Unambiguous characterisation of dienylimines as intermediates in Fischer indolisation of *o*-substituted *N*-trifluoroacetyl enehydrazines

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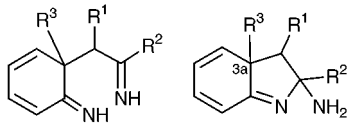
Thermal cyclisation of *o*-substituted *N*-trifluoroacetyl enehydrazines was systematically investigated and found to proceed *via* dienylimine intermediates, which were unambiguously characterised by X-ray and spectral analysis.

The Fischer indole synthesis provides a versatile and convergent route to a wide variety of indoles.[1] Although today the key step in Fischer indolisation is regarded as a [3,3]-sigmatropic rearrangement of the enehydrazines, which is related to the Cope and Claisen rearrangements,[1,2] there have been only a few reports on the isolation and characterisation of the dearomatised dienylimine (**1** or **2**) intermediates because of



1 **2**

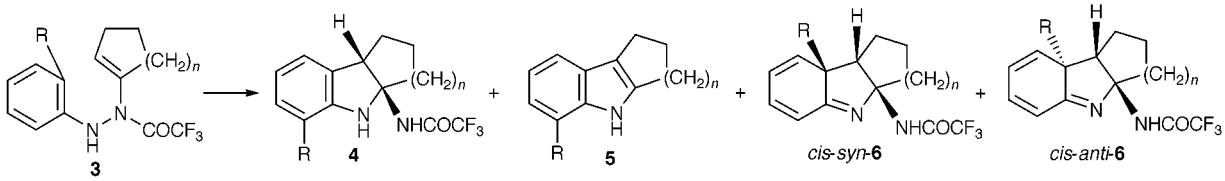
their instability. To the best of our knowledge, there has been only one paper[3] pertaining to the isolation of a pure dienylimine having a methyl group at the 3a-position in which the relative configurations at the 2-, 3- and 3a-positions remain to be established.

During the course of our investigation on reactivity of *N*-trifluoroacetyl enamine moieties,[4] we investigated the thermal cyclisation of *o*-substituted *N*-trifluoroacetyl enehydrazines under mild conditions and succeeded in the isolation and structure determination of the dienylimine intermediates in the Fischer indolisation. *o*-Substituted hydrazones are generally known to react more sluggishly than the *m*- and *p*-substituted analogs and sometimes give low yields of the desired indoles accompanied with side reactions.[1]

We first examined the thermal cyclisation of *N*-trifluoroacetyl enehydrazine **3a** having an *o*-methoxy group (Table 1). Previously, characterisation[1,5] of the dienylimine intermediate with a methoxy group had been attempted but found to be unsuccessful. A solution of **3a** in THF was heated at 65 °C for 10 h to give a mixture of indoline **4a** and two dienylimines **6a** in 63 and 36% yields, respectively (entry 1). Furthermore, **6a** was easily separated into two diastereomers, *cis-syn*-**6a** and *cis-anti*-**6a**, in a 5 : 1 ratio. The stereostructure of *cis-syn*-**6a** was established unambiguously by single-crystal X-ray analysis[6] (Fig. 1) and then the relative configuration of the isomeric *cis-anti*-**6a** was deduced from comparison of its ^{1}H and ^{13}C NMR spectra with those of *cis-syn*-**6a**. Therefore, we have now succeeded in the isolation and structure determination of the dienylimine intermediate in the Fischer indolisation of the *o*-methoxy enehydrazine. Additionally, the *cis-syn*-isomer was obtained as the major product.

Interestingly, the polarity of the organic solvent used influences both the product ratio of **4a** and **6a** and the reaction time (entries 2–4). In MeCN, the reaction proceeded smoothly to give a 1 : 1 mixture of **4a** and **6a** in 98% yield (entry 3). On the other hand, in non-polar hexane, **4a** was obtained as the major product in 75% yield, although prolonged reaction time was required for complete consumption of **3a** (entry 4). Heating the indoline **4a** in xylene at 138 °C afforded the corresponding indole **5a** in quantitative yield as a result of the elimination of

Table 1 Thermal cyclisation of *N*-trifluoroacetyl enehydrazines **3**



				Conditions			Yield (%)			
Entry	Substrate	R	*n*	Solvent	*T*/°C	*t*/h	Total	**4**	**5**	**6** (*cis-syn* : *cis-anti*)
1	**3a**	MeO	1	THF	65	10	99	63	—	36 (5 : 1)
2	**3a**	MeO	1	PhMe	90	7	98	69	—	29 (4 : 1)
3	**3a**	MeO	1	MeCN	80	5	98	51	—	47 (5 : 1)
4	**3a**	MeO	1	hexane	80	22	99	75	—	24 (4 : 1)
5	**3b**	MeO	2	PhMe	90	10	84	—	75	9 (2 : 1)
6	**3b**	MeO	2	MeCN	80	10	73	—	54	19 (2 : 1)
7	**3c**	Me	1	PhMe	90	8	74	14	42	18 (14 : 1)
8	**3c**	Me	1	MeCN	110	8	99	30	37	32 (7 : 1)
9	**3d**	Me	2	PhMe	110	10	78	—	71	7 (7 : 1)
10	**3d**	Me	2	MeCN	110	10	87	—	76	11 (6 : 1)
11	**3e**	Cl	1	PhMe	90	15	74	70	4	—
12	**3f**	NO_2	1	PhMe	110	29	31 (85)[a]	31 (85)[a]	—	—

[a] Yields in parentheses are for the recovered starting material.

