

p-TOLUENESULFONIC ACID AND CATION EXCHANGE RESIN IN APROTIC
SOLVENT: VALUABLE CATALYSTS FOR FISCHER INDOLIZATION

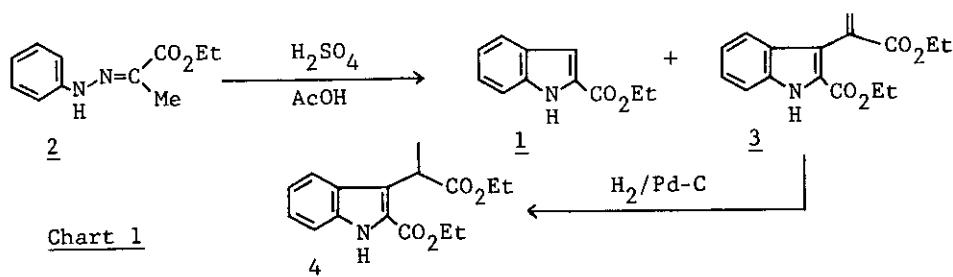
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Abstract—p-Toluenesulfonic acid and cation exchange resin
(Amberlyst-15) in aprotic solvent were found to serve as a good
catalyst for Fischer indolization in many cases. With this
condition ethyl indole-2-carboxylate was prepared more conve-
niently in better yield than by previous methods.

Fischer indolization^{1a} is the most valuable and widely-used method for synthesis
of indoles, and thus numerous combination of mineral, organic, or Lewis acids
with various solvents have been developed^{1b} for the catalyst. However, there have
not been so many examples^{1b,2} reported for the usage of aprotic solvents. We now
wish to report that p-toluenesulfonic acid (TsOH) and cation exchange resin
(Amberlyst-15) in aprotic solvent (benzene or toluene) have some advantages for
practical synthesis of various indoles by Fischer indolization.

In connection with our synthetic studies³ we needed a large amount of ethyl in-
dole-2-carboxylate (1), which is a stable equivalent of indole itself. Although
the Reissert method is considered⁴ as a standard one for preparing the indole (1),
the yield is neither satisfactory nor the procedure is necessarily convenient
because of the use of dangerous metal potassium. We reinvestigated the Fischer
indolization of ethyl pyruvate 2-(phenylhydrazone) (2) for the facile and improved
preparation of the indole (1), as Fischer indolization is suitable for laboratory
large scale experiment because of its easy-handling procedure.

At first we tried the Fischer indolization of the phenylhydrazone (2) with H₂SO₄/
AcOH as reported.⁵ However, this reaction afforded the indole (1) in only 38.8%
yield, accompanied with ethyl 2-(2-ethoxycarbonylindol-3-yl)acrylate (3) in 5.9%



yield. The yield of the acrylate (3) varied greatly every experiment. The structure of this compound (3) was determined spectroscopically and confirmed by the fact that it could be easily hydrogenated to a saturated compound (4). The formation of the acrylate (3) can be explained⁶ by the reaction of the indole (1) with an unreacted phenylhydrazone (2) or ethyl pyruvate, the latter of which would be formed by hydrolysis of 2, indicating a cause of decreasing yield of 1. Therefore we examined the condition using aprotic solvents, and finally found that refluxing of the phenylhydrazone (2) with TsOH in benzene (or toluene) gave the desired indole (1) as a sole product in an excellent yield (86%). As this condition has been in almost no use except our experiment in the abnormal Fischer indolization,⁷ this achievement prompted us to apply this condition to the Fischer indolization of other phenylhydrazones. A wide variety of indole derivatives including 2-acyl- and 2,3-dialkyl indoles could be prepared in good yields as is shown in the Table. The merit of TsOH suggested us to use the cation exchange resin due to its facility in handling. The cation exchange resin catalyst on Fischer indolization has been successfully used in only hydroxylic solvents,⁸ not being applied to the Fischer indolization of the phenylhydrazones unstable in hydroxylic solvents. We found that Amberlyst-15 in toluene^{8d} could be effective

