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A NOVEL ACID-CATALYZED REARRANGEMENT OF N-ARYL-N'-ARYLOXYUREAS TO BIPHENYL DERIVATIVES. A [5,5]-REARRANGEMENT INVOLVING THREE HETEROATOMS.

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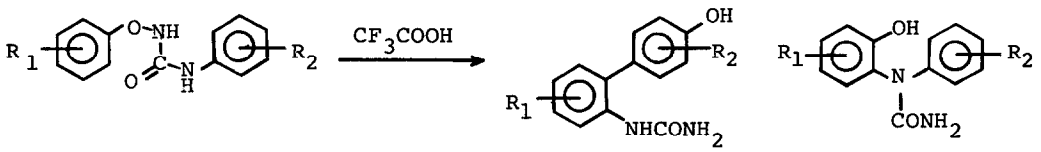
Abstract: In the presence of trifluoroacetic acid, N-phenyl-N'-phenoxyurea (1a) rearranges to N-(4'-hydroxy-2-biphenylyl)urea (2a) and N-carbamoyl-2-hydroxydiphenylamine (3a). The rearrangement is an intramolecular reaction, and the transition state of the breakage of the N-O bond is deduced to be polarized in the form $N^{\delta-}$--- $O^{\delta+}$. The reaction is entirely new and constitutes a fundamental aromatic rearrangement.

The benzidine rearrangement is a well-known aromatic rearrangement[1] which has long been the subject of mechanistic speculation. The major portion of the mechanism of the acid-catalyzed rearrangement of hydrazobenzene has recently been elucidated by Shine and coworkers.[2] The concerted [5,5]-sigmatropic pathway seems to be operative for the formation of benzidine. A similar aromatic rearrangement is the oxa-benzidine rearrangement of N,O-diarylhydroxylamines predicted by Dewar[3] and observed by several researchers;[4] the nitrogen-oxygen bond cleaves to give 4-amino-4'-hydroxybiphenyls. Acid-catalyzed [3,3]-rearrangements of O-aryl-N-acyl-[5] and O-aryl-N-sulfonylhydroxylamines[6] to catechol derivatives, and of N-alkyl-N'-aryloxyureas to N-alkyl-N-(2-hydroxyaryl)-ureas have also been reported.[7] These N-O bond-cleaving reactions may be interpreted as [3,3]-sigmatropic reactions of the protonated species, or hetero-Claisen rearrangements involving three hetero atoms. This paper describes an entirely new sigmatropic [5,5]-rearrangement involving three heteroatoms, i.e., two nitrogen atoms and an oxygen atom.

N-Phenyl-N'-phenoxyurea (1a), readily available by reaction of O-phenylhydroxylamine and phenyl isocyanate, was treated with trifluoroacetic acid in dichloromethane at room temperature for 2-3 hr to give N-(4'-hydroxy-2-biphenylyl)urea (2a, 50%) and N-carbamoyl-2-hydroxydiphenylamine (3a, 11%) as major products.[8] Minor products were N-(4'-hydroxy-4-biphenylyl)urea (1-2%), N-(2'-hydroxy-2-biphenylyl)urea (1-2%) and N-(2'-hydroxy-4-biphenylyl)urea (1-2%). When the 4-position of the phenoxy moiety of 1 was occupied by a methyl group, 1b (R_1=4-CH_3) gave only a diphenylamine derivative (3b, 68%), and no product

Scheme 1



1 2 3

could be isolated which might be formed via attack at the 4-position. While substitution by a 4-nitro group (i.e., 1c) suppressed the reaction under the conditions used, 2,6-dimethyl substitution enhanced the reaction rate, and 1d (R_1=2,6-$(CH_3)_2$) smoothly gave the urea derivative (2d, 58%). The 3,5-dimethyl-substituted compound (1e, R_1=3,5-$(CH_3)_2$) gave products (2e and 3e) corresponding to the products from 1a.

Table 1. Acid-catalyzed rearrangement of N-aryl-N'-aryloxyureas

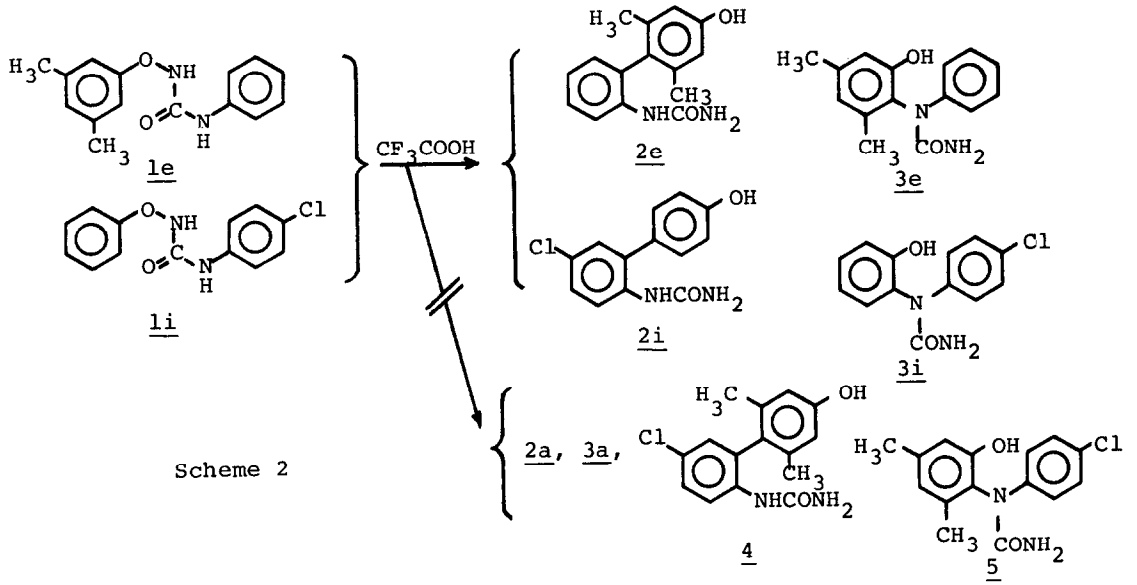
1	R_1	R_2	2 (Yield: %)	3 (Yield: %)
a	H	H	50	11
b	4-CH_3	H	—	68
c	4-NO_2	H	—	—a)
d	2,6-$(CH_3)_2$	H	58	—b)
e	3,5-$(CH_3)_2$	H	57	20
f	H	2',6'-$(CH_3)_2$	—	—c)
g	H	3',5'-$(CH_3)_2$	47	—d)
h	H	3',5'-$(NO_2)_2$	2	40
i	H	4'-Cl	46	16

