One-Pot Synthesis of Indoles from Ketones and Hydrazines under Mild Reaction Conditions

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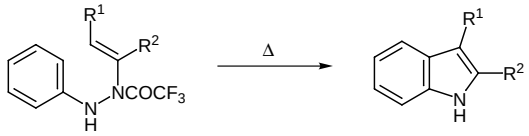
Received 16 April 2001; revised 25 May 2001

Abstract: A facile one-pot method is presented for the synthesis of indoles via condensation of ketone with hydrazine followed by acylation and rearrangement. This convenient synthetic method provides an easy and simple access to indoles.

Key words: *N*-trifluoroacetyl enehydrazine, ketone, indole, indoline, one-pot synthesis

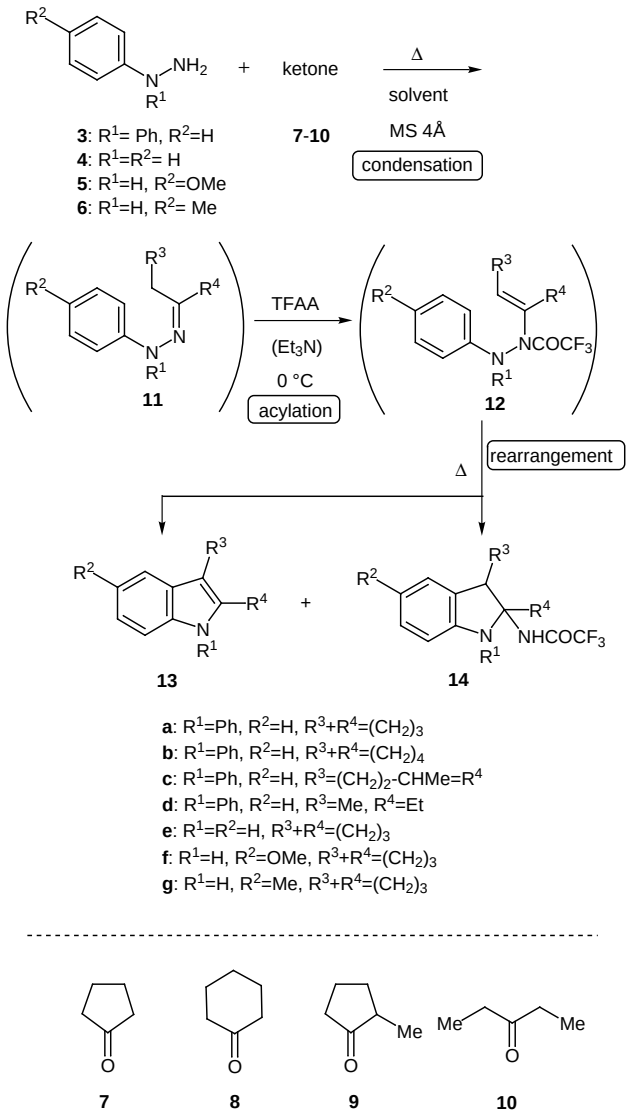
Compounds involving the indole nucleus have gained much attention due to their rich biological activity.[1] Although many synthetic routes to indoles have been developed,[1–3] there is still a need for concise and practical synthetic methods. Fischer indolization[3] involving the preparation of indoles from arylhydrazones has become one of the most versatile and widely studied reactions in organic chemistry. The requisite arylhydrazones are most commonly prepared by the condensation of carbonyl compounds with arylhydrazines. The development of one-pot approaches to indoles is a new subject of considerable interest because of their great significance in both economical and ecological points of view. However, there have only been a few reports[4] on the one-pot synthesis of indoles using Fischer indolization. Recently, we found a useful method for synthesis of indoles **2** via thermal cyclization of *N*-trifluoroacetyl enehydrazines **1** which proceeds smoothly even under non-acidic conditions (Scheme 1).[5] Considering the proposed reaction pathway involving several intermediates, we established a novel one-pot procedure for the synthesis of indoles from ketones and hydrazines under non-acidic reaction conditions.



