HETEROCYCLES, Vol. 24, No 2, 1986

STUDIES ON REACTIVE INTERMEDIATES. PART V.[1] REACTION OF KETENE DIMER WITH BENZIMIDAZOLE

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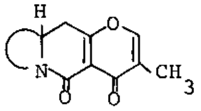
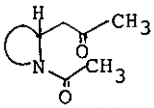
Abstract—Reaction of ketene dimer with benzimidazole in neat condition at room temperature, gave rise to 1-[*o*-(*N*-acetoacetylamino)phenyl]-3,5-diacetyl-4-hydroxypyridin-2(1*H*)-one (III), an adduct of one mole of benzimidazole and three moles of ketene dimer. Hydrolysis of compound III with 10 % hydrochloric acid gave the *N*-deacetoacetylated product (IV). Heating of compound III with 80 % sulfuric acid resulted in the formation of 1-(*o*-aminophenyl)-5-acetyl-4-hydroxypyridin-2(1*H*)-one (V). The reaction mechanism is discussed.

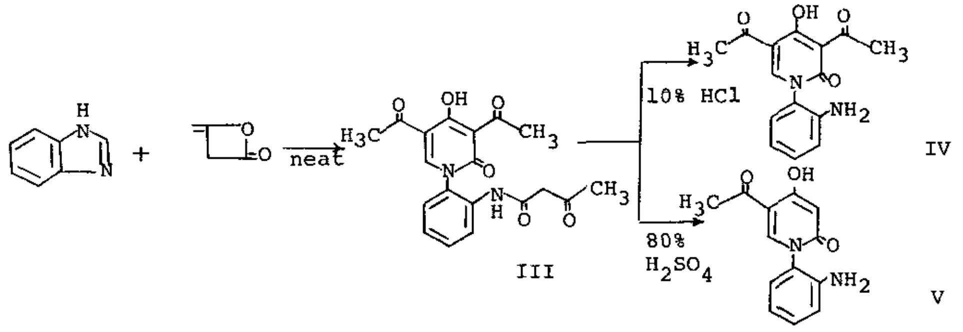
Reaction of ketene dimer with C=N bond of aromatic heterocycles, such as pyridine and quinoline, in aprotic solvents or neat condition, was previously reported to give the so-called Wollenberg-type compounds (I), respectively.[2,3] On the other hand, the same reaction in carboxylic acid medium, was reported to proceed in different manner. Namely, reaction of ketene dimer with benzimidazole or isoquinoline, in acetic acid medium, was reported to proceed through the formation of an N-acetyl-α-acetonyl-1,2-dihydro derivative (II).[4,5]


I

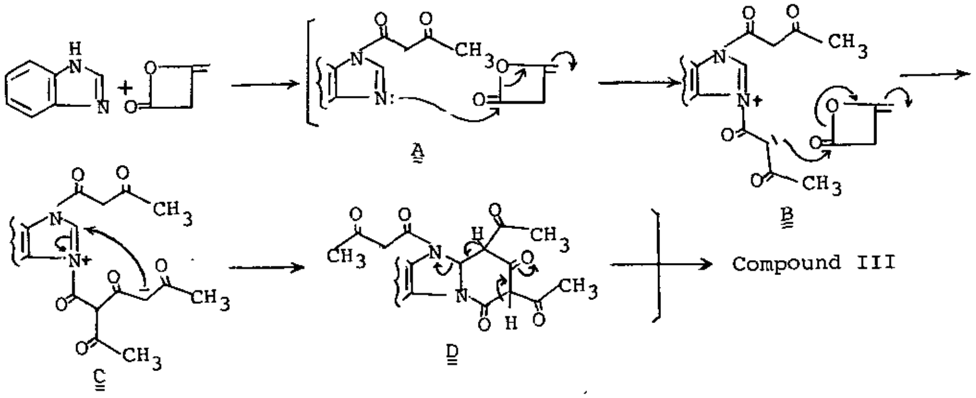

II

In continuation of our research concerning the reactivity of ketene dimer, reaction of this compound with benzimidazole in neat condition and non-polar solvent was investigated, which is the subject of this article.

Reaction of ketene dimer with benzimidazole in benzene, as aprotic solvent, did not proceed, and starting material was absolutely recovered. When ketene dimer was added to benzimidazole dropwise, while mixing in an ice-bath, a smooth exothermic reaction occurred. The reaction mixture was then transfered to room temperature, and allowed to stand for four days. After work-up and purification of the product, yellow prisms of mp 221-223°C were obtained in 11 % yield, together with dehydroacetic acid and *o*-phenylenediamine, resulted from ring rupturing of benzimidazole. On the basis of elemental analyses, spectral data, and chemical reactions, the structure of the product was assigned as 1-[*o*-(*N*-acetoacetylamino)phenyl]-3,5-diacetyl-4-hydroxypyridin-2(1*H*)-one (III), an adduct of one mole of benzimidazole and three moles of ketene dimer. Acid hydrolysis of compound III with 10 % hydrochloric acid resulted in the formation of 1-(*o*-aminophenyl)-3,5-diacetyl-4-hydroxypyridin-2(1*H*)-one (IV). Heating of compound III with 80 % sulfuric acid resulted in *N*-deacetoacetylation, together with C-3 deacetylation to give 1-(*o*-aminophenyl)-5-acetyl-4-hydroxypyridin-2(1*H*)-one (V).