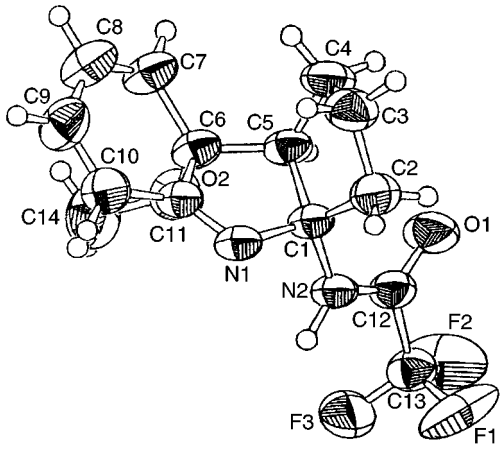
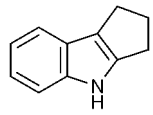


Fig. 1 ORTEP drawing of the molecule *cis-syn*-**6a** at the 50% probability level. The structure depicted is one of the independent molecules with the major component of the disordered CF_3 group.

trifluoroacetamide. Under the same conditions, both *cis-syn*-**6a** and *cis-anti*-**6a** were converted into indole **7**. Reaction of cyclohexene hydrazines **3b** proceeded slowly under similar mild conditions to give 7-methoxyindole **5b** as the major product with no detection of indoline **4b** (entries 5 and 6).



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It is well-known that Fischer indolisation of (2-methoxyphenyl)hydrazone gives 7-methoxyindole as a minor product and the abnormal 6-substituted indole as a major product, respectively. [1,7,8] On the other hand, our results indicate that the indolisation reaction of **3** proceeds preferentially at the unsubstituted position to give 7-methoxyindole as the major product. Consequently, the thermal cyclisation of **3** has provided a practical synthetic method for the 7-oxygenated indoles, which are known to be potential intermediates for the synthesis of biologically active compounds.

Next, we turned our attention to the corresponding *o*-methyl *N*-trifluoroacetyl enehydrazines **3c**,**d**. Reaction of **3d** proceeded smoothly at a high temperature (110 °C) to give **5d** with moderate regioselectivity, while **3c** afforded a mixture of **4c**, **5c**, *cis-syn*-**6c** and *cis-anti*-**6c** (entries 7, 8, 9 and 10). The *cis-syn* and *cis anti*-dienylimines **6c**,**d** were obtained as minor products. Their stereostructures were deduced from comparisons of their ^{1}H and ^{13}C NMR spectra with those of *cis-syn*-**6a**,**b** and *cis-anti*-**6a**,**b**. Brown [9] has reported that attempts to isolate a tricyclic dienylimine having a methyl group were unsuccessful. Therefore, our result is the first example of the isolation and structure determination of the tricyclic dienylimine with a methyl group.

When an electron-withdrawing group such as a chlorine or nitro group was present in the *o*-position, the indolisation occurred regioselectively at the unsubstituted position to give 7-substituted products (entries 11 and 12).

Finally, the isolation and structure determination of the dienylimines intermediates in the Fischer indolisation of *o*-methoxy and *o*-methyl enehydrazines provides good evidence for the postulated reaction mechanism, including a stereochemical rationalisation, particularly for the [3,3]-sigmatropic rearrangement step.

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Notes and references

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6 The crystal contains two independent molecules in the asymmetric unit. Both molecules have disordered CF_3 groups with occupancy factor of 0.67/0.33 and 0.81/0.19, respectively and one of the molecules has additional disorder at the fused cyclopentane (C_{17}-C_{18}) with occupancy factors of 0.56 and 0.44. *Crystal data* for *cis-syn*-**6a**: $C_{14}H_{15}F_3N_2O_2$, mp 140–141 °C, triclinic, $P\bar{1}$, a = 11.277(2), b = 12.015(2), c = 11.056(2) Å, α = 97.87 (1), β = 94.66(2), γ = 71.73(1)°, V = 1408.1(4) Å^3, Z = 4, μ = 1.056 mm^{-1}, D_c = 1.416 mg m^{-3}, F_{000} = 624, T = 293 K. Final R value was 0.0684 for 4788 reflections. CCDC 182/1467. See http://www.rsc.org/suppdata/cc/1999/2429/ for crystallographic data in .cif format.

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