1 **2**

Scheme 1

This one-pot synthesis of indoles consists of three steps as shown in Scheme 2. We envisioned that we could first prepare the required hydrazone **11** via condensation of the ketone with the hydrazine (the first step); then **11** could be subjected to acylation with TFAA to provide *N*-trifluoroacetylenehydrazine **12** (the second step). Subsequent [3,3]-sigmatropic rearrangement of **12** could provide the desired indole (the third step). Also, we felt that all these three operations could be conveniently carried out in one-pot without isolation of any compounds.

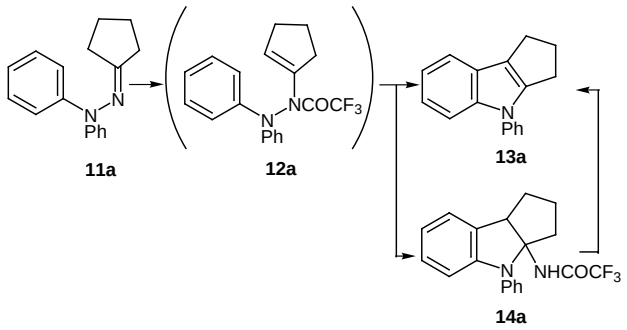


Scheme 2

Synthesis 2001, No. 11, 28 08 2001. Article Identifier:
1437-210X,E;2001,0,11,1635,1638,ftx,en;F03301SS.pdf.

ISSN 0039-7881

As a preliminary experiment, we first examined the preparation of indole from hydrazone **11a** without isolation of *N*-trifluoroacetyl enehydrazine **12a** (Scheme 3). The hydrazone **11a**, prepared from cyclopentanone (**7**) and diphenylhydrazine (**3**) was treated with TFAA in THF at 0 °C and subsequently, the reaction mixture containing the *N*-trifluoroacetyl enehydrazine **12a** was stirred under reflux for rearrangement to give the indole **13a** and indoline **14a** in 69% and 30% yield, respectively. In order to trap TFA formed, the acylation was carried out in the presence of Et_3N to give a 1:2.5 mixture of **13a** and **14a** in 99% combined yield, of which the latter was readily converted into indole **13a** by either treatment with 1 equivalent of TFA at 65 °C or by heating in xylene at 140 °C. These results suggested that this method was suitable for the synthesis of indoles.



Scheme 3

The present procedure was extended to one-pot synthesis of various types of indoles from ketones and hydrazines. The results are summarized in Table 1 (Scheme 2). We first chose a combination of commercially available cyclopentanone (**7**) and diphenylhydrazine (**3**). Condensation of **7** with **3** proceeded smoothly in the presence of molecular sieves 4 Å (MS 4 Å) in THF under reflux to give hydrazone **11a**. After the starting material had been consumed (TLC), TFAA was added to the same reaction vessel at 0 °C, and the reaction mixture was stirred under reflux whilst monitoring by TLC. This one-pot procedure afforded a 1:1 mixture of indole **13a** and indoline **14a** in 92% combined yield (entry 1). When benzene was used as solvent, the indole **13a** was obtained in 81% yield as a sole product (entry 2). In the absence of MS 4 Å, a prolonged reaction time was required for the preparation of hydrazone **11a**. Therefore, the presence of MS 4 Å is indispensable in the condensation step. The reaction of cyclohexanone (**8**) with **3** in benzene gave the indole **13b** as a sole product in 81% yield (entry 4). Under the same conditions, the substrate **9** having a substituent in the cyclopentanone ring was exclusively converted into the corresponding indole **13c** in 77% yield (entry 5). On the other hand, the reaction of **9** in the presence of triethylamine gave a mixture of **13c** and **14c** (entry 6). To demonstrate the generality, we next investigated the one-pot reaction of acyclic ketone **10** with diphenylhydrazine **3**. The indole **13d** was obtained in 86% yield (entry 7). The one-pot reaction of ketone **7** and *N*-monophenylhydrazine **4** gave the indole **13e**[6] in 25% yield accompanied by some unidenti-

