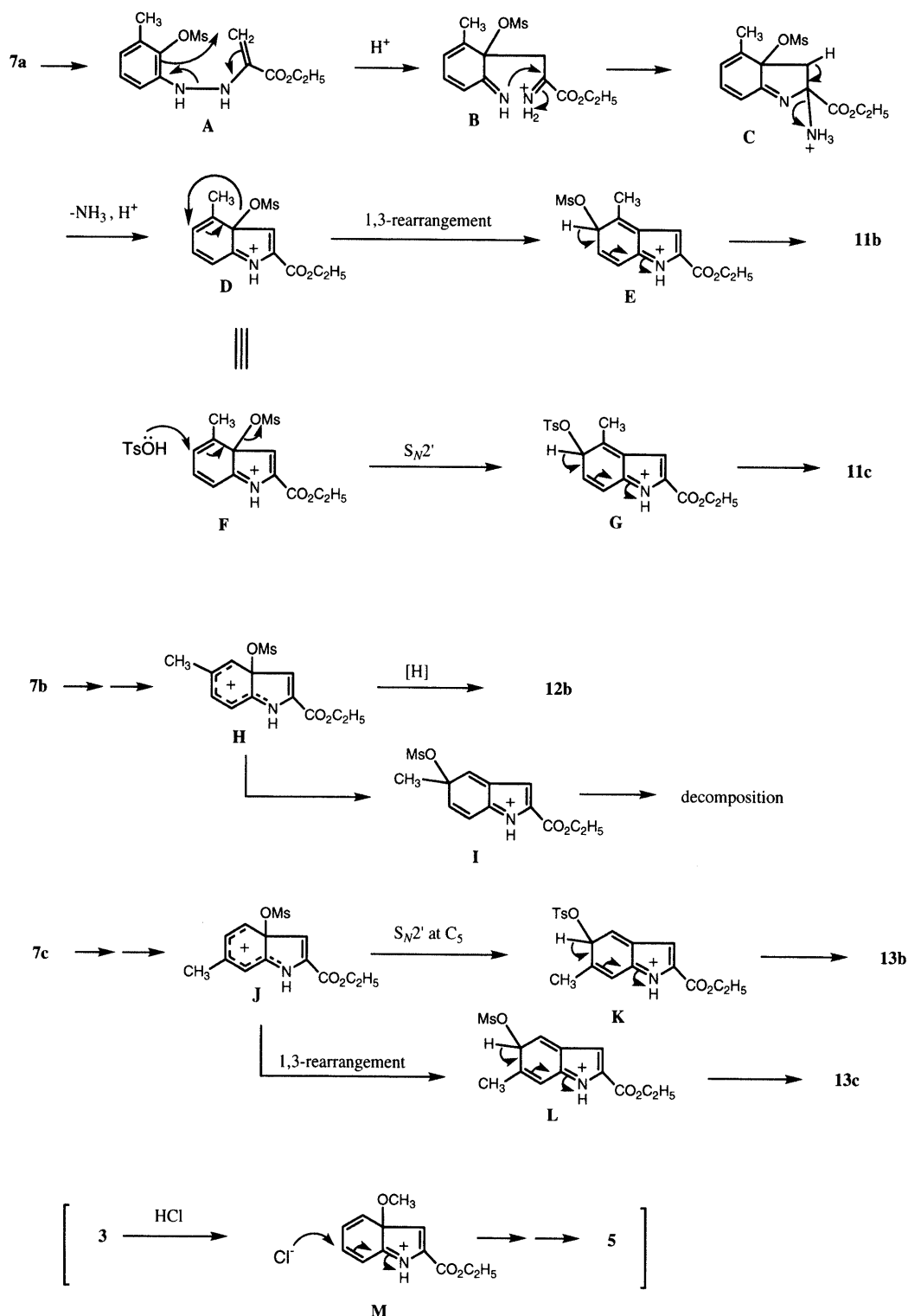


Chart 4

C_5 -position in intermediates **D** and **F**. The difference in these results depends on the greater leaving ability of the mesyloxy group than that of the methoxy one. The methyl group of **7a** seemed not to be an obstacle to the migration of the mesyloxy group (see the intermediate **D** in Chart 4).

In the case of **7b**, the position (indolic C_5) to which the mesyloxy group rearranged was occupied with the methyl group. Once the intermediate **I** formed, it should decompose, because it can not be aromatized easily. Only one abnormal product (**12b**) is formed by reductive elimination of the me-

syloxy group at the stage of the intermediate **H**. Since intermediate **I** did not give any abnormal product, the percentage of the normal 7-mesyloxyindole to the total indolic products is high (96%, see Table 1). On the other hand, the low percentage (58%, see Table 1) of the abnormal products (**13b**—**d**) was characteristic of the Fischer indolization of **7c**. The product **13d** is the same reduced one as **12b**.

