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CHEMISTRY OF O-ARYLHYDROXYLAMINES. A NOVEL ACID-CATALYZED REARRANGEMENT OF O-ARYL-N-ACETOACETYLHYDROXYLAMINES TO BENZOFURANS

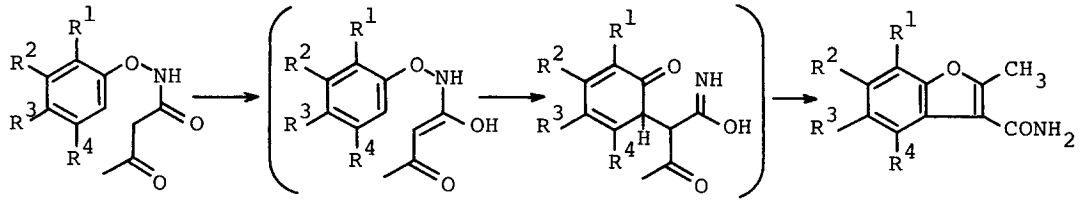
Yasuyuki Endo, Kohshi Namikawa and Koichi Shudo*

Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113, JAPAN

Abstract: Acid-catalyzed rearangement of O-aryl-N-acetoacetylhydroxylamines (**1**) affords 2-methylbenzofuran-3-carboxamides. Some abnormal rearrangements of the title compounds are also described.

Nitrogen-nitrogen bond cleavage of phenylhydrazine derivatives is involved in several useful and well-known rearrangements in the field of aromatic chemistry, i.e. the benzidine rearrangement and the Fischer indole synthesis. O-Phenylhydroxylamine, which is isoelectric with phenylhydrazine, may have similar reactivity. The oxa-benzidine rearrangement of N,O-diarylhydroxylamines[1] (the nitrogen-oxygen bond is cleaved to give 4-amino-4'-hydroxybiphenyls) and the rearrangement of O-aryloximes to give benzofurans[2] (the O-analog of the Fischer indole synthesis) have been reported. However, the N-O bond cleavage of O-phenylhydroxylamines initiates several new reactions other than those which would be expected from the reactions of phenylhydrazines. In previous papers, we have reported acid-catalyzed rearrangements of O-aryl-N-acyl-[3] and O-aryl-N-sulfonylhydroxylamines[4] to catechol derivatives, of N-alkyl-N'-aryloxyureas to 2-alkylaminophenol derivatives,[5] and of N-aryl-N'-aryloxyureas to biphenyl derivatives.[6] These reactions, involving the N-O bond cleavage, may be interpreted as [3,3]- or [5,5]-sigmatropic reactions of the protonated species. This paper describes a new C-C bond-forming rearrangement of O-aryl-N-acetoacetylhydroxylamines(**1a-i**).

O-Phenyl-N-acetoacetylhydroxylamine (**1a**), readily prepared by the reaction of O-phenylhydroxylamine and diketene in THF, was treated with a mixture of trifluoromethanesulfonic acid and trifluoroacetic acid (1:20) at 0°C for 0.5 hr to give 2-methylbenzofuran-3-carboxamide (**2a**) in a yield of 79%. Trifluoroacetic acid alone also works as the acid catalyst, but the rate is slower. Table 1 gives the yields of the rearrangement of substituted O-phenyl-N-acetoacetylhydroxylamines. These compounds were best purified by column chromatography on silica gel and were identified from the NMR and UV spectra. The products from meta-substituted substrates were identified as the 4- and 6-substituted 2-methylbenzofuran-3-carboxamides (Runs 6-9). The yields of the products from ortho-substituted substrates were somewhat lower (Runs 2-4), and no other identifiable product was isolated.

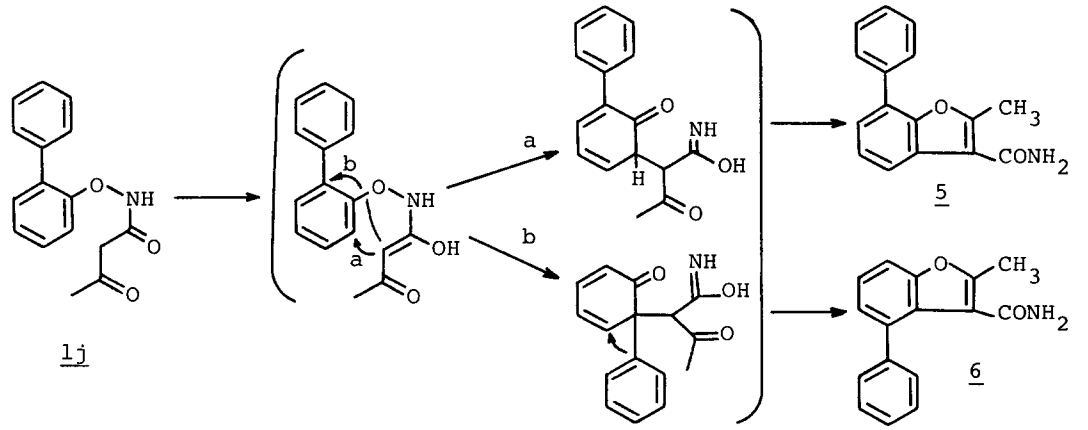


1a-i 3 2

Table 1. A Rerrangement of O-Aryl-N-acetoacetylhydroxylamines to Benzofurans.

compound	R^1	R^2	R^3	R^4	Yield(%)	
					6-substituted	4-substituted
1a	H	H	H	H	79	
1b	CH_3	H	H	H	44	
1c	CH_3	CH_3	H	H	44	
1d	CH_3	H	CH_3	H	34	
1e	H	CH_3	H	CH_3	67	
1f	H	CH_3	H	H	49	32
1g	H	t-C_4H_9	H	H	49	37
1h	H	C_6H_5	H	H	43	40
1i	H	OCH_3	H	H	77	4

By analogy with the Fischer indole synthesis, a plausible mechanism for this reaction consists of a [3,3]-sigmatropic rearrangement of the enolized species such as **3** and/or the protonated species, prototropic aromatization, cyclization of the resulting 2-(2-acetoacetamido)phenol intermediate and dehydration.

