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SYNTHESIS OF 2,4-DISUBSTITUTED INDOLES *VIA* THERMAL CYCLIZATION OF *N*-TRIFLUORO-ACETYL ENEHYDRAZINES

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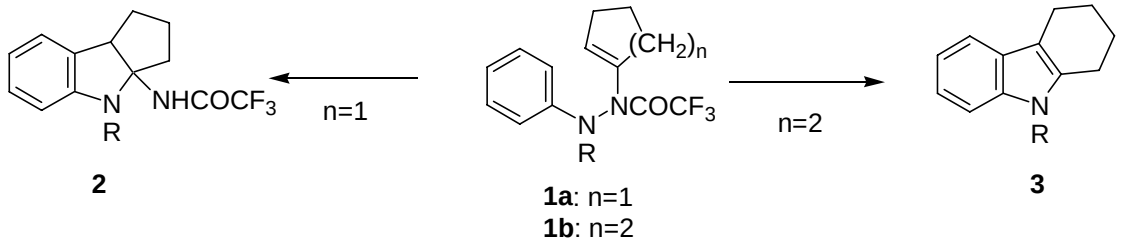
Abstract—Synthesis of naturally occurring indoles, 2,4-dimethylindole and 4-hydroxymethyl-2-methylindole by applying thermal cyclization of *N*-trifluoroacetyl enehydrazines is described.

INTRODUCTION

The indole nucleus has been recognized as one of the most important heterocycles due to their potential biological activities.[1] Therefore, there is continuously a need for developing concise and practical synthetic methods of indoles and the related compounds.[1,2] Recently, we have developed the thermal cyclization of *N*-trifluoroacetyl enehydrazines which would provide a novel method for preparing indolines and indoles under mild conditions and also in good to excellent yield.[3] For example, the thermal reaction of enehydrazine (**1a**) having a cyclopentenyl group proceeded smoothly at 65°C to give the indoline (**2**) in 99% yield while the cyclohexenylhydrazine (**1b**) was converted into the corresponding indole (**3**) under the similar conditions (Scheme 1).



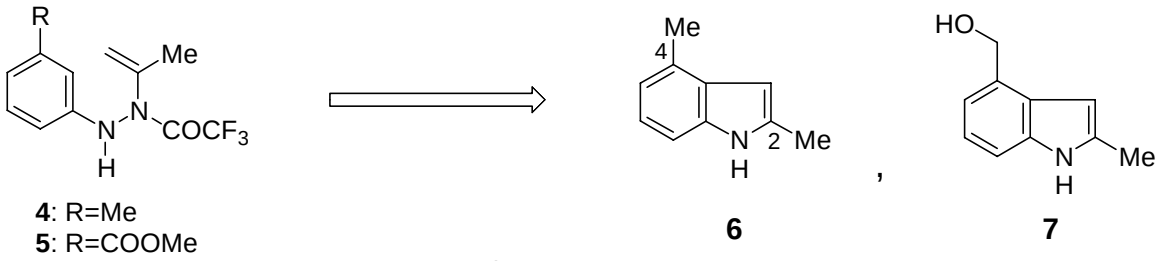
2 **1a**: n=1 **1b**: n=2 **3**

Scheme 1

As an extension of our research on the thermal cyclization of *N*-trifluoroacetyl enehydrazines, we now report a short synthesis of 2,4-dimethylindole (**6**) and 4-hydroxymethyl-2-methylindole (**7**), both of which were isolated from two species of European Basidomycetes (*Tricholoma virgatum* and *T. sciodes*).[4]

Since their biological activities have not been reported so far, synthesis of their indoles and the related compounds are important task in view of not only establishment of the practical synthetic method but also evaluation of their biological activities.

Our synthetic route is short and simple as shown in Scheme 2. The *N*-trifluoroacetyl enehydrazine (**4**) would be readily available *via* the conventional reaction sequence including condensation of 3-methylphenylhydrazine with acetone followed by acylation with trifluoroacetic anhydride (TFAA). The enehydrazine (**4**) would undergo [3,3] sigmatropic rearrangement to provide directly the desired indole (**6**). Similarly, the rearrangement of *N*-trifluoroacetyl enehydrazine (**5**) having a methoxycarbonyl group is expected to proceed and the subsequent reduction of the ester group would provide the indole (**7**) (Scheme 2).