The Electronic Effect of an Additional Substituent: Next, the Fischer indolization reactions of 4-substituted (2-mesyloxyphenyl)hydrazones (**7d**—**f**) were examined and the re-

Table 1. Summary of the Fischer Indolization of 7

X	Yield (%) of normal product	Yield (%) of abnormal product	Yield (%) (total)	Ratio (%) (normal/total)
H ²⁾	61	31	92	66
3-CH ₃ (7a)	73	10	83	88
4-CH ₃ (7b)	51	2	53	96
5-CH ₃ (7c)	50	36	86	58
4-OCH ₃ (7d)	55	14	69	80
4-Br (7e)	65	0	65	100
4-COOCH ₃ (7f)	53	0	53	100

was characteristic. In the ¹H-NMR spectrum of **16b**, addition of D₂O caused the disappearance of two NH signals at 6.83 and 11.00 ppm and a simultaneous decrease of integration of the C₄-olefinic proton at 6.83 ppm to 0.5H (C₄-H and one of two NH signals appear at the same position). This observation shows that the structure **16b** tautomerizes with the structure **16c**. The formation of **16b** is explained on the basis of the existence of two electron-withdrawing groups, a mesyl and an ester group, which cause a decrease of electron density in the benzene ring. Thus, the enehydrazine moiety attacks the *ortho* (2-)-position occupied by a mesyloxy group in a nucleophilic manner to give an intramolecular aromatic nucleophilic substitution (see **16d** in Chart 5). Such a reaction of phenylhydrazones in Fischer indolization has been unknown so far. The 1,2-dihydrocinnoline (**17**) was synthesized⁸⁾ for proving the second cyclization step in Fischer indolization, where the cinnoline⁹⁾ (**17**) was reduced to cleave the N–N bond to give the indole (**19**) via recyclozation of the proposed diamine intermediate (**18**). This compound (**16b**) was formed as a result of an intramolecular substitution reaction but was not an intermediate of Fischer cyclization. However, the formation of cinnoline (**16b**) was very interesting in investigating the reactivity of phenylhydrazone, especially the enehydrazine moiety.

Conclusions

The present results are summarized in Table 1. This table includes the ratio of the normal product to the total indolic product in each reaction.

Generally in the present Fischer indolization, the expected normal 7-sulfonyloxyindole was obtained in over 50% yield in all cases, regardless of the additional substituent on the (2-mesyloxyphenyl)hydrazones. On the other hand, the yield of the abnormal product varied depending on the position and the kind of the additional substituent. Even in the case where a large amount of the abnormal product was formed, the desired 7-sulfonyloxyindole could be separated from the by-products very easily by column chromatography. Thus, the Fischer indolization of the (2-sulfonyloxyphenyl)hydrazones can be used as a convenient and practical method for preparation of 7-oxygenated indoles. We propose that Fischer indolization of phenylhydrazone with an electron-withdrawing group proceeds more slowly and thus tends to occur at the more sterically unhindered and thus unoccupied *ortho*-position to give normal 7-substituted indole, whereas Fischer indolization with electron-donating group proceeds faster and thus tends to occur randomly at both the occupied and unoccupied *ortho*-positions to give a larger amount of abnormal

products. A more electron-withdrawing sulfonyl group such as trifluoromethanesulfonyl should give better results for obtaining 7-sulfonyloxyindole.

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-300 or on a Shimadzu IR-400 spectrometer (in Nujol, unless otherwise stated). ¹H-NMR spectra were measured on a Hitachi R-24B (60 MHz), unless otherwise stated. Deuteriochloroform was used as the solvent with tetramethylsilane as the internal reference, unless otherwise stated. The assignments of the NH signals were confirmed by disappearance of the signals after addition of deuterium oxide. Mass spectra (MS) were measured on JEOL JMS-01-SG-2, JEOL JMS-D300, and JEOL JMS-DX303 spectrometers with a direct inlet system. For column chromatography, Silica gel 60 (70–230 mesh ASTM, Merck, unless otherwise stated), and for thin layer chromatography (TLC), Silica gel 60F₂₅₄ (Merck) were used. All identifications of products were done by analysis of MS, IR spectra, and especially NMR spectra. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet; br, broad; Ar, aromatic; BP, base peak; HRMS, high resolution mass spectrum.

2-Hydrazino-4-methylphenol *p*-Toluenesulfonate (10b) A solution of isoamyl nitrite (3.11 ml, 23.2 mmol) was added dropwise to a suspension of 2-amino-4-methylphenol hydrochloride (3.19 g, 20 mmol) in EtOH (10 ml) at 5 °C to give the diazonium solution. The resulting diazonium solution was then added dropwise to a suspension of anhydrous SnCl₂ (7.56 g, 40.8 mmol) and TsOH·H₂O (4.08 g, 21.4 mmol) in EtOH (40 ml) at 5 °C and the whole was stirred for 1 h. Et₂O (60 ml) was added to the reaction mixture. The resulting precipitates were collected by filtration and washed with Et₂O to give the desired phenylhydrazine *p*-toluenesulfonate (**10b**) (3.93 g, 63%). Recrystallization from MeOH–Et₂O gave colorless prisms, mp 156–158 °C. Anal. Calcd for C₁₄H₁₈N₂O₄S: C, 54.18; H, 5.85; N, 9.03. Found: C, 53.91; H, 5.80; N, 8.73. IR $\nu_{\max}$ cm⁻¹: 3280 (NH), 3120 (OH). ¹H-NMR (DMSO-*d*₆) δ : 2.17 (3H, s, Ar-CH₃), 2.27 (3H, s, Ar-CH₃), 6.61 (2H, s, 5- and 6-H), 6.69 (1H, s, 3-H), 7.03 (2H, d, *J* = 8 Hz, 5 or 6-H), 7.43 (2H, d, *J* = 8 Hz, 5 or 6-H), 9.50 (2H, br s, OH or NH).

