FISCHER INDOLE SYNTHESIS IN THE ABSENCE OF A SOLVENT

Kiyoshi Matsumoto,*[a] Akinori Tanaka,[a] Ikemi Yukio,[a] Naoto Hayashi,[a] Mitsuo Toda[b] and Robert A. Bulman[c]

[a] Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan

[b] Faculty of Engineering, Shizuoka University, Hamamatsu 432-8561, Japan

[c] National Radiological Protection Board, Chilton, Didcot, Oxfordshire OX11 0RQ, UK

Abstract : The traditional Fischer synthesis of indoles has been investigated and it has been shown that the reaction proceeds in good yield in the absence of a solvent.

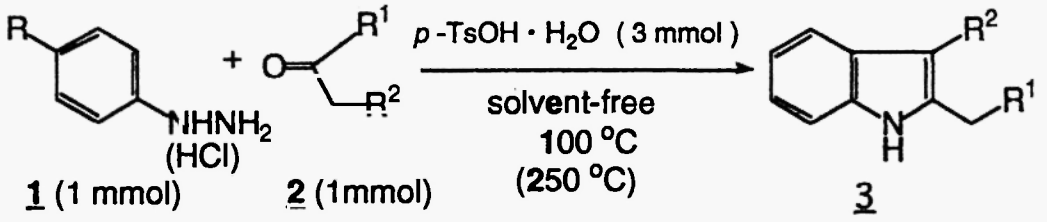
Introduction

In 1883, while studying the reactivity of arylhydrazines and arylhydrazones, Emil Fischer found that, under acidic conditions, enolizable arylhydrazones undergo rearrangement and loss of ammonia to provide indole products (1-3). Subsequent studies suggested a mechanism for the Fischer indole synthesis that proceeds through an initial acid-catalyzed tautomerization of an arylhydrazone to an ene-hydrazine. The ene-hydrazine then undergoes [3,3]-sigmatropic rearrangement to produce a bis-imine intermediate. Subsequent aromatization of the iminocyclohexadiene ring followed by intramolecular nucleophilic attack produces an aminal, which after loss of ammonia affords the indole product (4). Over 100 years after the initial discovery, the Fischer indole synthesis remains the most commonly employed method for the preparation of indoles (5,6) Since a novel entry into the Fischer indole synthesis via a palladium-catalyzed strategy for the preparation of hydrazones has recently been developed particularly by Buchwald (7,8), the scope of Fischer indole synthesis has expanded. Recently combinatorial syntheses of indole derivatives have been reported (9). On the other hand, many advantages of solvent free reactions have been recognized such as reduced pollution, low costs, and simplicity in process and handling (10). We now report that the classical Fischer indole synthesis can be achieved in the absence of a solvent that is followed by a simple work up of the reaction products.

Results and Discussion

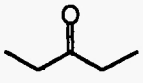
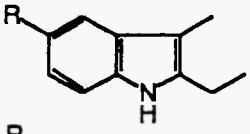
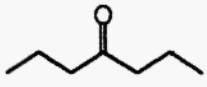
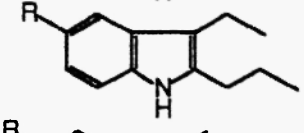
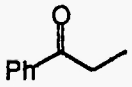
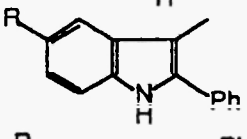
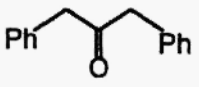
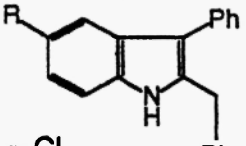
A mixture of phenylhydrazine **1a** , 3-pentanone, and *p*-toluenesulfonic acid (molar ratio 1:1:3) was heated, with mixing, in a test tube, on a water bath, at around 100 °C for 5 min. The crude product was collected by filtration, washed with water and dried to give 2-ethyl-3-methylindole in

82 % yield. Other examples of the reaction products are summarized in Table 1.



Scheme 1

Table 1 Fischer indole synthesis with acyclic ketones

Entry	Ketone	Indole	Yield (%)
1			**a** : 82 **b** : 100 **c** : 78
2			**a** : 85
3			**a** : 88[a] **b** : 79 **c** : 99
4			**a** : 100[a] **b** : 100

a : R = H, **b** : R = CH_3, **c** : R = Cl

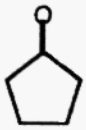
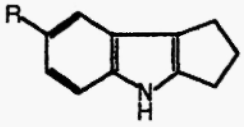
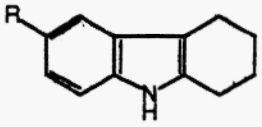
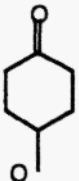
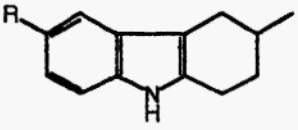
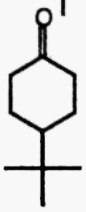
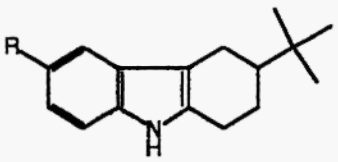
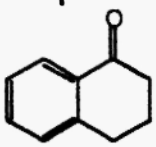
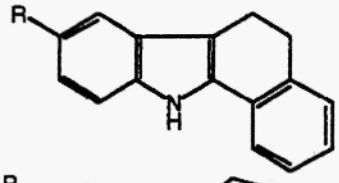
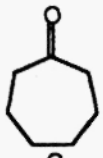
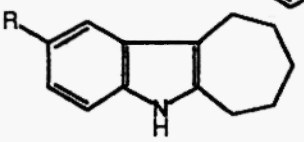
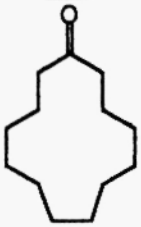
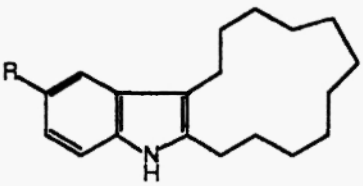
[a] Cl_3CCO_2H was used.