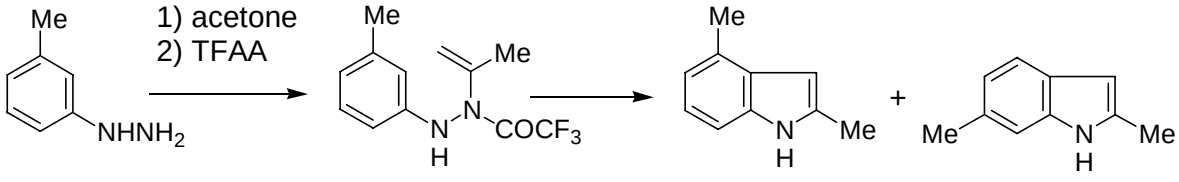
4: R=Me
5: R=COOMe

6 , **7**

Scheme 2

RESULTS AND DISCUSSION

We first investigated the thermal cyclization of *N*-trifluoroacetyl-*N'*-(3-methylphenyl)enehydrazine (**4**) (Scheme 3, Table 1). **4** was prepared by condensation of hydrazine (**8**) with acetone followed by acylation of the corresponding hydrazone with TFAA in the presence of triethylamine at 0°C.



8 **4** **6** **9**

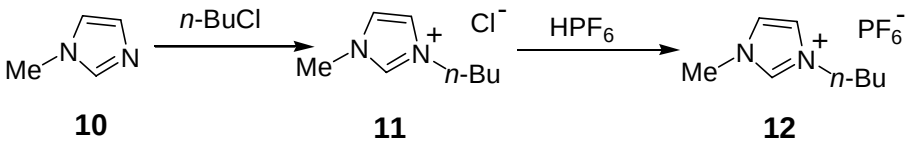
Scheme 3

Table 1. Thermal Cyclization of *N*-Trifluoroacetyl Enehydrazine (**4**)

entry	conditions (°C)	time (h)	yield (%)	
			6	**9**
1	THF (65)	7	---	---
2	toluene (120)	7	38	38
3	neat (140)	6	31	5
4	chlorobenzene (130)	5	16	16
5	ionic liquid (**12**) (140)	3	26	13

The trifluoroacetyl enehydrazine (**4**) exhibited a molecular ion peak at *m/z* 258 in MS spectrum and IR absorption at 1717 cm^{-1} due to the trifluoroacetamide group, and showed ^{1}H-NMR signals due to methyl protons at δ 2.05 and 2.31 (each 3H s), and olefinic protons at δ 5.01 and 5.11 (each 1H, br s), respectively. The thermal cyclization of **4** proceeded smoothly in toluene at 120°C to give a 1 : 1 mixture of 2,4-dimethylindole (**6**) and 2,6-dimethylindole (**9**) in 76% yield.[5] When **4** was heated in THF at 65°C, cyclized indoles were not obtained and the starting material (**4**) was completely recovered (Table 1, entries 1 and 2). The spectral data of **6** and **9** were identical with those of the respective authentic sample reported in the literatures.[4,6,7]

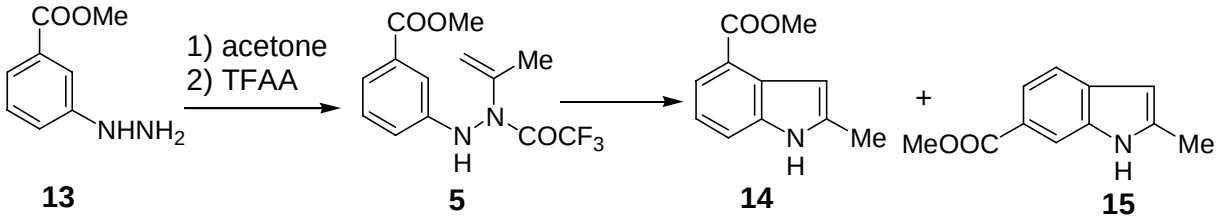
In order to improve the yield of the desired product (**6**), we examined the thermal cyclization of **4** under other reaction conditions as shown in Table 1. Recently ionic liquid has been focused much attention as a useful solvent based on substantial rate enhancement, good yields, and high selectivity by control of temperature in various types of organic reactions.[8] When no solvent was used, **6** was obtained as the major product but in low yield (entry 3). The conditions using either chlorobenzene or ionic liquid were not effective for improvement of the yield of the desired product (**6**) (entries 4 and 5). The ionic liquid used is imidazolium salt (**12**) which was prepared from 1-methylimidazole (**10**) by the known method[9] (Scheme 4).



