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Anionic [3,3], [2,3] and [1,2] Rearrangements of Aliphatic and Aromatic Acyl Hydrazines with N-N Bond Cleavage.

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Abstract: *N*-Acyl-*N'*-phenylhydrazines rearrange under basic conditions to afford *o*-aminophenylacetamides. This reaction can be rationalized in terms of [3,3] sigmatropic shifts of enolized intermediates. The Sommelet-Hauser-type and Stevens-type rearrangements of both aromatic and aliphatic acylhydrazines compete with the [3,3] rearrangement. © 1997 Elsevier Science Ltd.

The Fisher indole synthesis is a long-known and effective synthetic method. The major portion of the rearrangement has been elucidated to be 3,4-diaza[3,3] sigmatropic rearrangement of enhydrazines.[1] The [3,3] shifts were interpreted in terms of charge-accelerated rearrangement of the protonated form at the most basic site of enhydrazines.[2] Some analogs of the Fisher indole synthesis with hydrazine derivatives and strong bases were mentioned in early reports,[3] but these base-catalyzed rearrangements have not received much attention since. In connection with the development of [3,3] rearrangement with cleavage between hetero-atoms, we previously reported the base-catalyzed rearrangement of *N*-phenyl-*O*- acylhydroxylamines to *o*-aminophenylacetic acids.[4,5] We have also reported the aliphatic version of 3,4-diaza[3,3] rearrangements, *i.e.*, the anionic rearrangement of *N,N'*-diacylhydrazines[6] and *N*-acyl-*N'*-enhydrazines.[7] These investigations indicated that the carboxamide enolate can be employed as a component of [3,3] rearrangement precursors. In this paper, we wish to report regiospecific synthesis of anilines having a carboxyl-functionalized alkyl group in the *ortho* position by means of anionic 3,4-diaza [3,3] rearrangements of *N*-acyl-*N'*-phenylhydrazines. We also describe new Sommelet-Hauser-type and Stevens-type rearrangements of both aromatic and aliphatic acylhydrazines competing with the [3,3] rearrangements.

Treatment of *N,N'*-dimethyl-*N*-acetyl-*N'*-phenylhydrazines (**1a**), readily available by acylation of *N,N'*-dimethyl-*N*-phenylhydrazine,[8] with 2.5 eq of lithium diisopropylamide (LDA) in toluene at room temperature for 24 h gave *N*-methyl-2-methylaminophenylacetamide (**2a**) in 54% yield. The substituent effects for R^1 and R^2 and solvent effects are summarized in Table1. The reactants with a primary or secondary acyl substituent on the nitrogen (**1a**, **1b**, **1c**, **1d**) smoothly rearranged in toluene to [3,3] products (**2a**, **2b**, **2c**, **2d**; runs 1,3,5,7) in 54-61% yields. However, reaction of the substrates with a tertiary acyl substituent (**1e** and **1f**) afforded no [3,3] products. In our previous investigation on anionic [3,3] rearrangement of *N*-phenyl-*O*-acylhydroxylamines, *N*-phenyl-*N,O*-diisobutyrylhydroxylamine rearranged to the [3,3] product in 88% yield.[4] In the rearrangement of *N*-phenyl-*O*-acylhydroxylamines, appreciable amounts of *para* isomers (formally [3,5] products such as **3**) were isolated, which suggested that an

intramolecular ionic pathway is involved. In contrast, the present rearrangement of *N,N'*-dimethyl-*N*-acyl-*N'*-phenylhydrazines gave no [3,5] product **3** in any case. These differences between N-O bond cleavage and N-N bond cleavage may reflect the fact that the N-O bond in the transition state is significantly polarized, while the N-N bond is not.