2-Hydrazino-5-methylphenol *p*-Toluenesulfonate (10c) Prepared from 2-amino-5-methylphenol hydrochloride (3.19 g, 20.0 mmol) according to the preparation of 2-hydrazino-4-methylphenol *p*-toluenesulfonate (**10b**). Yield 5.03 g (81%), mp 207–220 °C (dec.). IR $\nu_{\max}$ cm⁻¹: 3290 (NH). ¹H-NMR (DMSO-*d*₆) δ : 2.13 (3H, s, Ar-CH₃), 2.25 (3H, s, Ar-CH₃), 6.42–7.48 (8H, m, Ar-H, NH or OH), 9.60 (4H, br NH or OH). MS *m/z* [FAB (dithiothreitol/thioglycerol = 1/3)]: 311 (M⁺ + 1, 18%), 122, 124 (BP). This compound was used for the next reaction without further purification.

General Method of Ethyl Pyruvate 2-(2-Methanesulfonyloxy)phenylhydrazone Derivatives (7) a) From Ethyl Pyruvate and a 2-Hydrazinophenol Derivative *p*-Toluenesulfonate (**10**): Ethyl pyruvate (1.05 ml, 9.58 mmol) and triethylamine (1.30 ml, 9.33 mmol) were added to a suspension of 2-hydrazinophenol *p*-toluenesulfonate (6.44 mmol) in CH₂Cl₂ (8 ml) under ice-cooling and the whole was stirred for 15 min. The reaction mixture was diluted with CH₂Cl₂ (150 ml), and washed with 5% HCl, saturated NaHCO₃, and brine. The organic layer was dried over MgSO₄ and evaporated to dryness *in vacuo* to give a yellow solid. This solid was dissolved in CH₂Cl₂ (20 ml). MsCl (15.6 mmol) and Et₃N (2.20 ml, 15.8 mmol) were added to this solution under ice-cooling and stirred for 15 min. The reaction mixture was diluted with CH₂Cl₂ (150 ml), and washed with 5% HCl, saturated NaHCO₃, and brine. The organic layer was dried over MgSO₄ and evaporated to dryness *in vacuo* to give the crude products.

These products were column-chromatographed on silica gel using benzene–AcOEt (10 : 1) to give (*Z*)- and (*E*)-hydrazone (**7**).

b) By the Japp–Klingemann Reaction: To a solution of the 2-aminophenol derivative (4.48 mmol) in acetonitrile (10 ml) were added concentrated HCl (1.75 ml), H₂O (5 ml) and a solution of NaNO₂ (327 mg, 4.74 mmol) in H₂O (5 ml) under ice-cooling to give the diazonium solution. This diazonium solution was added dropwise to a solution of 50% aqueous KOH (2 ml) and ethyl 2-methylacetoacetate (0.635 ml, 4.49 mmol) in EtOH (5 ml) under ice-cooling. After the addition of the diazonium solution was complete, the reaction mixture was poured into ice-water (50 ml) and extracted with Et₂O. The organic layer was washed with brine, and dried over MgSO₄. Evaporation of the solvent *in vacuo* gave a solid. This solid was dissolved in CH₂Cl₂ (9 ml), and to this solution MsCl (7.82 mmol) and triethylamine (7.89 mmol) were added under ice-cooling. The mixture was stirred for 15 min under ice-

cooling, poured into water (50 ml) and extracted with CH_2Cl_2 . The organic layer was washed with 10% HCl, saturated NaHCO_3 , and brine, and dried over MgSO_4 . Evaporation of solvent *in vacuo* gave the crude products. The crude products were chromatographed on silica gel using benzene–AcOEt (20:1) to give the (*E*)- and (*Z*)-hydrazone (7).

Ethyl Pyruvate 2-[2-(Methanesulfonyloxy)-3-methyl]phenylhydrazone (7a): Prepared by the b) method from 2-amino-6-methylphenol methanesulfonate (1.19 g, 5.91 mmol). (*Z*)-7a: Yield 147 mg (8%), pale orange needles from AcOEt–hexane, mp 122–124 °C. *Anal.* Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_5\text{S}$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.55; H, 5.76; N, 8.68. MS m/z : 314 (M^+ , 33%), 162 (BP). IR ν_{max} cm^{-1} : 3230 (NH), 1685 (CO). $^1\text{H-NMR}$ δ : 1.33 (3H, t, $J=7$ Hz, CH_2CH_3), 2.15 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 3- CH_3), 2.38 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 3- CH_3), 3.37 (3H, s, SO_2CH_3), 4.26 (2H, q, $J=7$ Hz, OCH_2CH_3), 6.70–7.65 (3H, m, 4, 5, and 6-H), 12.17 (1H, br s, NH). (*E*)-7a: Yield 1.29 g (69%), pale orange needles from AcOEt–hexane, mp 106–108 °C. *Anal.* Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_5\text{S}$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.37; H, 5.76; N, 8.76. MS m/z : 314 (M^+ , 26%), 162 (BP). IR ν_{max} cm^{-1} : 3340 (NH), 1700 (CO). $^1\text{H-NMR}$ δ : 1.37 (3H, t, $J=7$ Hz, CH_2CH_3), 2.10 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 3- CH_3), 2.31 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 3- CH_3), 3.32 (3H, s, SO_2CH_3), 4.31 (2H, q, $J=7$ Hz, OCH_2CH_3), 6.70–7.75 (3H, m, 4, 5, and 6-H), 8.59 (1H, br s, NH).

