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REACTION OF N,O-DIACYLARYLHYDROXYLAMINE WITH CARBON NUCLEOPHILES.

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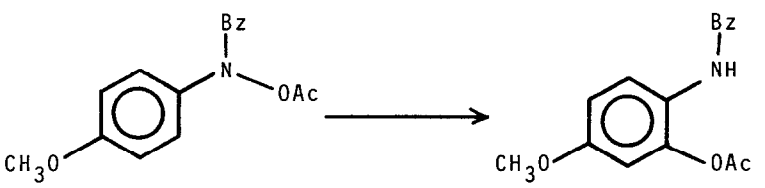
In extention of the previous studies on nucleophilic reactions of arylhydroxylamines[1] with the hydroxyl group as the leaving group, the reactivity of N,O-diacylarylhydroxylamine, in which the possible leaving group is the acetoxy group, with carbon nucleophiles is evaluated in this paper. The current concept[2] that carcinogenetic arylhydroxamic acids are further activated by O-esterification (acylation, sulfonation, and phosphorylation) to electrophilic reactants capable of interacting with cellular nucleophiles, promoted us to study the chemical aspect of N,O-diacylarylhydroxylamines. The present paper deals with a quite mild reaction of N-benzoyl-O-acetyl-(4-methoxyphenyl)hydroxylamine (1) with phenols and indoles. The work on acyloxymigration[3] of N,O-diacylarylhydroxylamines as well as the chemistry of anilenium ions[4] suggested us that the presence of 4-methoxy group would enhance the heterolytic reactivity of the N-O bond. The compound was also chosen because it relates closely to a key metabolite of phenacetin[5] and is expected to have a similar reactivity to those of some activated carcinogens.[2,6]

When a tetrahydrofuran or methylene chloride solution of 1[7] was heated at 40°C, 2-acetoxy-4-methoxy-N-benzoylaniline (2)[8] was obtained in a quantitative yield. However, 1 reacted very rapidly with phenol in tetrahydrofuran at 20°C. The product was confirmed as N-benzoyl-4-hydroxy-4'-methoxydiphenylamine[9] (3a; 37%) together with 2 (41%). Corresponding products (3b, c) were obtained in the reaction of o- and m- cresol. In every case the attack of the nitrogen atom occurred at the para position of the hydroxyl group of the phenols.



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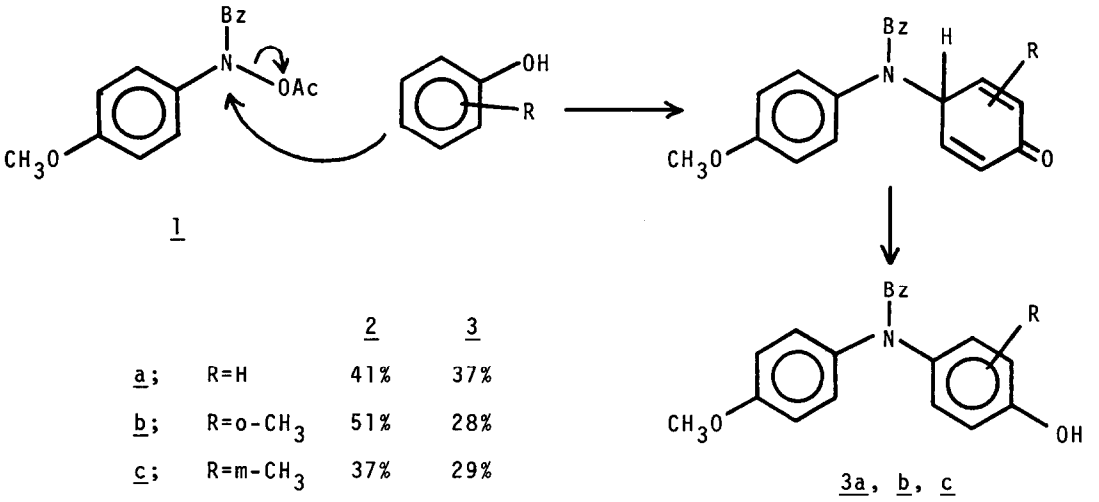
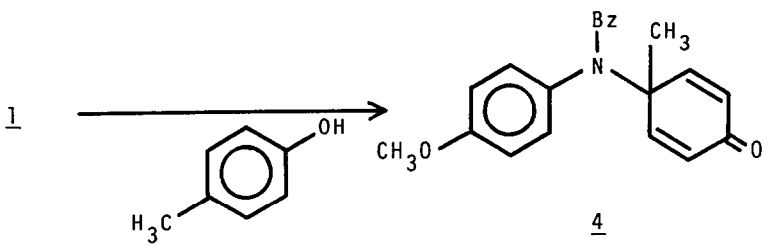