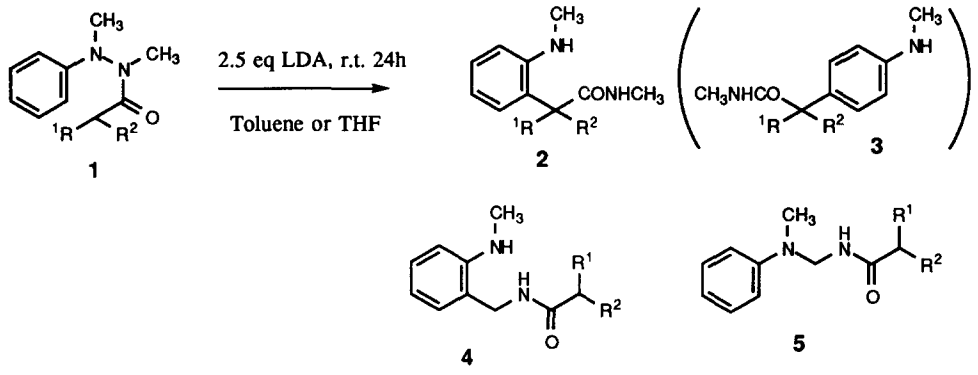


Table 1. Anionic [3,3] Rearrangement of *N,N'*-Dimethyl-*N*-acyl-*N'*-phenylhydrazines (**1**)

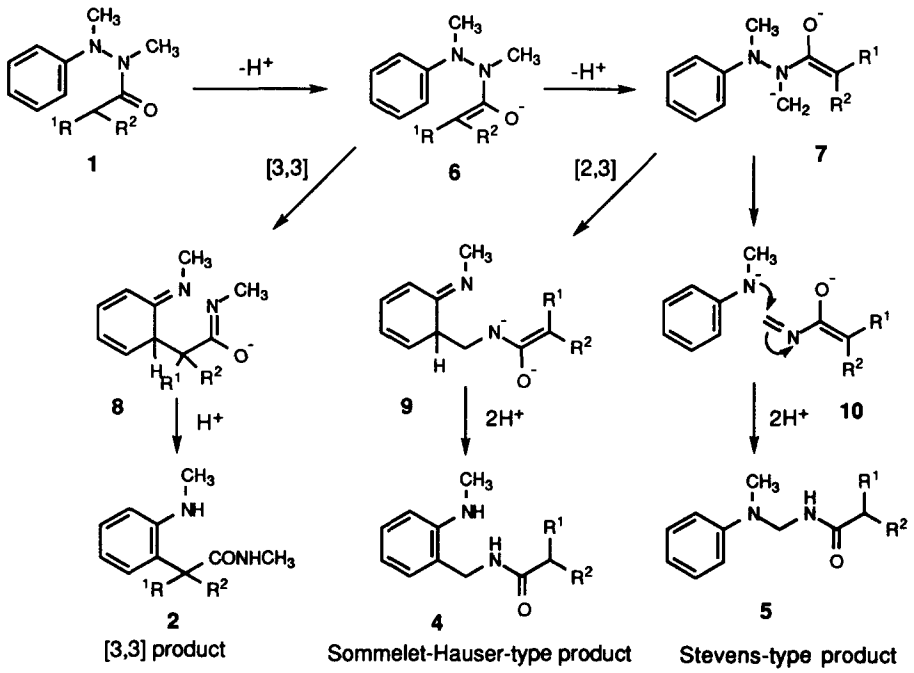
Run	Compound	R^1	R^2	Solvent	Yield (%) 2	4	5
1	a	H	H	toluene	54	0	0
2				THF	60	0	0
3	b	Ph	H	toluene	61	0	0
4				THF	55	0	0
5	c	CH_3	H	toluene	54	0	0
6				THF	81	0	0
7	d	$C(CH_3)_3$	H	toluene	56	8	8
8				THF	20	4	58
9	e	CH_3	CH_3	toluene	0	26	14
10				THF	0	4	50
11	f	$-(CH_2)_5-$		toluene	0	24	30
12				THF	0	3	61

All starting materials were added to LDA solution at -78°C under Ar. After stirring for 10 min at -78°C, the temperature was raised to room temperature. The reaction solvents contain approximately 25% hexanes. Yields are isolated yields.