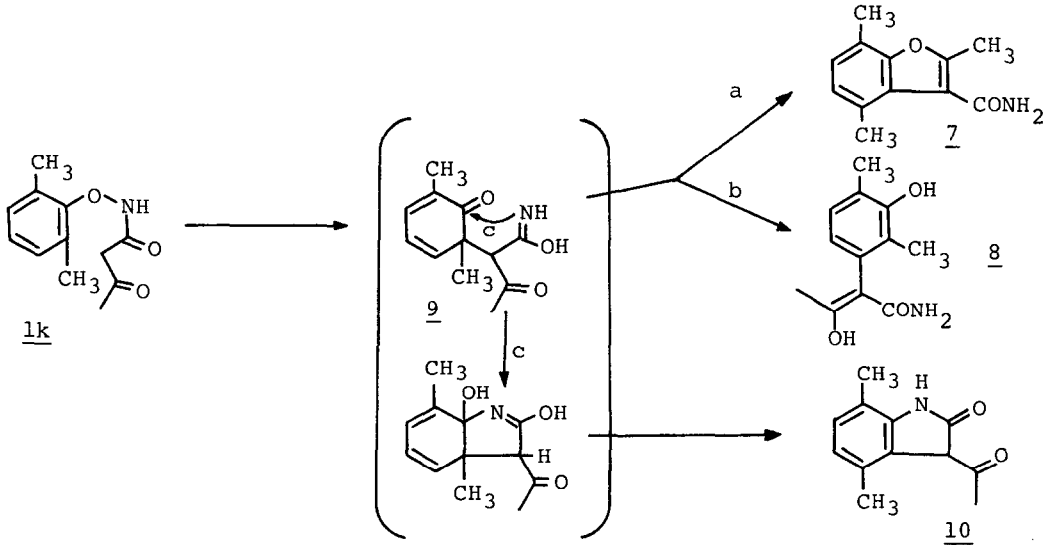


1j 5 6

O-(2-Biphenylyl)hydroxylamine (**1j**), prepared from O-(2-biphenylyl)hydroxylamine, was treated with a mixture of trifluoromethanesulfonic acid and trifluoroacetic acid (1:50) at 0°C for 0.5 hr to give 2-methyl-7-phenylbenzofuran-3-carboxamide (**4**, 19%) and 2-methyl-4-phenylbenzofuran-3-carboxamide (**5**, 17%). Based on Fischer indole chemistry,[7] the formation of the latter product can be interpreted in terms of a [3,3]-rearrangement of the intermediate (**6**) to

the occupied ortho position, followed by dienone-phenol rearrangement involving 1,2-migration of the phenyl group, cyclization and hydration. The process is very similar to the abnormal Fischer indole synthesis[7,8]: the 2-biphenylhydrazone of ethyl pyruvate rearranges in the presence of a Lewis acid in acetic acid to give 4-phenylindole-2-carboxylic acid ethyl ester in 21% yield in addition to the normal cyclized product, 7-phenylindole-2-carboxylic acid ethyl ester (61%).[8]

When O-(2,6-dimethylphenyl)-N-acetoacetylhydroxylamine (**1k**) was treated with a mixture of trifluoromethanesulfonic acid and trifluoroacetic acid (1:5) at room temperature for 16 hr, 2,4,7-trimethylbenzofuran-3-carboxamide (**7**, 15%) and an enolized 3-(2-actoacetamido)-2,6-xylenol (**8**, 73%) were obtained. The formation of the latter product can be interpreted in terms of dienone-phenol rearrangement involving 1,2-migration of the acetoacetamide group of the intermediate (**9**). On the other hand, when **1k** was treated with trifluoroacetic acid at refluxing temperature for 3 hr, an unexpected product, 4,7-dimethyl-3-acetyloxindole (**10**), was formed in a 89% yield. A possible mechanism for the formation of **10** consists of nucleophilic attack of the nitrogen atom of the imino group on the carbonyl group of the dienone at the stage of the intermediate (**9**). The difference of reaction site may be dependent on the acidity of the solution. The dienone-phenol rearrangement is accelerated with increasing acidity. Thus, in the strongly acidic medium (trifluoromethanesulfonic acid-trifluoroacetic acid 5:1; the acidity function H_0 is presumed to be -8~-10), the intermediate **9** may be rapidly converted to **7** and **8** (paths a,b). On the other hand, in the relatively weakly acidic medium (trifluoroacetic acid; H_0 is -2.8), the life time of the intermediate **9** may be sufficiently long to allow attack by the imino group which is not sufficiently protonated. Thus, **9** is converted into oxindole **10**, with accompanying methyl migration.



The rearrangements described here, of which we have given only a few examples, seem to be of general applicability, and present a novel application of N-O bond cleavage in aromatic chemistry.

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