10 **11** **12**

Scheme 4

We next investigated the thermal cyclization of enehydrazine (**5**) having a methoxycarbonyl group as shown in Scheme 5 and Table 2.



13 **5** **14** **15**

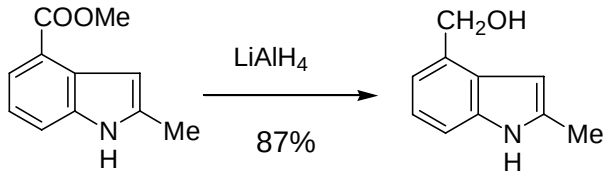
Scheme 5

Table 2. Thermal Cyclization of *N*-Trifluoroacetyl Enehydrazine (**5**)

entry	conditions (°C)	time (h)	yield (%)	
			14	**15**
1	acetonitrile (80)	8	---	---
2	toluene (120)	38	60	21
3	neat (150)	2	28	13
4	chlorobenzene (130)	5	55	20
5	ionic liquid (**12**) (140)	6	9	---

Similarly, the thermal cyclization of **5** proceeded in toluene at 120°C to give the methyl indole-4-carboxylate (**14**)[6,10] and methyl indole-6-carboxylate (**15**)[11] in 60 and 21% yields, respectively, although prolonged reaction time was required for complete consumption of **5** (entry 2).[5] When chlorobenzene (at 130°C) was used as solvent, the reaction completed for less long time (entry 4).

As shown in Table 2, in the case of **5**, the desired 2,4-disubstituted indole (**14**) was obtained as the major product. Regioselectivity giving 2,4-disubstituted indoles as a major product in the rearrangement of **5** is similar to that in the Fischer indolization[12] of the hydrazones having an electron withdrawing at *m*-position. The reduction of the ester (**14**) with $LiAlH_4$ gave the alcohol (**7**) in 87% yield. The spectral data of **7** were identical with those of the authentic sample[4] reported in the literature (Scheme 6).



14 **7**

Scheme 6

In conclusion, we succeeded in the concise synthesis of 2,4-disubstituted indoles (**6** and **7**) *via* the thermal cyclization of *N*-trifluoroacetyl enehydrazines (**4** and **5**). Biological evaluation of these indoles (**6** and **7**) and further applications of this thermal cyclization to indole synthesis are in progress.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

^{1}H-NMR spectra were measured using Varian Gemini-200 (200 MHz) and Varian Gemini-300 (300 MHz) instruments for solutions in deuteriochloroform, unless otherwise stated (tetramethylsilane was used as the internal reference); *J* values are given in Hz. IR spectra were measured with a Perkin Elmer 1600 FTIR machine for solutions in chloroform, unless otherwise stated and MS spectra were taken with Hitachi M-4100 spectrometer. Mps were determined with a Kofler-type hot-stage apparatus and are uncorrected. All reactions were performed under nitrogen and extracts from the reaction mixtures were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. TLC was performed on precoated silica gel $60F_{254}$ (0.25 mm thick, Merck) with UV detection at 254 and 300 nm. Medium-pressure column chromatography (MPCC) was undertaken on a 530-4-10V apparatus

(Yamazen) with Lobar größe B (310-25, Lichroprep Si60, Merck) as column absorbent. All products described in this paper were found to be homogeneous by TLC, MPCC, and ^{1}H-NMR spectra.