Ethyl Pyruvate 2-[2-(Methanesulfonyloxy)-4-methyl]phenylhydrazone (7b): Prepared by a) method from 2-hydrazino-5-methylphenol *p*-toluenesulfonate (10b) (2.00 g, 6.44 mmol). (*Z*)-7b: Yield 388 mg (19%), pale yellow needles from benzene–hexane, mp 130–131 °C. *Anal.* Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_5\text{S}$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.74; H, 5.80; N, 8.98. MS m/z : 314 (M^+ , 46%), 235 (BP). IR ν_{max} cm^{-1} : 3250 (NH), 1675 (CO). $^1\text{H-NMR}$ δ : 1.30 (3H, t, $J=7$ Hz, CH_2CH_3), 2.10 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 4- CH_3), 2.23 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 4- CH_3), 3.20 (3H, s, SO_2CH_3), 4.22 (2H, q, $J=7$ Hz, OCH_2CH_3), 6.95 (1H, d, $J=8$ Hz, 5- or 6-H), 7.00 (1H, s, 3-H), 7.43 (1H, d, $J=8$ Hz, 5- or 6-H), 12.10 (1H, br s, NH). (*E*)-7b: Yield 1.12 g (55%), colorless prisms from benzene–hexane, mp 129–131 °C. *Anal.* Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_5\text{S}$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.59; H, 5.76; N, 8.95. MS m/z : 314 (M^+ , 36%), 235 (BP). IR ν_{max} cm^{-1} : 3330 (NH), 1690 (CO). $^1\text{H-NMR}$ δ : 1.35 (3H, t, $J=7$ Hz, CH_2CH_3), 2.08 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 4- CH_3), 2.27 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 4- CH_3), 3.20 (3H, s, SO_2CH_3), 4.28 (2H, q, $J=7$ Hz, OCH_2CH_3), 6.94 (1H, s, 3-H), 7.02 (1H, d, $J=8$ Hz, 5- or 6-H), 7.54 (1H, d, $J=8$ Hz, 5- or 6-H), 8.16 (1H, br s, NH).

Ethyl Pyruvate 2-[2-(Methanesulfonyloxy)-5-methyl]phenylhydrazone (7c): Prepared by the a) method from 2-hydrazino-4-methylphenol *p*-toluenesulfonate (10c, R=H) (2.00 g, 6.44 mmol). (*Z*)-7c: Yield 391 mg (19%), pale yellow needles from benzene–hexane, mp 109–110 °C. *Anal.* Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_5\text{S}$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.38; H, 5.88; N, 8.67. MS m/z : 314 (M^+ , 26%), 162 (BP). IR ν_{max} cm^{-1} : 3240 (NH), 1665 (CO). $^1\text{H-NMR}$ δ : 1.34 (3H, t, $J=7$ Hz, CH_2CH_3), 2.15 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 5- CH_3), 2.33 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 5- CH_3), 3.21 (3H, s, SO_2CH_3), 4.28 (2H, t, $J=7$ Hz, OCH_2CH_3), 6.65 (1H, dd, $J=2$, 8 Hz, 4-H), 7.12 (1H, d, $J=8$ Hz, 3-H), 7.40 (1H, d, $J=2$ Hz, 6-H), 12.20 (1H, br s, NH). (*E*)-7c: Yield 1.22 g (60%), pale orange needles from benzene–hexane, mp 94–96 °C. *Anal.* Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_5\text{S}$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.71; H, 5.76; N, 8.78. MS m/z : 314 (M^+ , 31%), 235 (BP). IR ν_{max} cm^{-1} : 3320 (NH), 1685 (CO). $^1\text{H-NMR}$ δ : 1.35 (3H, t, $J=7$ Hz, CH_2CH_3), 2.10 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 5- CH_3), 2.34 (3H, s, $\text{N}=\text{C}-\text{CH}_3$ or 5- CH_3), 3.17 (3H, s, SO_2CH_3), 4.29 (2H, t, $J=7$ Hz, OCH_2CH_3), 6.68 (1H, dd, $J=2$, 8 Hz, 4-H), 6.99 (1H, d, $J=8$ Hz, 3-H), 7.47 (1H, d, $J=2$ Hz, 6-H), 8.24 (1H, br s, NH).

Ethyl Pyruvate 2-[2-(methanesulfonyloxy)-4-methoxy]phenylhydrazone (7d): Prepared by the b) method from (2-methanesulfonyloxy-4-methoxyphenyl)hydrazine *p*-toluenesulfonate (10d, R=Ms) prepared by reduction of 5-methoxy-2-nitrophenol (1.24 g) by catalytic hydrogenation over 5% Pd–C. (*E*)-7d: Yield 816 mg (49%), pale yellow plates from benzene–hexane, mp 100–102 °C. *Anal.* Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_6\text{S}$: C, 47.27; H, 5.49; N, 8.48. Found: C, 47.13; H, 5.50; N, 8.63. MS m/z : 330 (M^+ , 35%), 251 (BP). IR ν_{max} cm^{-1} : 3370 (NH), 1700 (CO). $^1\text{H-NMR}$ δ : 1.34 (3H, t, $J=7$ Hz, CH_2CH_3), 2.09 (3H, s, $\text{N}=\text{C}-\text{CH}_3$), 3.22 (3H, s, SO_2CH_3), 3.74 (3H, s, OCH_3), 4.27 (2H, q, $J=7$ Hz, OCH_2CH_3), 6.73 (1H, d, $J=2.5$ Hz, 3-H), 6.83 (1H, dd, $J=2.5$, 9 Hz, 5-H), 7.60 (1H, d, $J=9$ Hz, 6-H), 8.10 (1H, br s, NH).