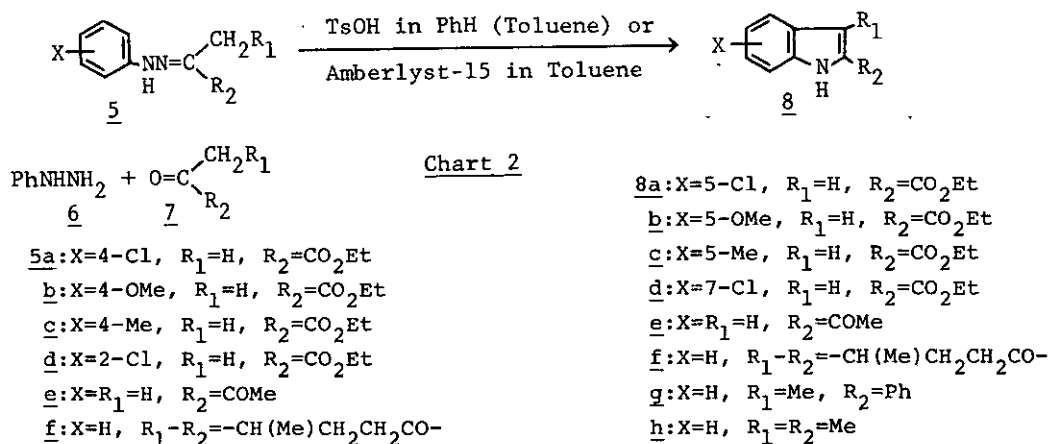


Table. The Results of the Fischer Indolization

Run	starting material mp(°C) (lit. mp)	TsOH (in solvent)		Amberlyst-15 (in toluene)		Products (1,8) mp(°C) (lit. mp)
		condition	yield(%)	condition	yield(%)	
1	<u>E-2</u> :117-119 (117-118) ^{12a}	refl. 1h (benzene)	86	110°C, 3.5h 63		<u>1</u> :124-125.5 (122) ⁵
2	<u>E-5a</u> :140-141 (138) ^{12b}	refl. 5h (benzene)	89	110°C, 8h 70		<u>8a</u> :171.5-172.5 (167-168) ^{12b}
3	<u>Z-5b</u> :99-100 (97) ^{12c}	70°C 1h (toluene)	69	110°C, 3.5h 37		<u>8b</u> :158-160 (154-157) ^{14c}
4	<u>E-5c</u> :106-107 (108) ^{12d}	r.t. 5h (benzene)	82	110°C, 5h (87) ^a		<u>8c</u> :163-165.5 (163-164) ^{12d}
5	<u>E-5d</u> :53-55 (55-56.5) ^{11a}	refl. 12h (toluene)	75	110°C, 10h 52		<u>8d</u> :111-112.5 (113.5-114) ^{11a}
6	<u>E-5e</u> :134.5-136 (132-134) ^{12a}	refl. 5h (toluene)	35	110°C, 9h 43		<u>8e</u> :157-158 (154-155) ¹⁰
7	<u>Z-5f</u> :146-149 (137-140) ^{12e}	r.t. 2.5h (benzene)	85	90°C, 3.5h 80		<u>8f</u> :139-140 (145-146) ^{12e}
8	<u>6</u> , <u>7</u> (R ₁ =Me, R ₂ =Ph)	refl. 4.5h (toluene)	82	110°C, 1h 50		<u>8g</u> :95-97 (96-98) ^{8a}
9	<u>6</u> , <u>7</u> (R ₁ =R ₂ =Me)	80°C, 45min (toluene)	76	80°C, 50min 38		<u>8h</u> :104-106.5 (103-106) ^{8a}
10	<u>6</u> , <u>7</u> (R ₁ =H, R ₂ =CO ₂ Et)	refl. 1.5h (benzene)	71	—————		<u>1</u> :121-124

a: The resin ground down was used.