Trifluoroacetic Acid 1-(1-Methyl-1-ethenyl)-2-(3-methylphenyl)hydrazide (4) A solution of 3-methylphenylhydrazine (**8**) (1.23 g, 10 mmol) and acetone (1.46 mL, 20 mmol) in EtOH (50 mL) was refluxed for 2.5 h. The reaction mixture was concentrated under reduced pressure to give the crude hydrazone. To a solution of the crude hydrazone in CH_2Cl_2 (80 mL) were added Et_3N (4.2 mL, 30 mmol) and TFAA (3.25 g, 20 mmol) at 0°C. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by MCC (*n*-hexane-ethyl acetate = 5 : 1) gave the *N*-trifluoroacetyl enehydrazine (**4**) (2.6 g, 52%) as a colorless oil. IR : 1717 ($NCOCF_3$) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 2.05 and 2.31 (each 3H, s), 5.01 and 5.11 (each 1H, br s), 6.05 (1H, br s), 6.60 (2H, br s), 6.80 (1H, br d, *J*=8 Hz), 7.16 (1H, t, *J*=8 Hz). HRMS *m/z* : Calcd for $C_{12}H_{13}N_2OF_3$ (M^+) 258.0979. Found : 258.0973.

Thermal Cyclization of Enehydrazine (4) in Toluene (Table 1, entry 2) A solution of **4** (40 mg, 0.16 mmol) in toluene (10 mL) was refluxed for 7 h, monitoring the reaction by TLC. The reaction mixture was concentrated under reduced pressure. Purification of the residue by MPCC (*n*-hexane-ethyl acetate = 20 : 1) gave 2,4-dimethylindole (**6**)[4,6,7] (8.8 mg, 38%) as pale yellow oil and 2,6-dimethylindole (**9**)[7] (8.8 mg, 38%) as colorless crystals, mp 81-82 °C (*n*-hexane-Et_2O) [lit.,[7] mp 86°C]. **6**: IR : 3473 (NH) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 2.47 and 2.52 (each 3H, s), 6.25 (1H, s), 6.87 (1H, br d, *J*=8 Hz), 7.03 (1H, t, *J*=8 Hz), 7.14 (1H, br d, *J*=8 Hz), 7.89 (1H, br s). HRMS *m/z* : Calcd for $C_{10}H_{11}N$ (M^+) 145.0891. Found : 145.0895. **9**: IR : 3474 (NH) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 2.41 and 2.43 (each 3H, s), 6.15 (1H, s), 6.89 (1H, dd, *J*=8, 2 Hz), 7.07 (1H, br s), 7.38 (1H, br d, *J*=8 Hz), 7.72 (1H, br s). HRMS *m/z* : Calcd for $C_{10}H_{11}N$ (M^+) 145.0891. Found : 145.0892.

Thermal Cyclization of Enehydrazine (4) in Ionic Liquid (12) (Table 1, entry 5) A solution of **4** (62 mg, 0.24 mmol) in 1-butyl-3-methylimidazolium hexafluorophosphate (**12**)[9] (1 mL) was heated at 140°C for 3 h, monitoring the reaction by TLC. The reaction mixture was diluted with water and extracted with HCl_3. The organic phase was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by MPCC (*n*-hexane-ethyl acetate = 20 : 1) to give 2,4-dimethylindole (**6**) (9 mg, 26%) and 2,6-dimethylindole (**9**) (2.5 mg, 13%). The spectral data of these compounds (**6**) and (**9**) were identical with those reported in the literature,[4,6,7] respectively.