Table 1 One-Pot Synthesis of Indoles and Indolines

					Reaction Time (h)[a]				Yield (%)		
Entry	Hydrazine	Ketone	Solvent	Et_3N	i)	ii)	iii)	Product	**13**+**14**	**13**	**14**
1	**3**	**7**	THF	–	9	2	9	**13a**+**14a**	92	47	45
2	**3**	**7**	benzene	–	6	3	3	**13a**	81	81	–
3	**3**	**8**	THF	–	6	1.5	1	**13b**	58	58	–
4	**3**	**8**	benzene	–	1.5	1	3	**13b**	81	81	–
5	**3**	**9**	benzene	–	15	4	5	**13c**	77	77	–
6	**3**	**9**	benzene	+	16	4	5	**13c**+**14c**	90	19	71
7	**3**	**10**	benzene	+	20	1	3.5	**13d**	86	86	–
8	**4**	**7**	benzene	–	1	1	2.5	**13e**	25	25	–
9	**4**	**7**	benzene	+	0.5	0.5	12.5	**13e**+**14e**	35	31	4
10	**4**	**7**	toluene	+	1	1	16	**13e**	45	45	–
11	**5**	**7**	THF	+	2	1	5	**13f**+**14f**	47	23	24
12	**5**	**7**	benzene	+	4	2	5	**13f**	33	33	–
13	**6**	**7**	benzene	+	4	2	7	**13g**	39	39	–

[a] i) Reaction time for condensation reaction (first Step); ii) Reaction time for acylation reaction (second Step); iii) Reaction time for rearrangement reaction (third Step).

fied compounds (entry 8). The acylation of intermediary hydrazone **11e** with TFAA in the presence of triethylamine improved the yield of indole **13e** (31%), along with the indoline **14e** and the corresponding enehydrazine (entry 9). Furthermore, the one-pot reaction in boiling toluene gave the corresponding indole **13e** in 45% yield (entry 10). The one-pot reaction of **7** with hydrazine **5** having the *p*-methoxy group in benzene ring afforded indole **13f**[7] and indoline **14f** (entries 11, 12). Similarly, the one-pot reaction of **7** with hydrazine **6** having the *p*-methyl group in benzene ring gave indole **13g**[8] (entry 13).

We compared the yields of indoles and indolines in one-pot synthesis with those in stepwise synthesis (isolations of both hydrazones and *N*-trifluoroacetyl enehydrazines (intermediates) in each step). Indoline **14a** was obtained from hydrazine **3** in total 87% yield in the stepwise process, while **13a** and **14a** were obtained in 92% combined yield by the one-pot process. Furthermore, **13b** and **13d** were obtained in 44% and 11% total yields, respectively, via the stepwise process, compared to 81% and 86% yields, respectively, via the above one-pot process. Therefore, the one-pot synthesis is generally preferable to the stepwise process for the preparation of indoles.

The advantages of this one-pot procedure are as follows: (i) the tedious isolation of the intermediates **11** and **12** is unnecessary; (ii) the crucial rearrangement proceeds under mild conditions to give indoles and indolines in moderate to excellent yield; (iii) furthermore, in boiling benzene or toluene, indoles were obtained as a sole product.

In addition to the previously reported[5] multi-step synthesis of indoles and indolines via thermal cyclization of *N*-trifluoroacetyl enehydrazines, the newly found one-pot procedure disclosed a broader aspect of the potentiality of thermal cyclization of *N*-trifluoroacetyl enehydrazine, thus establishing the one-pot synthesis as a simple and useful method for construction of various types of indoles and indolines.

^{1}H NMR spectra were recorded at 200 MHz, 300 MHz, or 500 MHz. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI method. Medium-pressure column chromatography (MCC) was performed using Lobar Größe B (E. Merck 310-25, Lichroprep Si60).

