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# Thermal cyclization of *N*-trifluoroacetyl enehydrazines under mild conditions: A novel entry into the Fischer indole synthesis

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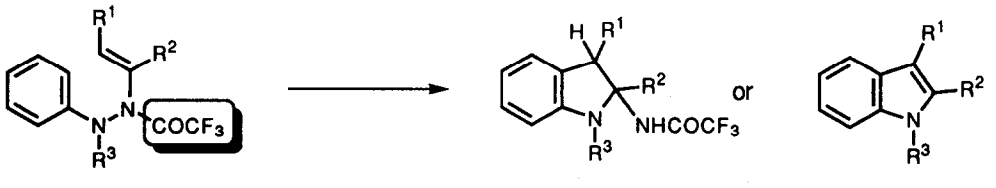
**Abstract:** An efficient thermal cyclization of *N*-trifluoroacetyl enehydrazines for the synthesis of indoles is described.


The indole nucleus is an important element in many pharmacologically active compounds. The Fischer indole synthesis is the most widely used method for the preparation of indoles.[1] However, two major drawbacks to the Fischer indole synthesis are that yields are sometimes low[1-3] with numerous byproducts being formed, and the reactions involving unsymmetrical hydrazines or ketones often give products with low regioselectivity.[1,4-7] Particularly, the low yields are a persistent problem in the Fischer indole synthesis. Although the Fischer indole synthesis is usually carried out in the presence of an acid catalyst, the acid may cause decomposition of the indole produced and, therefore, thermal cyclization in the absence of a catalyst (without a catalyst) appears to offer advantages over the acid-catalyzed procedure. However, a high temperature (180-250 ℃) is required for such cyclization. In order to solve these problems in the Fischer indolization under the conventional conditions, we investigated thermal cyclization of *N*-trifluoroacetyl enehydrazines **1** at below 90 ℃ and established a new and efficient version of the Fischer indolization (Scheme 1). The newly-found reaction provides an alternative method for the synthesis of indoles **3** and indolines **2**. Although the Fischer indolization of *N*-acetyl enehydrazine has previously been reported,[8] it required either an elevated temperature (170 ℃) or an acid catalysis (dichloroacetic acid) to achieve successful cyclization.




1 2 3

**Scheme 1**

We first examined the thermal cyclization of *N'*,*N'*-diphenylcyclopentenyl-*N*-trifluoroacetyl enehydrazine **4a** (Table 1). **4a** was prepared by acylation of the corresponding hydrazone **7** with trifluoroacetic anhydride (TFAA) at 0 ℃. A solution of **4a** in THF was heated at 65 ℃ for 5 h to give the indoline **5a** in 99% yield

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(entry 2). Surprisingly, the reaction also proceeded at room temperature but required prolonged reaction time (entry 1). Reductive deamination of **5a** with sodium cyanoborohydride proceeded smoothly to give the corresponding indoline unsubstituted at the 3a-position in quantitative yield. In general, it is difficult to isolate 2-aminoindolines such as **5a**[1] which is proposed as an intermediate of Fischer indolization. To our knowledge, the literature contains only a few references[9-11] pertaining to the isolation of 2-aminoindoline derivatives. The thermal cyclization of **4a** in xylene at 138 ℃ gave the indole **6a** in 92% yield (entry 3). Under the same conditions, the indoline **5a** was converted into the indole **6a** in quantitative yield as a result of the elimination of trifluoroacetamide. The reaction of *N'*-monophenyl enehydrazine **4b** proceeded smoothly in toluene at 90 ℃ to give the indoline **5b** along with the unreacted starting material (entry 4). In this case, upon prolonged heating the indoline **5b** was converted into the corresponding indole **6b**. The substituent effect in the cycloalkene part of *N*-trifluoroacetyl enehydrazines was then investigated (entries 5-7). The indolines **5c,d**[12] and indole **6e** were obtained in high yields under similar mild conditions. In the cases of cyclohexenehydrazines **4f,g**, the indoles **6f,g** were obtained as the sole product with no isolation of the indolines (entries 8, 9).

