

**ANIONIC HETERO[3,3]REARRANGEMENTS.
N-ACYL-N'-ENYLHYDRAZINES TO PYRROLIDINONES**

Yasuyuki Endo* and Koichi Shudo

Faculty of Pharmaceutical Sciences, University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract *N*-Acyl-*N'*-enylhydrazines rearrange upon treatment with base to afford 5-amino-2-pyrrolidinones. The rearrangement can be rationalized in terms of initial stereospecific [3,3]sigmatropic shifts of the enolates followed by intramolecular addition of the nitrogen atom of the amide group to the imino group.

The 3,4-diaza [3,3]sigmatropic rearrangement is important in the fields of synthetic and mechanistic organic chemistry.¹ Both aromatic and aliphatic versions of 3,4-diaza [3,3]sigmatropic shifts are well known. An example of the former is the first step in the conversion of *N*-aryl-*N'*-enylhydrazines to indole.² An example of the latter is the acid-catalyzed rearrangement of bis(enyl)hydrazine, derived from cyclohexanone and *N,N'*-dimethylhydrazine, to a pyrrole derivative.³

We previously reported anionic rearrangements of *N,O*-diacylhydroxylamines⁴ and *N,N'*-diacylhydrazines⁵ to succinic acid derivatives. The C-C bond-forming rearrangement can be rationalized in terms of hetero [3,3]sigmatropic shifts of dienolated precursors. These investigations indicate that the carboxamide enolate can be employed as a component of [3,3]sigmatropic rearrangement precursors. From the viewpoint described above, an *N*-acyl-*N'*-enylhydrazine enolate, corresponding to the *N*-aryl-*N'*-enylhydrazine intermediate in the Fischer indole synthesis, should undergo a similar [3,3]sigmatropic rearrangement. In this paper, we wish to report the facile anionic [3,3] sigmatropic rearrangement of *N,N'*-dimethyl-*N*-acyl-*N'*-enylhydrazines to afford the 5-methylamino-*N*-methyl-2-pyrrolidinones and related reactions.

N,N'-Dimethyl-*N*-acylhydrazines, readily available by partial acylation of *N,N'*-dimethylhydrazine, were transformed into *N,N'*-dimethyl-*N*-acyl-*N'*-enylhydrazines by condensation with suitable ketones in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate in benzene at refluxing temperature. After purification by alumina column chromatography,⁶ several *N*-acyl-*N'*-enylhydrazines in which the enyl group is stabilized by a neighboring phenyl group or a cyclic structure (**1**, **6**, **9** and **12**) were isolated as relatively stable liquid. These compounds were characterized chiefly by nmr spectral data.⁷ When the *N*-phenacetyl-*N'*-cyclohexenylhydrazine (**1a**) was treated with 1.5 eq. of LDA at 0°C for 30 min and 20°C for 2 h in THF, the product isolated was a bicyclic compound (**2a**) as a single stereoisomer in a yield of 40%. The structure was confirmed by ¹H- and ¹³C-nmr and nuclear Overhauser experiments.⁸ The other *N*-acyl-*N'*-enylhydrazines (**1b**, **6**, **9** and **12**) smoothly rearranged with the same conditions to give the corresponding 5-methylamino-*N*-methylpyrrolidinone derivatives (**2b**, **7**, **10**, **13**) in 41-64% yields (Table 1).

The first step of the rearrangement can be rationalized in terms of [3,3]sigmatropic shifts of the transition state (**3**), which consists of *E*-enamine-*Z*-enolate, according to the Fischer reaction. However, the basic and mild conditions of the rearrangement suggests participation of the anionic character in a similar manner to the oxy-Cope rearrangement.⁹ The resulting rearranged intermediate (**4**) is transformed to **2** by intramolecular addition of the nitrogen atom of the amide group to the imino group.

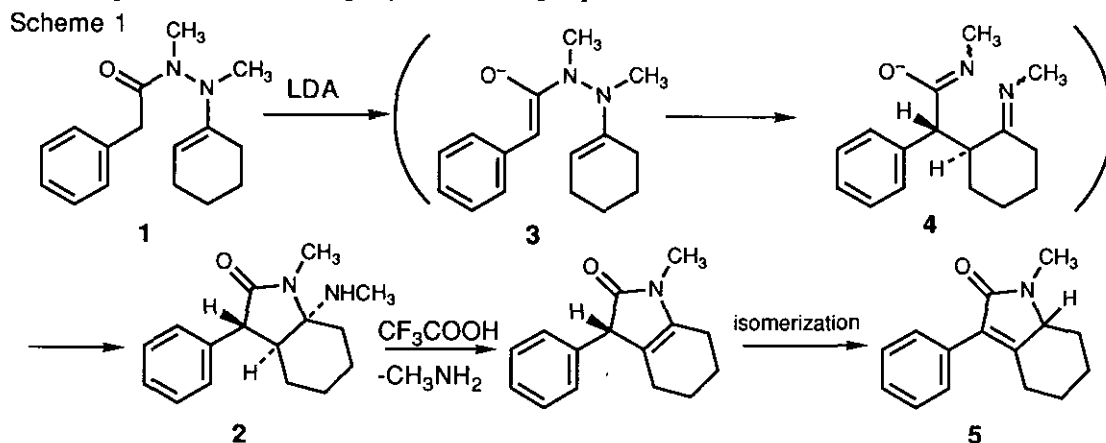
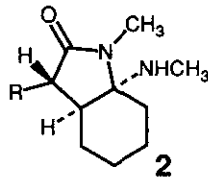
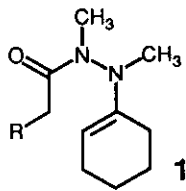
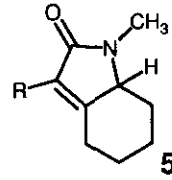