for the Fischer indolization as is shown in the table, whereas commonly used cation exchange resin Amberlite IR-120^{8a} was reported to be ineffective in aprotic solvent. 2-Acetylinole^{9,10} (8e) was safely prepared in better yield than by the reported method; that is, the Fischer indolization with polyphosphoric acid^{9a,b} caused acyl rearrangement to give 3-acetylinole and the other method^{9a} gave 8e in worse yield. No abnormal product^{7,11} was formed with *o*-substituted phenylhydrazone (Run 5) by this method. The use of the resin ground down increased the yield of indoles to some extent (Run 4). Although the resin method seemed to be less effective than the TsOH method, it should be emphasized that almost pure product is obtained after removal of resin by filtration and that the recovered

resin can be recycled. For the more convenient preparation of indoles, the one-pot synthesis starting from phenylhydrazine (6) and ketone (7) was also tried. The mixture of 6 and 7 was treated with TsOH in a same way as phenylhydrazones (5) to give the corresponding indoles in excellent yields (Runs 8,9,and 10). This one-pot procedure is suitable and convenient to laboratory large scale preparation. Consequently the TsOH in benzene was found to serve as the effective catalyst and the Amberlyst-15 in toluene to serve as an easy-handling catalyst for Fischer indolization. By the reaction under this condition ethyl indole-2-carboxylate (1) can be prepared more efficiently and conveniently than by other methods.

EXPERIMENTAL

All melting points were measured on a micro melting point hot stage (Yanagimoto) and are uncorrected. IR, $^1\text{H-NMR}$ and mass spectra were obtained with Shimadzu IR-400, Hitachi R-24B (60 MHz), and JEOL JMS-01-SG-2 spectrometers, respectively. Preparation of the Phenylhydrazones. All phenylhydrazones in this paper were prepared according to the reported methods cited in the table.

Identification of Indoles. The indoles prepared were spectroscopically characterized and identical with known samples on their melting points.

Fischer Indolization of Ethyl Pyruvate 2-(Phenylhydrazone) (2) with $\text{H}_2\text{SO}_4/\text{AcOH}$.

To a solution of the phenylhydrazone (2) (618 mg) in AcOH (10 ml) was added conc. H_2SO_4 (0.5 ml) and the mixture was heated at 80-85°C for 1 h. The reaction mixture was poured into ice-water, extracted with benzene. The organic layer was washed with 10% Na_2CO_3 and sat. NaCl, dried over MgSO_4 , and evaporated to dryness. The residue was chromatographed over silica gel [hexane-AcOEt (10:1) as an eluant]. The first eluate was ethyl indole-2-carboxylate (1) (220 mg, 38.8%), mp 123-125.5°C (lit.^{4,5}, mp 122.5-124°C), which was identical with an authentic sample.⁴ The second eluate was ethyl 2-(2-ethoxycarbonylindol-3-yl)acrylate (3) (53 mg, 5.9%). Recrystallization from benzene gave colorless needles, mp 84.5-85.5°C. IR (Nujol): 3280(NH), 1710(C=O) cm^{-1} . $^1\text{H-NMR}$ (δ , CDCl_3): 1.25 and 1.35 (each 3H, t, $J=7.0$ Hz, CH_2CH_3), 4.22 and 4.32 (each 2H, q, $J=7.0$ Hz, OCH_2CH_3), 5.88 and 6.62 (each 1H, d, $J=2.0$ Hz, olefinic H), 7.00-7.70 (4H, m, ArH), 9.20 (1H, br s NH). MS m/z : 287(M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 67.15; H, 6.06; N, 4.89.