4-Methylphenylhydrazine **1b** and 4-chlorophenylhydrazine **1c**, both commercially available as their hydrochlorides, were reacted at 250 °C in the absence of *p*-toluenesulfonic acid for 1 min. Unfortunately, however, the present method is not amenable to ketones such as acetone and acetophenone that are not easily enolizable and, thus, do not afford the corresponding indoles.

The present method, which is extremely simple, has proved particularly useful for the preparation of indoles from carbocyclic ketones. These results are shown in Table 2. In some cases, trichloroacetic acid was found to be superior to *p*-toluenesulfonic acid. For example, when a mixture of **1a**, cyclohexanone, and *p*-toluenesulfonic acid (molar ratio 1:1:3) was heated at 100 °C for 5 min and worked up as above, the resulting 1,2,3,4-tetrahydrocarbazole was contaminated with a slight

amount of *p*-toluenesulfonic acid. In contrast, a pure product was isolated when trichloroacetic acid was used. This is the acid of choice for the reactions of cyclic ketones with **1a**. The catalyzing effectiveness of trichloroacetic acid is indicated in Table 2.

Table 2 Fischer inodole synthesis with cyclic ketones

Entry	Ketone	Indole	Yield (%)
1			**a** : 46[a] **b** : 100 **c** : 100
2			**a** : 94[a] **b** : 94 **c** : 91
3			**a** : 99[a]
4			**a** : 100[a] **b** : 100 **c** : 84
5			**a** : 98[a] **b** : 90 **c** : 91
6			**a** : 100[a] **b** : 96 **c** : 90
7			**a** : 100[a] **b** : 98 **c** : 100

a : R = H, **b** : R = CH_3, **c** : R = Cl

[a] Cl_3CCO_2H was used.

Conclusion

The Fischer indole synthesis was successfully achieved without solvent in a simple procedure with excellent yields but with some minor limitations. Whereas some of the Fischer indole syntheses described by Vogel (11) employ anhydrous zinc chloride and hence conc. hydrochloric acid to remove the zinc chloride catalyst, the reaction conditions employed here use neither zinc chloride nor hydrochloric acid. These reactions conditions are much more in line with the aspirations of green chemistry.

Experimental

General procedure for one-pot synthesis of indoles from 1a without solvent

A mixture of phenylhydrazine **1a** (108 mg, 1.0 mmol), ketones (1 mmol) and *p*-toluenesulfonic acid monohydrate (570 mg, 3 mmol) [or trichloroacetic acid (490 mg, 3 mmol) was heated, with swirling, in test tube at 100 °C for 5 min. Water was added to the cooled mixture which was filtered. The retentate was washed with water and dried in vacuum to give the corresponding analytically pure indoles.

2-Phenyl-3-methylindole : mp 80- 81°C; ν_{max}/cm^{-1} 3420; ^1H NMR($CDCl_3$) δ 2.47(s, 3H), 7.14(t, J= 7Hz, 2H), 7.20(t, J=7.6Hz, 2H), 7.33(m, 2H), 7.48(m, 2H), 7.59(m,3H), 8.02(bs,1H,NH); ^{13}C NMR($CDCl_3$) δ 9.66(q),108.73(s), 110.65(d, C7), 118.98(d, C5) 119.53(d, C6), 122.32(d, C4), 127.32(d, C4') 127.74(d, C3',C5'), 128.61(d, C2',C6'), 130.05, 133.39,134.03,135.85(each s). Anal. Calcd. for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 87.01; H, 6.36; N, 6.56.

General procedure for one-pot synthesis of indoles from 4-methylphenylhydrazine (HCl salt) 1b or 4-chlorophenylhydrazine (HCl salt) 1c without solvent

A mixture of either **1b** (1 mmol), or **1c**, and the various ketones (1 mmol) was heated, at 250 °C, in a test tube for 1 min with swirling and worked up as above.

8-Methyl-1,2,3,4-tetrahydrocalbazole: mp.126-127 °C:ν_{max}/cm^{-1} 3396; ^1H NMR($CDCl_3$)δ 1.81-1.99 (m, 4H), 2.67-2.77 (m, 4H), 7.06(t, J=7.32, 1H), 7.10 (t, J=7.94, 1H), 7.27(d, J=7.94, 1H), 7.32(d, J=7.32, 1H); ^{13}C NMR($CDCl_3$)δ 20.91(t), 23.23(t), 23.26(t), 23.30(t), 110.22(s), 110.31(d), 117.72(d), 119.11(d), 121.11(d), 127.84(s), 134.04(s), 135.66(s). Anal. Calcd. for $C_{13}H_{15}N$: C, 84.28 H, 8.16; N, 7.56. Found: C, 83.96; H, 8.19; N, 7.45

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