This type of the reactivity of ketene dimer is considered as an abnormal one, and the reaction mechanism is proposed as shown in the following chart.



Namely, acetoacetylation of benzimidazole gave the intermediate A, further reaction of which with ketene dimer would form the dipolar intermediate B. Reaction of this intermediate with ketene dimer would give rise to intermediate C, which through intermediate D and further ring rupturing would transform to compound III.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope and are uncorrected. The ^{1}H-NMR spectra were obtained from a Varian T-60 spectrometer, and chemical shifts (δ) are in ppm relative to tetramethylsilane as an internal standard. IR spectra were obtained from a Unicam SP 1000 infrared spectrometer. Mass spectra were determined on a Varian Model Mat CH5 instrument.

Reaction of Ketene Dimer with Benzimidazole

Ketene dimer (7.2 g, 0.085 mol) was added dropwise to benzimidazole (1 g, 0.008 mol) while mixing in an ice-bath. A smooth exothermic reaction occurred, and the suspension turned to a yellow solution. After the addition was completed, the reaction mixture was transfered to room temperature, and allowed to stand for four days. The precipitate was filtered, washed with ether, and purified by recrystallization from acetone to give yellow prisms (0.345 g, 11 % yield), mp 221-223°C.[6] MS: m/z 370 (M^+). ^{1}H-NMR (CF_3COOH) δ: 2.29 (3H, s), 2.80 (3H, s), 3.04 (3H, s), 3.85 (2H, s), 7.50-7.80 (4H, m, phenyl ring protons), 9.05 (1H, s), 9.22 (1H, bs). IR (KBr) ν_{max}: 3285, 1710 (sh), 1680 cm^{-1}. Anal. calcd for $C_{19}H_{18}N_2O_6$ (III): C, 61.61; H, 4.90; N, 7.50. Found: C, 61.85; H, 5.00; N, 7.80.

Hydrolysis of Compound III with 10 % Hydrochloric Acid to Give Compound IV

A mixture of compound III (0.4 g) in 10 % hydrochloric acid (15 ml) was refluxed for 7 h. After cooling, the mixture was extracted with chloroform (20 ml x 3). The organic layer was dried over anhydrous sodium sulfate, and condensed under reduced pressure. The solid residue was purified by recrystallization from benzene to give yellow needles (0.22 g, 71 % yield), mp 181-182°C. MS: m/z 286 (M^+). ^{1}H-NMR (CF_3COOH) δ: 2.85 (6H, s), 7.45-7.90 (4H, m, phenyl ring protons), 8.68 (1H, s). IR (KBr) ν_{max}: 3340, 1670 (sh), 1650 cm^{-1}. Anal. calcd for $C_{15}H_{14}N_2O_4$ (IV): C, 62.93; H, 4.93; N, 9.79. Found: C, 63.48; H, 5.28; N, 9.51.

Deacylation Reaction of Compound III to Give Compound V

A mixture of compound III (0.2 g) and 80 % sulfuric acid (10 ml) was heated at 80-90°C for 10 min. After cooling, the mixture was treated with crushed-ice. The precipitate was then filtered, dried, and purified by recrystallization from acetone to give pale yellow prisms (0.095 g, 75 % yield), mp 202-205°C. MS: m/z 244 (M^+). ^{1}H-NMR (CF_3COOH) δ: 2.80 (3H, s), 6.60 (1H, s), 7.40-7.90 (4H, m, phenyl ring protons), 8.60 (1H, s). IR (KBr) ν_{max}: 3360, 1670 cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O_3$ (V): C, 63.92; H, 4.95; N, 11.47. Found: C, 64.12; H, 4.85; N, 11.53.

ACKNOWLEDGEMENT

The authours wish to thank the Central Analysis Room of Pharmaceutical Institute, Tohoku University for elemental analyses. Thanks are also to Ms. P. Mohammadi and Mrs. N. Akhavan Kharrazi for their technical asisstance.

REFERENCES AND NOTES

1. Part IV: M. Daneshtalab and A. Hojaji Najafabadi, Iranian J. Chem. & Chem. Eng., **6**, in press.
2. T. Kato, T. Kitagawa, and Y. Yamamoto, Yakugaku Zasshi, 1963, **83**, 267.
3. T. Kato and T. Kitagawa, Yakugaku Zasshi, 1964, **84**, 874.
4. T. Kato and M. Daneshtalab, Chem. Pharm. Bull., 1976, **24**, 1640.
5. H. Yamanaka, T. Shiraishi, T. Sakamoto, and H. Matsuda, Chem. Pharm. Bull., 1981, **29**, 1049.
6. Dehydroacetic acid, as a dimer of ketene dimer, and o-phenylenediamine, as a degradative product of benzimidazole, were isolated from the ethereal filtrate, in this reaction.

Received, 11th October, 1985