Trifluoroacetic Acid 1-(1-Methyl-1-ethenyl)-2-[3-(methoxycarbonyl)phenyl]hydrazide (5) According to the procedure given for the preparation of **4**, condensation of methyl 3-hydrazinobenzoate (**13**) (1.46 g, 8.6 mmol) with acetone (1.26 mL, 9.2 mmol) followed by the acylation of the resulting hydrazone with TFAA (2.37 mL, 17.2 mmol) gave *N*-trifluoroacetyl enehydrazine (**5**) (1.45 g, 56%) as pale yellow crystals, mp 109-110 °C (*n*-hexane-ethyl acetate). IR : 1721 ($NCOCF_3$) cm^{-1}. ^{1}H-NMR (200 MHz) δ : 2.07 and 3.91 (each 3H, s), 5.04 and 5.13 (each 1H, br s), 6.30 (1H, br s), 6.99 (1H, br d, *J*=8 Hz), 7.36 (1H, br t, *J*=8 Hz), 7.48 (1H, br s). 7.66 (1H, br d, *J*=8 Hz). HRMS *m/z* : Calcd for $C_{13}H_{13}N_2O_3F_3$ (M^+) 302.0876. Found : 302.0886. Anal. Calcd for $C_{13}H_{13}N_2O_3F_3 \cdot 1/10C_6H_{14}$: C, 52.52; H, 4.67; N, 9.02. Found: C, 52.48; H, 4.42; N, 8.98.

Thermal Cyclization of Enehydrazine (5) in Toluene (Table 2, entry 2) A solution of **5** (76 mg, 0.25 mmol) in toluene (28 mL) was refluxed for 38 h, monitoring the reaction by TLC. The reaction mixture was concentrated under reduced pressure. Purification of the residue by MPCC (*n*-hexane-ethyl acetate = 5 : 1) gave methyl 2-methyl-1*H*-indole-4-carboxylate (**14**) (28 mg, 60%) as colorless crystals, mp 128-130°C (*n*-hexane-Et_2O) [lit.,[10] mp 131-132°C] and methyl 2-methyl-1*H*-indole-6-carboxylate (**15**) (10 mg, 21%) as colorless crystals, mp 149-150°C (*n*-hexane-ethyl acetate). **14**: IR : 3471 (NH), 1707 (COOMe) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 2.50 and 3.97 (each 3H, s), 6.86 (1H, br s), 7.14 (1H, t, *J*=8.5 Hz), 7.47 (1H, br d, *J*=8.5 Hz), 7.85 (1H, dd, *J*=8.5, 1 Hz), 8.10 (1H, br s). HRMS *m/z* : Calcd for $C_{11}H_{11}NO_2$ (M^+) 189.0789. Found : 189.0799. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.77; H, 5.82; N, 7.28. **15**: IR : 3468 (NH), 1703 (COOMe) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 2.48 and 3.92 (each 3H, s), 6.27 (1H, s), 7.50 (1H, br d, *J*=8 Hz), 7.76 (1H, dd, J=8.5, 1.5 Hz), 8.03 (1H, br s), 8.15 (1H, br s). HRMS *m/z* : Calcd for $C_{11}H_{11}NO_2$ (M^+) 189.0789. Found : 189.0802. Anal. Calcd for $C_{11}H_{11}NO_2 \cdot 1/10AcOEt$: C, 69.29; H, 5.81; N, 7.09. Found: C, 69.14; H, 5.79; N, 7.09.

2-Methyl-1*H*-indole-4-methanol (7) To a stirred solution of methyl 2-methyl-1*H*-indole-4-carboxylate (**14**) (47 mg, 0.25 mmol) in THF (10 mL) was added $LiAlH_4$ (38 mg, 1 mmol) at 0°C. After being stirred at the same temperature for 2 h, usual work-up followed by purification of the crude alcohol by MPCC (*n*-hexane-ethyl acetate = 10 : 1) gave the methanol (**7**) (35 mg, 87%) as colorless crystals, mp 80-82 °C (*n*-hexane-ethyl acetate) [lit.,[4] mp 80-81°C]. IR : 3472 (NH, OH) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 2.47 (3H, s), 4.94 (2H, s), 6.35 (1H, m), 7.08 (1H, br d, *J*=8 Hz), 7.11 (1H, t, *J*=8 Hz), 7.21 (1H, br d, *J*=8 Hz), 7.97 (1H, br s). HRMS *m/z* : Calcd for $C_{10}H_{11}NO$ (M^+) 161.0840. Found : 161.0852. Anal. Calcd for $C_{11}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.49; H, 6.96; N, 8.52. The spectral data of **7** were identical with those reported in the literature.[4]

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