Conversion of Hydrazone 11a into Indole 13a and Indoline 14a

(i) In the absence of Et_3N

To a solution of the hydrazone **11a** (250 mg, 1 mmol) in THF (3 mL) was added TFAA (210 mg, 1 mmol) under a N_2 atm at 0 °C. After stirring at this temperature for 1 h, the reaction mixture was refluxed for 5 h, monitoring the reaction by TLC. The reaction mixture was concentrated under reduced pressure. Purification of the residue by MCC (hexane–EtOAc, 9:1) afforded indole **13a** (161 mg, 69%) and indoline **14a** (104 mg, 30%).

(ii) In the presence of Et_3N

To a solution of the hydrazone **11a** (250 mg, 1 mmol) in THF (3 mL) was added Et_3N (303 mg, 3 mmol) and TFAA (210 mg, 1 mmol) under a N_2 atm at 0 °C. After stirring at this temperature for 1 h, the reaction mixture was refluxed for 5 h, monitoring the reaction by TLC. The reaction mixture was concentrated under reduced pressure. Purification of the residue by MCC (hexane–EtOAc, 9:1) afforded indole **13a** (65 mg, 28%) and indoline **14a** (247 mg, 71%).

One-Pot Reaction; General Procedure

To a solution of the hydrazine (1 mmol) in THF (15 mL) was added the ketone (5 mmol) and MS 4 Å (4 g) under a N_2 atm at r.t., and the reaction mixture was refluxed for 0.5–20 h, monitoring the reaction by TLC. After cooling to 0 °C, TFAA (2 mmol)[9] was added to the reaction mixture. [In the case of entries 6, 7, 9–13 (Table 1), TFAA (2 mmol) and Et_3N (3 mmol) were added.] After stirring at the same temperature for 0.5–4 h, the reaction mixture was refluxed for 1–16 h, monitoring the reaction by TLC. The reaction mixture was then filtered to remove MS 4 Å, and the filtrate was concentrated under reduced pressure. Purification of the residue by MCC afforded the indole and indoline as shown in Table 1. Analytical data for the indoles and indolines are summarized in Table 2.

Table 2 Spectral Data for Indoles **13** and Indolines **14**

Product	Mp (°C)[a]	^{1}H NMR (300 MHz, $CDCl_3$ / TMS) δ (ppm), *J* (Hz)	IR ν (cm^{-1})	Molecular Formula	HRMS (*m/z*)
13a	–	2.55 (br quint, 2H, *J* = 7.0), 2.91 (pseudo-t, 4H, *J* = 7.0), 7.10–7.52 (m, 9H)	3010, 1599, 1501 1450, 1209	$C_{17}H_{15}N$	233.1177
14a	137–140	1.58 (m, 1H), 1.81–1.90 (m, 2H), 2.18 (m, 1H), 2.26–2.47 (m, 2H), 3.95 (dd, 1H, *J* = 10.0, 3.0,), 6.58 (br d, 1H, *J* = 8.0), 6.77 (br s, 1H), 6.83 (br t, 1H, *J* = 8.0), 7.08 (br t, 1H, *J* = 8.0), 7.16 (br d, 1H, *J* = 8.0), 7.24–7.31 (m, 3H), 7.42–7.47 (m, 2H)	3425, 3024, 1725, 1593, 1498	$C_{19}H_{17}F_3N_2O$	346.1277
13b	–	1.89 (br quint, 4H, *J* = 3.0), 2.60 (m, 2H), 2.80 (m, 2H), 7.02–7.54 (m, 9H)	2939, 1599, 1502, 1459	$C_{18}H_{17}N$	247.1357
13c	–	0.92 (d, 3H, *J* = 6.5), 2.10 (m, 1H), 2.86 (m, 3H), 3.46 (m, 1H), 7.11 (m, 2H), 7.35 (m, 2H), 7.44–7.50 (m, 5H)	2961, 2861, 1598, 1502, 1450, 1377	$C_{18}H_{17}N$	247.1360