Ethyl Pyruvate 2-[2-(4-Bromo-2-methanesulfonyloxy)phenyl]hydrazone (7e): Prepared by the b) method from 2-amino-5-bromophenol (843 mg, 4.48 mmol). (*Z*)-7e: Yield 105 mg (6%), colorless needles from benzene–hexane, mp 154–156 °C. *Anal.* Calcd for $\text{C}_{12}\text{H}_{15}\text{BrN}_2\text{O}_5\text{S}$: C, 38.01; H, 3.99; N, 7.39. Found: C, 37.75; H, 3.96; N, 7.31. MS m/z : 380 (M^+ + 2, 32%), 378 (M^+ , 31%), 78 (BP). IR ν_{max} cm^{-1} : 3240 (NH), 1670 (CO). $^1\text{H-NMR}$ δ : 1.35 (3H, t, $J=7$ Hz, CH_2CH_3), 2.15 (3H, s, $\text{N}=\text{C}-\text{CH}_3$), 3.27 (3H, s, SO_2CH_3), 4.29 (2H, q, $J=7$ Hz, OCH_2CH_3), 7.22–7.65 (3H, m, Ar-H),

12.22 (1H, br s, NH). (*E*)-7e: Yield 1.30 g (77%), colorless needles from benzene–hexane, mp 125–127 °C. *Anal.* Calcd for $\text{C}_{12}\text{H}_{15}\text{BrN}_2\text{O}_5\text{S}$: C, 38.01; H, 3.99; N, 7.39. Found: C, 37.78; H, 4.01; N, 7.33. MS m/z : 380 (M^+ + 2, 48%), 378 (M^+ , 47%), 78 (BP). IR ν_{max} cm^{-1} : 3340 (NH), 1700 (CO). $^1\text{H-NMR}$ δ : 1.37 (3H, t, $J=7$ Hz, CH_2CH_3), 2.11 (3H, s, $\text{N}=\text{C}-\text{CH}_3$), 3.28 (3H, s, SO_2CH_3), 4.31 (2H, q, $J=7$ Hz, OCH_2CH_3), 7.31 (1H, d, $J=2$ Hz, 3-H), 7.37 (1H, dd, $J=2$, 8 Hz, 5-H), 7.61 (1H, d, $J=8$ Hz, 6-H), 8.27 (1H, br s, NH).

Ethyl Pyruvate 2-[2-(Methanesulfonyloxy)-4-methoxycarbonyl]phenylhydrazone (7f): Prepared by b) method from methyl 4-amino-3-hydroxybenzoate (1.68 g, 10.05 mmol) *via* ethyl pyruvate 2-(2-hydroxy-4-methoxycarbonyl)phenylhydrazone (6f). (*E*)-7f: Yield 2.27 g (63%), colorless needles from benzene–hexane, mp 151–152 °C. *Anal.* Calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_7\text{S}$: C, 46.92; H, 5.06; N, 7.82. Found: C, 46.65; H, 5.05; N, 7.80. MS m/z : 358 (M^+ , 29%), 206 (BP). IR ν_{max} cm^{-1} : 3310 (NH), 1705 (CO). $^1\text{H-NMR}$ δ : 1.36 (3H, t, $J=7$ Hz, CH_2CH_3), 2.13 (3H, s, $\text{N}=\text{C}-\text{CH}_3$), 3.30 (3H, s, SO_2CH_3), 3.86 (3H, s, CO_2CH_3), 4.30 (2H, q, $J=7$ Hz, OCH_2CH_3), 7.69 (1H, d, $J=8$ Hz, 6-H), 7.78 (1H, d, $J=2$ Hz, 3-H), 7.94 (1H, dd, $J=2$, 8 Hz, 5-H), 8.46 (1H, br s, NH).

Fischer Indolization of Phenylhydrazone Derivatives (7). Representative Procedure for Fischer Indolization of Ethyl Pyruvate 2-[2-(Methanesulfonyloxy)-3-methyl]phenylhydrazone (7a) A solution of $\text{TsOH} \cdot \text{H}_2\text{O}$ (1.141 g, 6.00 mmol) in benzene (15 ml) was refluxed in a Dean–Stark water separator for 1.5 h. To this solution was added a solution of the phenylhydrazone ((*E*)-7a) (472 mg, 1.50 mmol) in benzene (15 ml), and the whole was refluxed for 3.5 h. The reaction mixture was poured into ice-water (50 ml) and extracted with AcOEt. The organic layer was washed with saturated NaHCO_3 and brine, and dried over MgSO_4 . Evaporation of the solvent *in vacuo* gave a pale orange solid (475 mg), which was column-chromatographed on silica gel using hexane–AcOEt (4:1) to give ethyl 7-methanesulfonyloxy-6-methylindole-2-carboxylate (11a), ethyl 5-methanesulfonyloxy-4-methylindole-2-carboxylate (11b), and ethyl 5-(*p*-toluenesulfonyloxy)-4-methylindole-2-carboxylate (11c).