		2	3
a;	R=H	41%	37%
b;	R=o-CH_3	51%	28%
c;	R=m-CH_3	37%	29%

1

3a, b, c

The reaction with p-cresol is instructive, since the isolation of 2,5-cyclohexadienone was accomplished. A similar reaction of 1 with p-cresol in tetrahydrofuran gave 4-methyl-4-(N-benzoyl-4'-methoxyphenylamino)-2,5-cyclohexadienone[10] (4; 32%) as the major product together with 2 (43%). The structure of 4 was deduced from nmr (up-field shift of methyl (δ 1.55 ppm) and the presence of enone hydrogens), ir (the presence of two carbonyl groups and the absence of NH), and uv (in 95% ethanol, λ_{max}(nm) (log ε) 231 (4.62), 276 (4.04).) This reaction seems to be the first example of the attack on an ipso position by an electron-dificient nitrogen except nitration. The steric hinderance near the nitrogen atom is so much that the ipso attack is surprising.



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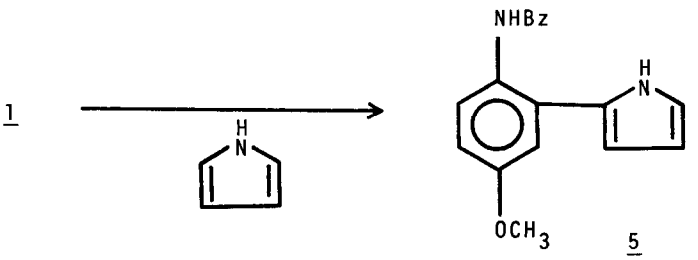
Pyrrole and indoles are also good nucleophiles. The reaction with pyrrole in tetrahydrofuran proceeded smoothly, and the products isolated were 2-aminophenylpyrrole[12] (5; 42%) and 2 (36%).



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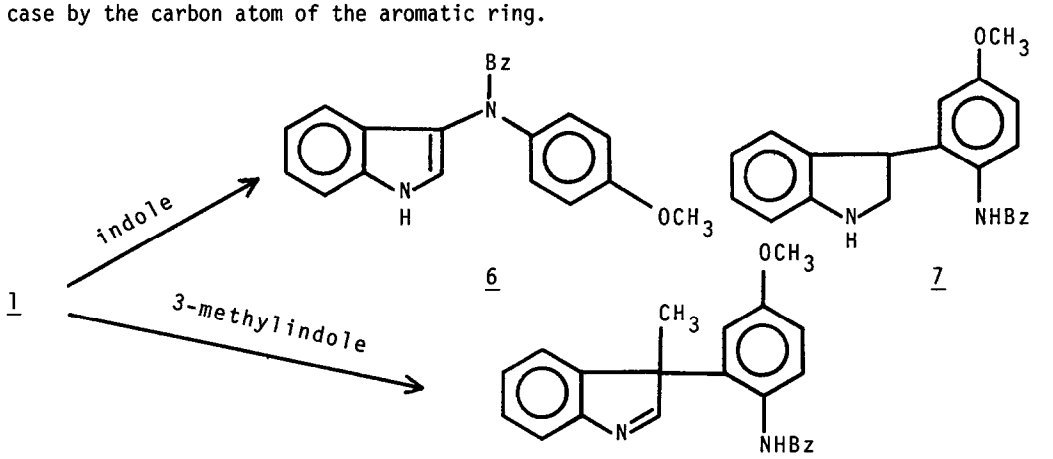
The reaction with indole gave 3-phenylaminoindole[13] (6; 12%), 3-aminophenylindole[13] (7; 15%), and 2 (59%). The reaction with 3-methylindole gave an indolenine derivative[13] (8; 36%) and 2 (51%). The structural proof of 8 was obtained by nmr (up-field shift of methyl (δ 1.68 ppm) and H-2 of indolenine (δ 5.92 ppm)) and uv (in 95% ethanol, λ_{max} (nm) (log ε) 235 (4.34), 270 (4.16), 285 (4.11)). Thus, an ipso attack of 1 was again observed, but in this case by the carbon atom of the aromatic ring.