Table 1

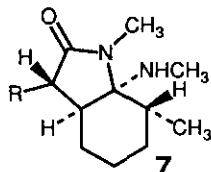
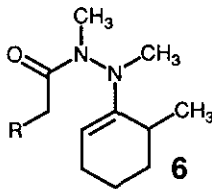
<i>N</i> -Acyl- <i>N'</i> -enyldiazine	Rearranged and Cyclized Product	Deaminated Product
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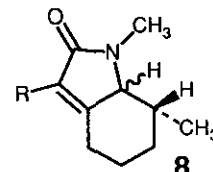
a R = C₆H₅ 40%
b R = CH₃ 41%



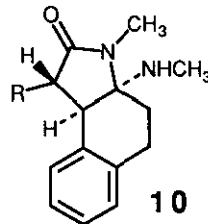
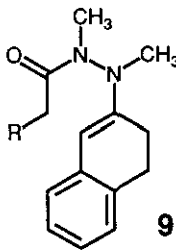
a R = C₆H₅ 79%



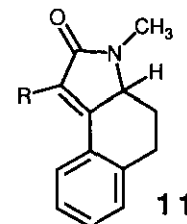
a R = C₆H₅ 42%



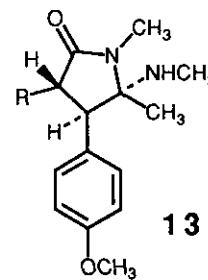
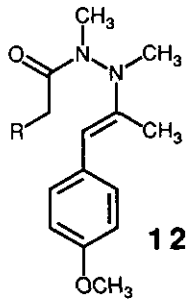
a R = C₆H₅ 79%
 (α : β = 1 : 5)



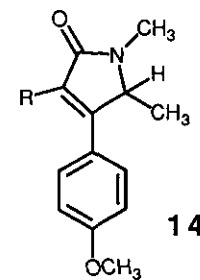
a R = C₆H₅ 46%
b R = CH₃ 45%



a R = C₆H₅ 82%



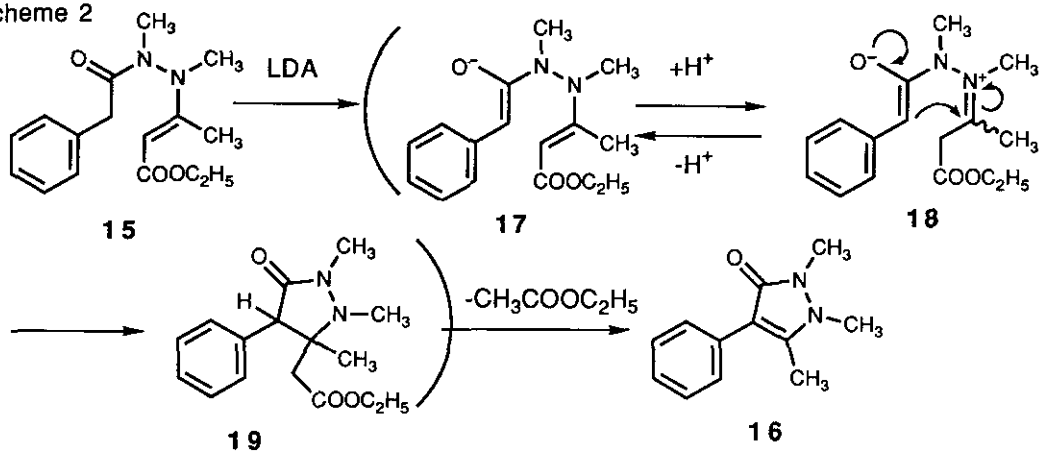
a R = C₆H₅ 64%
b R = CH₃ 43%



a R = C₆H₅ 88%

Treatment of phenyl-substituted analogs of 5-methylamino-*N*-methyl-2-pyrrolidinones (**2a**, **7a**, **10a**, **13a**) with trifluoroacetic acid gave 2,5-dihydro-*N*-methylpyrrol-2-ones (**5a**, **8a**, **11a**, **14a**). The reaction can be explained by protonation at the methylamino group followed by elimination of methylamine to give a cationic intermediate, in which the relatively acidic proton between the phenyl and carbonyl groups is abstracted to give the products.