Ethyl 7-Methanesulfonyloxy-6-methyl-2-carboxylate (11a): Yield 334 mg (73%), colorless needles from AcOEt–hexane, mp 119–121 °C. *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_5\text{S}$: C, 52.52; H, 5.08; N, 4.71. Found: C, 52.42; H, 5.06; N, 4.76. MS m/z : 297 (M^+ , 27%), 172 (BP). IR ν_{max} cm^{-1} : 3380 (NH), 1715 (CO). $^1\text{H-NMR}$ (400 MHz) δ : 1.41 (3H, t, $J=7$ Hz, CH_2CH_3), 2.46 (3H, s, 6- CH_3), 3.33 (3H, s, SO_2CH_3), 4.40 (2H, q, $J=7$ Hz, OCH_2CH_3), 7.01 (1H, d, $J=8$ Hz, 5-H), 7.20 (1H, d, $J=2$ Hz, 3-H), 7.51 (1H, d, $J=8$ Hz, 4-H), 9.32 (1H, br s, NH).

Ethyl 5-Methanesulfonyloxy-4-methylindole-2-carboxylate (11b): Yield 46 mg (10%), colorless plates from EtOH, mp 176–178 °C. *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_5\text{S}$: C, 52.52; H, 5.08; N, 4.71. Found: C, 52.16; H, 5.06; N, 5.01. MS m/z : 297 (M^+ , 28%), 172 (BP). IR ν_{max} cm^{-1} : 3290 (NH), 1680 (CO). $^1\text{H-NMR}$ (400 MHz) (acetone- d_6) δ : 1.38 (3H, t, $J=7$ Hz, CH_2CH_3), 2.57 (3H, s, 4- CH_3), 3.31 (3H, s, SO_2CH_3), 4.38 (2H, q, $J=7$ Hz, OCH_2CH_3), 7.28 (1H, d, $J=9$ Hz, 7-H), 7.29 (1H, d, $J=1$ Hz, 3-H), 7.43 (1H, d, $J=9$ Hz, 6-H), 11.10 (1H, br s, NH).

The presence of 11c was suggested by observation of MS spectrum [m/z 373 (M^+)] of the mother liquor obtained from the recrystallization of 11a.

The Fischer Indolization of Ethyl Pyruvate 2-[2-(Methanesulfonyloxy)-4-methyl]phenylhydrazone (7b) The hydrazone (7b) (472 mg, 1.50 mmol) was treated with TsOH prepared from $\text{TsOH} \cdot \text{H}_2\text{O}$ (856 mg, 4.50 mmol) in benzene (15 ml) for 1.75 h at 50 °C to give ethyl 7-methanesulfonyloxy-5-methylindole-2-carboxylate (12a) and ethyl 5-methylindole-2-carboxylate (12b).

Ethyl 7-Methanesulfonyloxy-5-methylindole-2-carboxylate (12a): Yield 229 mg (51%), pale yellow prisms from benzene–hexane, mp 130.5–132.5 °C. *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_5\text{S}$: C, 52.52; H, 5.08; N, 4.71. Found: C, 52.42; H, 5.11; N, 4.92. MS m/z : 297 (M^+ , 37%), 172 (BP). IR ν_{max} cm^{-1} : 3340 (NH), 1705 (CO). $^1\text{H-NMR}$ (500 MHz) δ : 1.41 (3H, t, $J=7$ Hz, CH_2CH_3), 1.60 (3H, s, 5- CH_3), 3.25 (3H, s, SO_2CH_3), 4.40 (2H, q, $J=7$ Hz, OCH_2CH_3), 7.07 (1H, d, $J=1$ Hz, 4- or 6-H), 7.17 (1H, d, $J=2$ Hz, 3-H), 7.41 (1H, d, $J=1$ Hz, 6- or 4-H), 9.21 (1H, br s, NH).

Ethyl 5-Methylindole-2-carboxylate (12b): Yield 6 mg (2%), colorless needles from benzene, mp 159–161 °C. IR ν_{max} cm^{-1} : 3310 (NH), 1680 (CO). $^1\text{H-NMR}$ (400 MHz) δ : 1.41 (3H, t, $J=7$ Hz, CH_2CH_3), 2.44 (3H, s, 5- CH_3), 4.40 (2H, q, $J=7$ Hz, OCH_2CH_3), 7.14 (1H, m, 3-H), 7.15 (1H, dd, $J=8$ Hz, 6-H), 7.31 (1H, d, $J=8$ Hz, 7-H), 7.46 (1H, s, 4-H), 8.80 (1H, br s, NH).

This compound was identical with the reported sample (lit.⁷⁾ mp 163–165.5 °C).

The Fischer Indolization of Ethyl Pyruvate 2-[2-(Methanesulfonyloxy)-5-methyl]phenylhydrazone (7c) The (*E*)-hydrazone (7c) (472 mg,

1.50 mmol) was treated with TsOH prepared from TsOH·H₂O (1.141 g, 6.00 mmol) in benzene (15 ml) under reflux for 2.5 h to give four compounds, **13a**—**13d**.

Ethyl 7-Methanesulfonyloxy-4-methylindole-2-carboxylate (13a): Yield 224 mg (50%), colorless prisms from benzene–hexane, mp 146–148 °C. *Anal.* Calcd for C₁₃H₁₅NO₅S: C, 52.52; H, 5.08; N, 4.71. Found: C, 52.39; H, 5.12; N, 4.74. MS *m/z*: 297 (M⁺, 22%), 172 (BP). IR $\nu_{\max}$ cm⁻¹: 3470 (NH), 1710 (CO). ¹H-NMR (400 MHz) δ : 1.42 (3H, t, *J*=7 Hz, CH₂CH₃), 2.56 (3H, s, 4-CH₃), 3.23 (3H, s, SO₂CH₃), 4.43 (2H, q, *J*=7 Hz, OCH₂CH₃), 6.91 (1H, d, *J*=8 Hz, 5-H), 7.13 (1H, d, *J*=8 Hz, 6-H), 7.28 (1H, d, *J*=2 Hz, 3-H), 9.36 (1H, br s, NH).