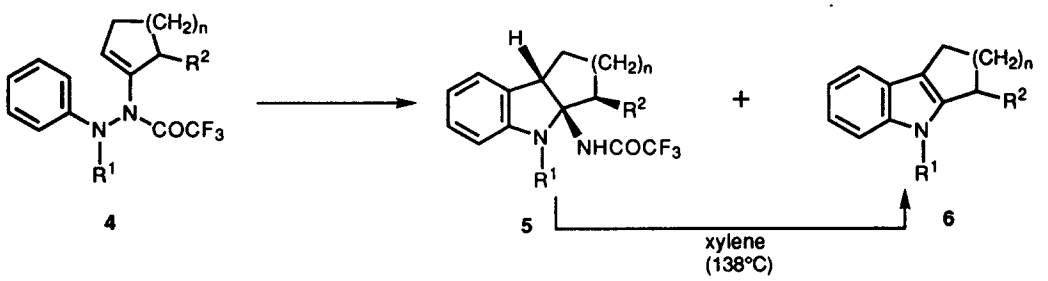



Table 1. Thermal cyclization of the *N*-trifluoroacetyl enehydrazines **4a-g**

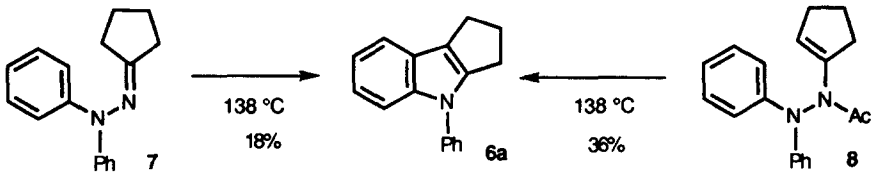
| Entry | Substrate | Conditions | Time (h) | Yield (%) 5 | Yield (%) 6 |
|---|---|---|---|---|---|
| 1 | **4a** : $R^1$=Ph, $R^2$=H, n=1 | A | 480 | 98 | — |
| 2 | **4a** : $R^1$=Ph, $R^2$=H, n=1 | B | 5 | 99 | — |
| 3 | **4a** : $R^1$=Ph, $R^2$=H, n=1 | D | 4 | — | 92 |
| 4 | **4b** : $R^1$=$R^2$=H, n=1 | C | 7 | 56 | — |
| 5 | **4c** : $R^1$=Ph, $R^2$=Me, n=1 | B | 5 | 76 | — |
| 6 | **4d** : $R^1$=Ph, $R^2$=$CH_2SPh$, n=1 | A | 168 | 99 | — |
| 7 | **4e** : $R^1$=H, $R^2$=Me, n=1 | C | 7 | — | 99 |
| 8 | **4f** : $R^1$=Ph, $R^2$=H, n=2 | B | 11 | — | 53 |
| 9 | **4g** : $R^1$=Ph, $R^2$=Me, n=2 | C | 9 | — | 89 |

condition A: standing at r.t. (25 °C); condition B: heating at 65 °C in THF;
condition C: heating at 90 °C in toluene; condition D: heating at 138 °C in xylene.

The difference between the structures of products (indolines **5a-d** from cyclopentenehydrazines **4a-d** and indoles **6f,g** from cyclohexenehydrazines **4f,g**) could be explained as follows.[9] The indole double bond is not readily accomodated in a fused system such as 1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indoles in which the two rings are five-membered and rather rigid. On the other hand, it is clear that no comparable difficulty exists

in the elimination of trifluoroacetamide when the more flexible six-membered cyclohexane ring is present as shown in **6f,g**. The regioselective thermal cyclization of *N*-trifluoroacetyl enehydrazines prepared from unsymmetrical ketones would be useful for synthesis of various polycyclic indole alkaloids.

In order to investigate the electronic effect of the trifluoroacetyl group, we examined the thermal cyclization of hydrazone **7** and the *N*-acetyl enehydrazine **8** (Scheme 2). These cyclizations did not proceed at 65-90 ℃ and a high temperature (138 ℃) was required for successful cyclization. However, the yield of indole **6a** was low (18-36 %) probably due to decomposition of the product. This result suggests that the "non-catalytic" thermal cyclization involving [3,3]-sigmatropic rearrangement of the *N*-trifluoroacetyl enehydrazines is an efficient method for the indole synthesis.




**Scheme 2**

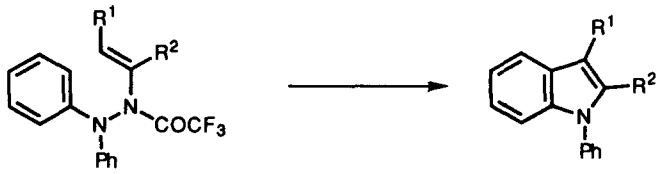



Table 2. Thermal cyclization of the *N*-trifluoroacetyl enehydrazines **9a-c**

| Entry | Substrate | Conditions | Time (h) | Yield (%) **10** |
|---|---|---|---|---|
| 1 | **9a** : $R^1$= $R^2$=Me | B | 10 | 79 |
| 2 | **9b** : $R^1$=Me, $R^2$=Et | B | 4 | 69 |
| 3 | **9b** : $R^1$=Me, $R^2$=Et | A | 480 | 50 |
| 4 | **9c** : $R^1$=H, $R^2$=Et | C | 10 | 77 |

condition A: standing at r.t. (25 °C); condition B: heating at 65 °C in THF;
condition C: heating at 90 °C in toluene.

To demonstrate the generality of the cyclization of *N*-trifluoroacetyl enehydrazines, we next investigated thermal cyclization of the acyclic substrates **9a-c** (Table 2). Under similar conditions, **9a-c** readily afforded the corresponding indoles **10a-c**. Since thermal cyclization of *N*-trifluoroacetyl enehydrazines occurred with no isomerization of olefin under mild conditions, the substituted indoles such as 2-mono- and 2,3-disubstituted indoles were selectively obtained as the sole product. The high reactivity of *N*-trifluoroacetyl enehydrazines would be explained as follows. The facility of conversion of *N*-trifluoroacetyl enehydrazines to indoles depends on the reaction rate of [3,3]-sigmatropic rearrangement and the reactivity would increase because of a

small energy difference between LUMO[13] of an olefin substituted with the trifluoroacetamido group and HOMO of another olefin of the phenyl ring.

In conclusion, we have now established a novel synthetic route to indoles *via* thermal cyclization of *N*-trifluoroacetyl enehydrazines which proceeds smoothly under mild conditions. Further work on application of this method to the synthesis of biologically active natural products having an indole nucleus is in progress.

**Acknowledgement**

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**References and Notes**

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12. The stereostructure of **5d** was established unambiguously by single-crystal X-ray analysis. The relative configuration of **5c** was deduced from comparison of the $^1$H-NMR spectrum with that of **5d**.
13. Energy levels (eV) of LUMO of several olefins shown below were calculated with a semiempirical MOPAC method utilizing a PM3 Hamiltonian and the CAChe system (SONY Tektronix).