Ethyl 2-(2-Ethoxycarbonylindol-3-yl)propionate (4). A solution of the acrylate (3) (200 mg) in EtOH (20 ml) was hydrogenated under an atmospheric pressure at room

temperature in the presence of 5% Pd-C (100 mg). When uptake of hydrogen was complete, the catalyst was filtered and the solution was concentrated to dryness *in vacuo*. The residue was recrystallized from hexane-Et₂O to give colorless fine needles (160 mg, 80%), mp 59-60.5°C. IR (Nujol): 3310 (NH), 1715, 1690 (C=O) cm⁻¹. ¹H-NMR (δ, CDCl₃): 1.16 and 1.44 (each 3H, t, J=7.0 Hz, OCH₂CH₃), 1.63 (3H, d, J=7.0 Hz, CH-CH₃), 4.15 and 4.41 (each 2H, q, J=7.0 Hz, OCH₂CH₃), 4.85 (1H, q, J=7.0 Hz, CH-CH₃), 6.90-7.80 (4H, m, ArH), 8.85 (1H, br s, NH). MS m/z: 289 (M⁺). Anal. Calcd for C₁₆H₁₉NO₄: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.48; H, 6.87; N, 4.98.

The Fischer Indolization with TsOH in Benzene Typified by the Preparation of Ethyl Indole-2-carboxylate (1). To a solution of TsOH·H₂O [(856 mg, 4.5 mmol), previously dehydrated by refluxing in benzene] in benzene (10 ml) was added the hydrazone (4) (618 mg, 3 mmol), and the whole was refluxed for 1 h. The reaction mixture was diluted with benzene, washed with aq. NaHCO₃, dried over MgSO₄, and evaporated to dryness *in vacuo* to give the crude material (0.51 g). This was passed through a short column of silica gel [hexane-AcOEt (10:1) as an eluent] to yield ethyl indole-2-carboxylate (1) (485 mg, 85.5%), mp 124-125.5°C. Recrystallization from benzene-hexane gave colorless needles, mp 125-126°C.

The Fischer Indolization with Amberlyst-15 in Toluene Typified by the Preparation of 3,4-Dihydro-4-methylcarbazole-1-one (8f). Amberlyst-15 (472 mg, 2.31 mmol eq.) was added to a solution of 4-methyl-2-phenylhydrazonocyclohexanone (5f) (200 mg, 0.925 mmol) in toluene (10 ml), and the whole was heated at 90°C with stirring for 3.5 h. When the reaction was complete, the resin was filtered off and washed with ethyl acetate. The combined filtrate and washings were evaporated to dryness *in vacuo* to yield 4-methyl-3,4-dihydrocarbazole-1-one (8f) (155 mg) as solid. After passing through a short column of silica gel, the solid (147 mg, 79.9%) was recrystallized from benzene-hexane to give colorless prisms, mp 139-140°C.

One-pot Synthesis of Ethyl Indole-2-carboxylate (1). The mixture of phenylhydrazine (6) (10.8 g, 0.10 mol) and ethyl pyruvate (11.6 g, 0.10 mol) in benzene (300 ml) was refluxed for 1.5 h in the presence of a trace amount of TsOH in a round-bottomed flask equipped with Dean-Stark apparatus to remove water. This solution was added to a cooled solution of dehydrated TsOH in benzene (300 ml), which was prepared from TsOH·H₂O (28.5 g, 0.15 mol) by using Dean-Stark apparatus, and the mixture was refluxed for 1.5 h. After the reaction was complete, the reaction

mixture was washed successively with 5% aq. HCl, 5% aq. NaOH, and sat. aq. NaCl. After drying over MgSO_4 , this benzene solution was directly passed through a column of Al_2O_3 (150 g) and evaporated to give 14.42 g of pale yellow solid, which was recrystallized from EtOH to give the pure product (11.90 g), mp 121-124°C. From the mother liquor further crops of 1 (1.47 g) were obtained. The total yield was 71%.

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Received, 24th January, 1984