Ethyl 6-Methyl-5-(*p*-toluenesulfonyloxy)indole-2-carboxylate (13b): Yield 115 mg (21%), colorless needles from benzene–hexane, mp 189–193 °C. *Anal.* Calcd for C₁₉H₁₉NO₅S: C, 61.11; H, 5.13; N, 3.75. Found: C, 61.06; H, 5.08; N, 3.82. MS *m/z*: 373 (M⁺, 34%), 218 (BP). IR $\nu_{\max}$ cm⁻¹: 3310 (NH), 1680 (CO). ¹H-NMR (400 MHz) δ : 1.40 (3H, t, *J*=7 Hz, CH₂CH₃), 2.21 (3H, s, Ar-CH₃), 2.46 (3H, s, Ar-CH₃), 4.40 (2H, q, *J*=7 Hz, OCH₂CH₃), 7.11 (1H, m, 3-H), 7.17 (1H, s, 4- or 7-H), 7.28 (1H, s, 4- or 7-H), 7.32 (2H, d, *J*=8 Hz, Ar-H), 7.75 (2H, d, *J*=8 Hz, Ar-H), 8.81 (1H, br s, NH).

Ethyl 5-Methanesulfonyloxy-6-methylindole-2-carboxylate (13c): Yield 60 mg (14%), colorless needles from benzene–hexane, mp 162–163.5 °C. *Anal.* Calcd for C₁₃H₁₅NO₅S: C, 52.52; H, 5.08; N, 4.71. Found: C, 52.26; H, 5.05; N, 4.77. MS *m/z*: 297 (M⁺, 34%), 218 (BP). IR $\nu_{\max}$ cm⁻¹: 3320 (NH), 1695 (CO). ¹H-NMR δ : 1.40 (3H, t, *J*=7 Hz, CH₂CH₃), 2.44 (3H, s, 6-CH₃), 3.18 (3H, s, SO₂CH₃), 4.38 (2H, q, *J*=7 Hz, OCH₂CH₃), 7.08 (1H, m, 3-H), 7.17 (1H, s, 4- or 7-H), 7.51 (1H, s, 4- or 7-H), 9.00 (1H, br s, NH).

Ethyl 6-Methylindole-2-carboxylate (13d): Yield 4 mg (1.4%), colorless prisms from benzene–hexane, mp 123–127 °C. This compound was identical with an authentic sample (lit.¹⁰) mp 126–129 °C).

The Fischer Indolization of Ethyl Pyruvate 2-[2-(Methanesulfonyloxy)-4-methoxy]phenylhydrazones (7d) The hydrazone ((*E*)-**7d**) (250 mg, 0.757 mmol) was treated with TsOH prepared from TsOH·H₂O (432 mg, 2.27 mmol) in benzene (7.5 ml) at 50 °C for 50 min to give **14a**—**c**.

Ethyl 7-Methanesulfonyloxy-5-methoxyindole-2-carboxylate (14a): Yield 131 mg (55%), colorless prisms from AcOEt–hexane, mp 147–148 °C. *Anal.* Calcd for C₁₃H₁₅NO₆S: C, 49.83; H, 4.83; N, 4.47. Found: C, 49.53; H, 4.81; N, 4.53. MS *m/z*: 313 (M⁺, 32%), 234 (BP). IR $\nu_{\max}$ cm⁻¹: 3330 (NH), 1700 (CO). ¹H-NMR (400 MHz) δ : 1.41 (3H, t, *J*=7 Hz, CH₂CH₃), 3.26 (3H, s, SO₂CH₃), 3.85 (3H, s, OCH₃), 4.41 (2H, q, *J*=7 Hz, OCH₂CH₃), 6.94 (1H, d, *J*=2 Hz, 4- or 6-H), 7.04 (1H, d, *J*=2 Hz, 4- or 6-H), 7.17 (1H, d, *J*=2 Hz, 3-H), 9.22 (1H, br s, NH).

Ethyl 5-Methoxyindole-2-carboxylate (14b): Yield 17 mg (10%), colorless prisms from AcOEt–hexane, mp 163–164 °C. IR $\nu_{\max}$ cm⁻¹: 3320 (NH), 1680 (CO). ¹H-NMR δ : 1.39 (3H, t, *J*=7 Hz, CH₂CH₃), 3.81 (3H, s, OCH₃), 4.40 (2H, q, *J*=7 Hz, OCH₂CH₃), 6.85–7.45 (4H, m, Ar-H), 9.15 (1H, br s, NH). This compound was identical with an authentic sample (lit.⁷) mp 158–160 °C).

Ethyl 2-(2-Ethoxycarbonyl-5-methoxyindol-3-yl)acrylate (14c): Yield 9 mg (4%), colorless prisms from AcOEt–hexane, mp 141–143 °C. *Anal.* Calcd for C₁₇H₁₉NO₅: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.43; H, 6.09; N, 4.49. IR $\nu_{\max}$ cm⁻¹: 3290 (NH), 1720, 1675 (CO). ¹H-NMR (400 MHz) δ : 1.25 (3H, t, *J*=7 Hz, CH₂CH₃), 1.35 (3H, t, *J*=7 Hz, CH₂CH₃), 3.84 (3H, s, OCH₃), 4.23 (3H, q, *J*=7 Hz, OCH₂CH₃), 4.33 (2H, q, *J*=7 Hz, OCH₂CH₃), 5.91 (1H, d, *J*=1.5 Hz, ind-C=CH), 6.65 (1H, d, *J*=1.5 Hz, ind-C=CH), 7.00 (1H, d, *J*=2 Hz, 4-H), 7.01 (1H, dd, *J*=2, 9 Hz, 6-H), 7.31 (1H, d, *J*=9 Hz, 7-H), 8.92 (1H, br s, NH).