Table 2 Spectral Data for Indoles **13** and Indolines **14** (continued)

Product	Mp (°C)[a]	^{1}H NMR (300 MHz, $CDCl_3$ / TMS) δ (ppm), *J* (Hz)	IR ν (cm^{-1})	Molecular Formula	HRMS (*m/z*)
14c	92–94	0.95 (d, 3H, *J* = 7.5), 1.58–1.73 (m, 2H), 1.95 (m, 1H), 2.35–2.57 (m, 2H), 4.12 (dd, 1H, *J* = 8.0, 2.0), 6.39 (d, 1H, *J* = 8.0), 6.71 (br s, 1H), 6.78 (td, 1H, *J* = 8.0, 1.0), 7.02 (br t, 1H, *J* = 8.0), 7.14 (br d, 1H, *J* = 8.0), 7.24 (m, 3H), 7.41 (m, 2H)	3442, 3024, 1740, 1593, 1497	$C_{20}H_{19}F_3N_2O$	360.1445
13d	–	0.98 (t, 3H, *J* = 8.0), 2.34 (s, 3H), 2.68 (q, 2H, *J* = 8.0), 7.07 (m, 3H), 7.32 (m, 2H), 7.49 (m, 4H)	3009, 1598, 1500, 1206	$C_{17}H_{17}N$	235.1374
13e[6]	–	2.52 (br quint, 2H, *J* = 8.0), 2.84 (pseudo-t, 4H, *J* = 8.0), 7.07 (m, 2H), 7.28 (m, 1H), 7.42 (m, 1H), 7.76 (br s, 1H)	3477, 1666, 1611, 1468, 1228	$C_{11}H_{11}N$	157.0891
14e	–	1.66 (m, 1H), 1.74–1.88 (m, 2H), 2.20 (m, 1H), 2.31–2.42 (m, 2H), 3.69 (dd, 1H, *J* = 8.5, 2.0, 1H), 4.67 (br s, 1H), 6.57 (dd, 1H, *J* = 7.0, 1.0), 6.78 (td, 1H, *J* = 7.0, 1.0), 6.79 (br s, 1H), 7.07 (m, 2H)	3424, 2963, 1720, 1611, 1486	$C_{13}H_{13}F_3N_2O$	270.0962
13f[7]	–	2.52 (br quint, 2H, *J* = 7.0), 2.82 (pseudo-t, 4H, *J* = 7.5), 3.84 (s, 3H), 6.74 (dd, 1H, *J* = 8.5, 2.0), 6.91 (d, 1H, *J* = 2.0), 7.17 (br d, 1H, *J* = 8.5), 7.71 (br s, 1H)	3478, 2956, 1667, 1603, 1585, 1466 1296, 1228	$C_{12}H_{13}NO$	187.1007
14f	–	1.66 (m, 1H), 1.82 (m, 2H), 2.08 (m, 1H), 2.40 (m, 2H), 3.72 (br d, 1H, *J* = 8.0), 3.75 (s, 3H), 4.31 (br s, 1H), 6.52 (br d, 1H, *J* = 8.0), 6.65 (dd, 1H, *J* = 8.0, 2.0), 6.67 (d, 1H, *J* = 2.0)	3478, 1750, 1601, 1466, 1296, 1204	$C_{14}H_{15}F_3N_2O_2$	300.1095
13g[8]	–	2.43 (s, 3H), 2.52 (br quint, 2H, *J* = 7.0), 2.80 (pseudo-t, 4H, *J* = 7.0), 6.91 (br dd, 1H, *J* = 8.0, 1.0), 7.17 (br d, 1H, *J* = 8.0), 7.22 (br d, 1H, *J* = 1.0), 7.71 (br s, 1H)	3478, 1516, 1190, 804, 591	$C_{12}H_{13}N$	171.1048

[a] Mps are not given for oily products.

Acknowledgement

This work was supported in part by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan and a research grant from the Science Research Promotion Fund of the Japan Private School Promotion Foundation.

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