a) the starting compound was recovered under these conditions.
b) N-(4'-hydroxy-2',6'-dimethyl-4-biphenylyl)urea (11%)
c) N-(2,6-dimethylphenyl)urea (44%) and N-(4'-hydroxy-2,6-dimethyl-4-biphenylyl)urea (12%)
d) N-(3,5-dimethylphenyl)urea (32%)

Blockage of the 2',6'-positions of the anilino moiety by methyl groups (i.e., 1f, R_2=2',6'-$(CH_3)_2$) suppressed the [5,5]-rearrangement and resulted in production of N-(4'-hydroxy-2,6-dimethyl-4-biphenylyl)urea. While the substitution of the 3',5'-positions by methyl groups gave the [5,5]-rearrangement product (2g), the reaction of the dinitro compound (1h, R_2=3',5'-$(NO_2)_2$) yielded the diphenylamine (3h) as the major product. This suggests that the [5,5]-rearrangement is suppressed by the electron-withdrawing effect of the 3'- and 5'-

substituents. Thus, the N-O bond cleavage is facilitated by electron-donating nature of the phenoxy group, and the [5,5]-rearrangement is more favorable when the anilino group is electron-rich.

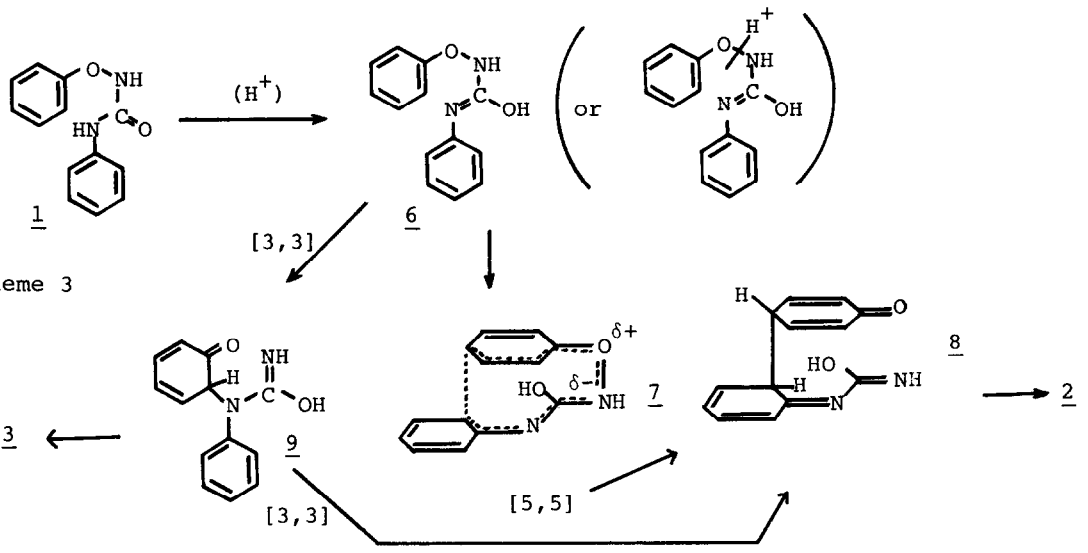
An important aspect of the reaction was revealed in a cross-over experiment carried out on a mixture of N-(3,5-dimethylphenoxy)-N'-phenylurea (1e) and N-(phenoxy)-N'-(4-chlorophenyl)urea (1i), the compounds with similar reactivities and similar product ratio (Scheme 2). The nonformation of cross-over products such as 2a, 3a, 4 and 5 is strong evidence for an intramolecular reaction: the two fragments from a given molecule do not become free of each other's influence long enough to allow the fragment from another molecule to intercede.



Scheme 2

By analogy with the benzidine rearrangement,[2] one plausible mechanism for the formation of 2 consists of a [5,5]-sigmatropic rearrangement of the enolized phenoxyureas (isoureas, 6)[9] or the protonated form which can be formed by acid catalysis from 1. The substituent effect suggests that the N-O bond is polarized in the form $N^{\delta-}$--- $O^{\delta+}$: the transition state (7) may have a phenoxenium ion[6,10] character in part (Scheme 3). Another possible mechanism is a double [3,3]-sigmatropic rearrangement (i.e., 6 → 9 → 8 → 2). This mechanism is less likely since Claisen rearrangement of an N-allyl group requires drastic thermal conditions.[11]

This reaction, for which we have given only a few examples, seems to be of general applicability, and is a novel one in aromatic chemistry. Detailed elucidation of the mechanism will require careful kinetic studies as done in the case of the benzidine rearrangement.



Scheme 3

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