The Fischer Indolization of Ethyl Pyruvate 2-[4-Bromo-2-(methanesulfonyloxy)]phenylhydrazones (7e) The hydrazone ((*E*)-**7e**) (190 mg, 0.501 mmol) was treated with TsOH, prepared from TsOH·H₂O (382 mg, 2.00 mmol), in toluene (5 ml) under reflux for 6 h to give **15**.

Ethyl 5-Bromo-7-methanesulfonyloxyindole-2-carboxylate (15): Yield 119 mg (65%), colorless needles from benzene–hexane, mp 138–139 °C. *Anal.* Calcd for C₁₂H₁₂BrNO₅S: C, 39.79; H, 3.34; N, 3.87. Found: C, 39.69;

H, 3.39; N, 3.81. MS *m/z*: 363 (M⁺+2, 24%), 361 (M⁺, 23%), 238 (BP). IR $\nu_{\max}$ cm⁻¹: 3260 (NH), 1705 (CO). ¹H-NMR (400 MHz) δ : 1.42 (3H, t, *J*=7 Hz, CH₂CH₃), 3.30 (3H, s, SO₂CH₃), 4.43 (2H, q, *J*=7 Hz, OCH₂CH₃), 7.18 (1H, d, *J*=2 Hz, 3-H), 7.36 (1H, d, *J*=1.5 Hz, 4- or 6-H), 7.79 (1H, d, *J*=1.5 Hz, 4- or 6-H), 9.37 (1H, br s, NH).

The Fischer Indolization of Ethyl Pyruvate 2-[2-(Methanesulfonyloxy)-4-methoxycarbonyl]phenylhydrazones (7f) The hydrazone ((*E*)-**7f**) (269 mg, 0.751 mmol) was treated with TsOH, prepared from TsOH·H₂O (858 mg, 4.51 mmol), in toluene (15 ml) under reflux for 14 h to give **16a**.

Ethyl 7-Methanesulfonyloxy-5-methoxycarbonylindole-2-carboxylate (16a): Yield 137 mg (53%), colorless needles from benzene–hexane, mp 159–160 °C. *Anal.* Calcd for C₁₄H₁₅NO₇S: C, 49.26; H, 4.43; N, 4.10. Found: C, 49.46; H, 4.38; N, 4.03. MS *m/z*: 341 (M⁺, 46%), 262 (BP). IR $\nu_{\max}$ cm⁻¹: 3330 (NH), 1715 (CO). ¹H-NMR (400 MHz) δ : 1.43 (3H, t, *J*=7 Hz, CH₂CH₃), 3.32 (3H, s, SO₂CH₃), 3.95 (3H, s, CO₂CH₃), 4.44 (2H, q, *J*=7 Hz, OCH₂CH₃), 7.34 (1H, d, *J*=2 Hz, 3-H), 7.89 (1H, d, *J*=1.5 Hz, 6-H), 8.42 (1H, d, *J*=1.5 Hz, 4-H), 9.58 (1H, br s, NH).

Fischer Indolization of 7f with PPA A mixture of (*E*)-ethyl pyruvate 2-[(2-methanesulfonyloxy)-4-methoxycarbonyl]phenylhydrazones (**7f**) (269 mg, 0.751 mmol) and PPA (3.5 g) was stirred at 80 °C for 1.25 h. The reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with saturated NaHCO₃ and brine, and dried over MgSO₄. Evaporation of solvent *in vacuo* gave a brown oil (210 mg). Column chromatography of this oil on silica gel using benzene–AcOEt gave **16a** and **16b**.

Ethyl 7-Methanesulfonyloxy-5-methoxycarbonylindole-2-carboxylate (16a): Yield 116 mg (45%), colorless needles from benzene–hexane, mp 158–160 °C.

This compound was identical with the sample obtained in the reaction of **7f** with TsOH as described above.

3-Ethoxycarbonyl-6-methoxycarbonyl-1,2-dihydrocinnoline (16b): Yield 58 mg (22%), pale yellow prisms from benzene–hexane, mp 266–269 °C. HRMS Calcd for C₁₃H₁₄N₂O₄: 262.0953. Found: 262.0934. MS *m/z*: 262 (M⁺, 97%), 216 (BP). IR $\nu_{\max}$ (KBr) cm⁻¹: 3480, 3340 (NH), 1685, 1640 (CO). ¹H-NMR (400 MHz) (DMSO-*d*₆) δ : 1.33 (3H, t, *J*=7 Hz, CH₂CH₃), 3.82 (3H, s, CO₂CH₃), 4.27 (2H, q, *J*=7 Hz, OCH₂CH₃), 6.83 (2H, s, 4-H and NH, changed to 0.5H by addition of D₂O), 7.19 (1H, d, *J*=8 Hz, 7- or 8-H), 7.57 (1H, d, *J*=8 Hz, 7- or 8-H), 8.23 (1H, s, 5-H), 11.00 (1H, br s, NH, disappeared by addition of D₂O).

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