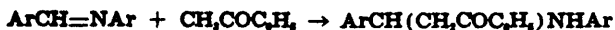


Addition of Acetophenone to Schiff Bases

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Some Schiff bases (Cancer Chemotherapy National Service Center, 1966) and their cobalt(II) derivatives (Hodnett and Willie, 1966) have shown significant activities against several transplantable tumors of mice. The purpose of this work was to prepare other derivatives of Schiff bases for determination of their antitumor properties.

Schiff bases, such as $\text{ArCH}=\text{NAr}$, possess a reactive double bond to which a variety of other chemical compounds may be added (Layer, 1963). Acetophenone is known to add (Kozlov et al. 1962) to several Schiff bases according to the following equation:



Since the *N*-arylamino ketones which would be obtained by the addition of acetophenone to *N*-salicylideneanilines would have the ability to coordinate with metals and might be effective against tumors, we wished to prepare some of them. Three kinds of catalysts were used: (1) a weak acid (an amine hydrochloride), (2) a strong acid (boron trifluoride etherate), and (3) a metal compound capable of complexing with the product (cobalt acetate). None of these attempts gave large yields of the desired compounds, but one new derivative of salicylaldehyde was obtained, and the yields of other compounds were improved over those reported in the literature.

The electronic effects of substitution on the *N*-aryl group of the Schiff bases which had been proposed earlier (Kozlov et al., 1962) were verified. Electrophilic groups on the *N*-aryl group increase the yield of addition product, while electron-donating groups on the same ring decrease the yield. It seems probable that the hydroxyl group of the salicylidene moiety, being strongly electron-releasing, had an adverse effect on the rate of addition of acetophenone to *N*-salicylideneaniline.

Boron trifluoride is a much better catalyst for this reaction than the

aniline hydrochlorides used. The cobalt ion is not a catalyst for the reaction, although it was hoped that the cobalt ion would bring the acetophenone and the Schiff base together in a favorable position for reaction.

The catalysis by a strong acid and the effects of substituent groups suggest that the acetophenone adds in the enol form as shown in Figure 1. If the addition of the acid occurred in the slow step of the reaction, electron-withdrawing groups would slow the reaction. Electron-withdrawing agents are known to speed the reaction. The effect of the acid is to polarize the C=N bond, producing a positive charge on the carbon atom involved. This electron-poor carbon atom then adds to the electron-rich C=C bond of the enol form of the acetophenone. It is known that both acids and bases speed the establishment of the keto-enol equilibrium; this rapid conversion may be a factor in the catalysis of the reaction. It would appear however that the depletion of electrons about the carbon atom of the C=N group could be the major factor in the catalysis of the reaction.

EXPERIMENTAL

Addition of Acetophenone to Schiff Bases—Method A—A Schiff base (10 mmoles) and acetophenone (10 mmoles) were dissolved in 20 ml of absolute alcohol, 1.5 g (11.5 mmoles) of aniline hydrochloride was added as a catalyst, and the reaction mixture was refluxed for 1 hr. The crystals which appeared upon cooling of the reaction mixture were separated by filtration and dried. The results are given in Table I.

Method B—Boron trifluoride etherate (20 mmoles) was added slowly with cooling to 20 mmoles of Schiff base dissolved in 80 mmoles of acetophenone. After standing an additional 10 min in the ice bath the solution was poured over 100 g of ice and water. The precipitate was separated, recrystallized from ethyl alcohol, and dried. The results are listed in Table I.

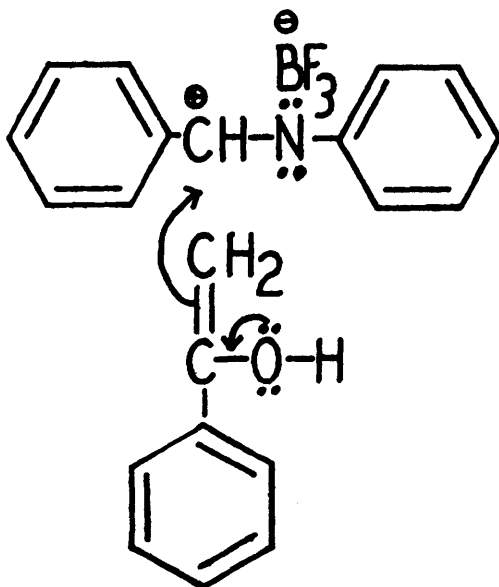


Figure 1. Transition State of Addition

TABLE I. ADDITION OF ACETOPHENONE TO $o\text{-R}^1\text{C}_6\text{H}_4\text{CH}=\text{NC}_6\text{H}_4\text{R}^2\text{-}p$

R ¹	R ²	Catalyst	Yield, %	Melting Point, C.	
				Observed	Reported
H	H	C ₆ H ₅ NH ₂ Cl	33	164-5	171-172*
OH	H	C ₆ H ₅ NH ₂ Cl	—	—	•
OH	NO ₂	<i>p</i> -O ₂ NC ₆ H ₄ NH ₂ Cl	8	—	•
OH	CH ₃	<i>p</i> -CH ₃ C ₆ H ₄ NH ₂ Cl	—	—	•
H	H	BF ₃ ·O(C ₂ H ₅) ₂	77	171-172	171-172*
OH	H	BF ₃ ·O(C ₂ H ₅) ₂	—	—	•
OH	NO ₂	BF ₃ ·O(C ₂ H ₅) ₂	15	282-284	•
OH	CO ₂ H	BF ₃ ·O(C ₂ H ₅) ₂	—	—	•
H	H	Co(OCOCH ₃) ₂	—	—	171-172*

*N. S. Kozlov and I. A. Shur. 1959. Zhur. Obshch. Khim. 29:2706-9; via Chem. Abst. 54:12045 (1960).

•Not previously reported.

Method C—*N*-Benzylideneaniline (50 mmoles) and cobalt acetate (50 mmoles) were ground to a fine powder and dissolved in 35 ml of ethanol. Acetophenone (50 mmoles) in 25 ml of ethanol was added, and the reaction mixture was heated at 70 - 76 C for 3 hr. No identifiable products were obtained from the mixture.

β-(*β*-Hydroxyphenyl)-*β*-(*β*-nitroanilino)propiofenone. — This compound was prepared from *p*-nitro-*N*-saliacylideneaniline and acetophenone using either *p*-nitroaniline hydrochloride or boron trifluoride etherate as a catalyst as shown in Table I. The compound is a dark brown solid with a melting point of 282 - 284 C (uncorrected). Elemental analysis showed 7.27% nitrogen; calculated for C₁₇H₁₄N₂O₄, 7.75% nitrogen. The infrared absorption spectrum of the compound in a potassium bromide pellet was taken with a Perkin-Elmer Model 137 Spectrometer. Absorption peaks were found at the following wave numbers (cm⁻¹): 3350 (medium), 3150 (weak), 1639 (strong), 1544 (strong), 1496 (strong), 1387 (medium), 1361 (strong), 1265 (medium), 1223 (medium), 1117 - 1060 (strong), 879 (weak), 861 (medium), 778 (strong), 758 (strong), and 685 (strong).

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