In the case of the reaction of **1e** under the LDA/toluene condition, **4e** and **5e** were isolated in 26 and 14% yields, respectively (run 9). The mechanism of the formation of these products can be explained in terms of an analogy with Sommelet-Hauser rearrangement and Stevens rearrangement in benzylammonium N-alkylide chemistry. The effect of variation of the solvent upon this rearrangement serves to illustrate further the mechanistic features. A change of the solvent did not affect the rearrangements of reactants with a primary or less bulky secondary acyl substituent on the nitrogen (**1a**, **1b**, **1c**; runs 2,4,6). However, a

significant change of the products occurred in the rearrangement of **1d** under LDA/THF condition. The major product was **5d** (58%, run 8). The ratio of the Stevens-type [1,2] product **5d** increased with increasing polarity of the solvent. Further, the formation of Sommelet-Hauser products and Stevens-type products was also affected in substrates with a tertiary acyl substituent (**1e** and **1f**). The ratio of the Stevens-type [1,2] product **5e** and **5f** increased with increasing polarity of the solvent (runs 9-12).

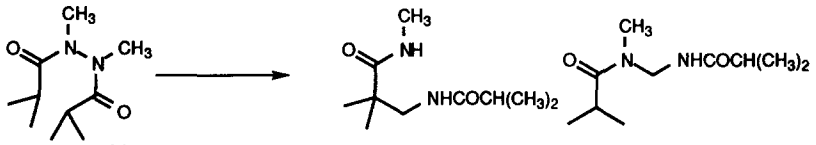
Scheme 1. Plausible Mechanism of the Rearrangement of **1**



Proposed mechanisms of the rearrangements are shown in Scheme 1. The formation of the amide enolate **6** is proved to be the first step of these rearrangements even when [1,2] and [2,3] rearrangements are major pathway. When **1e** was treated with LDA at room temperature for 10 min in toluene or THF and then quenched by D_2O, 60-70% of α-hydrogen of recovered starting material was exchanged by deuterium. None of *N*-methyl hydrogen was exchanged. The [3,3] rearrangements proceed via the enolate,[9] however, when the [3,3] shifts can not proceed smoothly by steric factors, further proton abstraction of the *N*-methyl occurs to give [1,2] and [2,3] products. In the field of ylide chemistry, similar [1,2] and [2,3] rearrangements have been well documented.[10] Recently, Sato et al. investigated the mechanism of [1,2] and [2,3] rearrangement of benzylammonium *N*-alkylides and reported that [2,3] shifts of the ylide initially occurred to give isotoluene derivatives (similar to **9**), which were then transformed into the Sommelet-Hauser and Stevens products.[11] The formation of **4** in the present rearrangement of *N,N'*-dimethyl-*N*-acyl-*N'*-phenylhydrazines can be interpreted by analogy with Sommelet-Hauser rearrangement. In general, less polar solvents and high temperature are favorable for the formation of Stevens products because of the radical nature of the intermediate. However, the formation of **5** in the present rearrangement is favored in a polar solvent as

compared with a less polar solvent. This suggests that the formation of the Stevens-type product (**5**) proceeds via an ionic intermediate such as **10**.

An aliphatic version of this rearrangement was also found. *N,N'*-Dimethyl-*N,N'*-isobutyrylhydrazine (**11**) was treated with 5 eq of LDA at 50°C for 3 h in THF to give the Sommelet-Hauser-type product (**12**) and the Stevens-type product (**13**) in 11% and 41% yields, respectively.



11 **12** **13**

In this paper, we have described base-catalyzed rearrangements of aromatic acylhydrazines. The [3,3] rearrangement should prove useful for the introduction of a functionalized acetic acid group onto an aromatic ring. The development of [1,2] and [2,3] rearrangements besides ylide intermediates suggests the synthetic utility of stabilization by an amide group of a neighboring carbanion.

References and Notes

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9. The [3,3] rearrangements do not require 2 equivalent of base. Treatment of **1b** with 1.25 eq of LDA in THF for 24 h gave the [3,3] product **2b** in 68% yield.
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