Scheme 2



Another reaction was observed in the case of the reaction of *N,N'*-dimethyl-*N*-phenacyl-*N'*-enylhydrazine (**15**), derived from *N,N'*-dimethyl-*N*-phenacylhydrazine and ethyl acetoacetate. Treatment of **15** with 1.5 eq of LDA in THF at 20°C for 2 h and 40°C for 2 h gave 1,2,5-trimethyl-4-phenylpyrazol-3-one (**16**) in a yield of 32%. The formation of **16** can be rationalized in terms of intramolecular addition of the carbon atom of the enolate to the iminium group in the transition state (**18**) followed by the elimination of ethyl acetate.

In conclusion, we have demonstrated the base-catalyzed 3,4-diaza [3,3]sigmatropic rearrangement of *N*-acyl-*N'*-enylhydrazines. The rearrangement is a new example of hetero [3,3]sigmatropic shifts and should be applicable to the synthesis of heterocycles.

REFERENCES AND NOTES

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6. The *N*-acyl-*N'*-enylhydrazines (**1,6,9** and **12**) were completely decomposed on a silica gel column and on tlc. The use of halogenated solvents should be avoided.
7. The measurements of nmr spectra were carried out employing CD₃OD as a solvent because the *N*-acyl-*N'*-enylhydrazines were decomposed in CDCl₃. The *N*-enyl structure is characterized by the olefinic proton at 4.5-5.5 ppm. The nmr spectral data of a representative product **1a** are given below. ¹H-Nmr (CD₃OD, 400 MHz): 1.50-1.70 (m, 4H), 1.80 (m, 2H), 2.08 (m, 2H), 2.58 (s, 3H), 2.79 (s, 3H), 3.73 (d, J=14.3 Hz, 1H), 3.89 (d, J=14.3 Hz, 1H), 4.78 (t, J=4.0 Hz, 1H), 7.20-7.30 (m, 5H); ¹³C-nmr (CD₃OD, 100 MHz): 23.37 (CH₂), 23.93 (CH₂), 25.21 (CH₂), 26.41 (CH₂), 27.66 (CH₃), 38.17 (CH₃), 40.71 (CH₂), 104.49 (CH), 127.61 (Ar), 129.36 (Ar), 130.41 (Ar), 136.75 (Ar), 143.37 (C), 176.15 (C=O). The structure of **1a** is characterized by a vinylic carbon signal at 104.49 ppm.
8. The nmr spectral data of **2a** are given below. The stereochemistry of **2a** is supported by the nuclear Overhauser difference spectra of **2a**. Saturation of the proton signal at 2.30 ppm (NHCH₃) results in a characteristic enhancement of the proton signal at 2.37 ppm which is due to the 4-position of the pyrrolidinone. ¹H-Nmr (CDCl₃, 400 MHz): 1.40-1.80 (m, 8H), 2.30 (s, 3H), 2.37 (bd, 1H, J=11.8 Hz), 2.74 (s, 3H), 3.47 (d, 1H, J=11.8 Hz), 7.20-7.35 (m, 5H); ¹³C-nmr (CDCl₃, 100 MHz): 20.55 (CH₂), 21.63 (CH₂), 21.80 (CH₂), 23.76 (CH₃), 27.32 (CH₃), 34.73 (CH₂), 42.56 (CH), 50.52 (CH), 76.50 (C), 126.92 (Ar), 128.74 (Ar), 128.83 (Ar), 138.77 (Ar), 173.75 (C=O). The structure of **2a** is characterized by a quaternary carbon signal at 76.50 ppm.
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10. The nmr spectral data of a representative product **5a** are given below. ¹H-Nmr (CDCl₃, 400 MHz): 1.13 (dddd, J=3.3, 3.3, 12.1, 12.1 Hz, 1H), 1.31 (dddd, J=4.0, 4.0, 12.8, 12.8, 12.8 Hz, 1H), 1.53 (dddd, J=3.3, 3.3, 13.5, 13.5, 13.5 Hz, 1H), 1.92 (bd, J=13.5 Hz, 1H), 1.98 (m, 1H), 2.26 (ddd, J=4.0, 4.0, 14.6 Hz, 1H), 3.71 (dd, J=5.5, 11.5 Hz, 1H), 7.32 (t, J=7.3 Hz, 1H), 7.41 (t, J=7.3 Hz, 2H), 7.48 (d, J=7.3 Hz, 2H).

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