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In these reactions we showed that 1 reacts with phenols, pyrrole, and indoles in the quite mild conditions, but the modes of the reactions are different among them. With phenols only the nitrogen atom was attacked, but with pyrrole and 3-methylindole only the carbon atom of the aromatic was attacked, and with indole the reaction showed the border-line case. In every case the most possible pathway to the products may involve a nucleophilic attack on the nitrogen atom or the carbon atom with the departure of the acetoxy ion. The nature of the carbon nucleophiles appears to decide whether the attack is occurred on the nitrogen atom or the carbon atom. Though kinetic experiments are necessary in order to discuss whether the reaction is unimolecular or bimolecular, a possible ion pair in the acetoxymigration[3] may be trapped by the carbon nucleophiles to give the products since these reactions compete with acetoxymigration. Similar reactions have been recently reported by Coates[14] and Gassman,[15] though these are intramolecular nucleophilic migrations.

Since carbon nucleophiles used in the experiments, in particular p-cresol and 3-methylindole, are reasonable chemical models for biological nucleophiles, the present reactions may give a suggestion on the understanding of adverse biological reactions caused by ultimate carcinogens or toxic metabolites.

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References and Notes

(1) K. Shudo and T. Okamoto, Tetrahedron Lett., 1839 (1973); T. Okamoto, K. Shudo, and T. Ohta, J. Am. Chem. Soc., 97, 7184 (1975); T. Ohta, K. Shudo, and T. Okamoto, Tetrahedron Lett., 101 (1976); K. Shudo, T. Ohta, Y. Endo, and T. Okamoto, ibid., 105 (1976).

(2) J. A. Miller, in "Chemical Carcinogenesis," Part A, Paul O. P. Ts'o and J. A. DiPaolo Ed., Mercel Dekker, Inc., N. Y., 1974, pp 61.

(3) J. R. Cox and M. F. Dunn, the ACS Abstracts of the 152nd Meeting, N. Y. (1966); S. Oae and T. Sakurai, Tetrahedron, 32, 2289 (1976) and references therein.

(4) P. G. Gassman and G. A. Campbell, J. Am. Chem. Soc., 94, 3891 (1972).

(5) R. Nery, Biochem. J., 122, 317 (1971); I. C. Calder, M. J. Creek, and P. J. Williams, Chem. Biol. Interaction, 8, 87 (1974); I. C. Calder and M. J. Creek, Aust. J. Chem., 29, 1801 (1976).

(6) J. A. Miller, Cancer Reseach, 30, 559 (1970) and references therein; Y. Kawazoe, M. Araki, G. F-Huang, T. Okamoto, M. Maeda, and H. Tada, Chem. Pharm. Bull. (Tokyo), 23, 3041 (1975).

(7) 1 was prepared from N-benzoyl-(4-methoxyphenyl)hydroxylamine with acetic anhydride in a solution of 1N sodium hydroxide and methylene chloride. Evaporation of the methylene chloride layer gave an oily product in the yield of 85-95%, which was almost pure judging from thin layer chromatography and its nmr spectra ($(CDCl_3$, δ) 2.17 (3H, s), 3.76 (3H, s), 6.77 (2H, d, J=8.5Hz), 7.24 (2H, d, J=8.5Hz)). 1 was used for the reactions without further purification and the yields of the products are based on N-benzoyl-(4-methoxyphenyl)hydroxylamine. All the new reaction products except 1 in this work were correctly analyzed.

(8) 2 was identified with authentic sample prepared from 2-hydroxy-4-methoxynitrobenzene.

(9) The structures of 3a, 3b, and 3c were deduced from nmr, ir, and uv spectra.

(10) The quinamine type rearrangement[11] of 4 was examined, but 4 was stable to hydrochloric acid or trifluoroacetic acid in ethanol or trifluoroethanol.

(11) B. Miller, J. Am. Chem. Soc., 86, 1127, 1135 (1964).

(12) 5: NMR (DMSO-d_6, δ) 6.19-6.36 (2H, m), 6.77 (1H, d of d, J=3.0, 8.0Hz), 6.78 (1H, m), 6.97 (1H, d, J=3.0Hz), 7.92 (1H, d, J=8.0Hz), 8.89 (1H, b), 10.52 (1H, b).

(13) The structures of 6, 7, and 8 were supported by nmr (H and ^{13}C), ir, and uv spectra.

(14) R. M. Coates and I. Md. Said, J. Am. Chem. Soc., 99, 2355 (1977).

(15) P. G. Gassman and H. R. Drewes, J. Am. Chem. Soc., 96, 3002 (1974).