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NOTE

Synthesis and Characterization of Imine and Hydrazone of 4-Chlorobenzaldehyde

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The synthesis of N-(4-Chlorobenzilidine)benzoic acid hydrazide (a hydrazone) and N-(4-chlorobenzilidine)-1-phenylethanolamine (an imine) have been reported.

Key Words: Synthesis, Imine, Hydrazone, 4-Chlorobenzaldehyde.

Nitrogen nucleophiles can add to carbonyl compounds to form a neutral tetrahedral addition intermediates which eventually will breakdown to form new double bonds by a mechanism known as an addition-elimination. An example is a class of reactions that is between compounds containing primary amino groups and ketones or aldehydes. Imine derivatives are relatively easy to prepare, starting with an aldehyde and a ketone with a primary amine. The C=N function of imines is a poor acceptor of nucleophiles. The main interest of these reactions was for the preparation of crystalline derivatives of ketones and aldehydes for characterization[1]. Recently, these types of reactions have been studied in great detail because they are models of processes that are of significance in biological reactions. The hydrolysis of imines occur readily in aqueous acid and has been studied by kinetic methods[2,3]. The chemistry of vitamin B_6 offers many examples of enzymatic and non-enzymatic processes that revolve around the formation and hydrolysis of the C=N bond.

Imines are difficult to isolate and purify due to their sensitivity to hydrolysis and to be useful *in vivo*, they must be reduced to amines in order to prevent their breakdown to the starting materials. This chemical act presents a limitation of the use of imines in biological systems.

Several examples in the literature support the conclusion that imines once formed are immediately reduced to be useful. Klemm *et al.*[4] outlined a procedure for the preparation of a radioiodinated derivative of ganglioside GM1. Carbon number 6 of the galactosyl residue of GM1 was oxidized to an aldehyde by galactose oxidase. The imine formed by the oxidation of GM1 with tyramine was reduced.

On the other hand, hydrazone derivatives of hydrazides may be more stable to hydrolysis, so once they are formed, there is no need to reduce them and this could offer a method for drug loading *via* dextran conjugates to monoclonal antibodies[5].

Hydrazones from hydrazines bearing electron withdrawing groups and aromatic or aliphatic aldehydes form and hydrolyse rapidly in water at neutral pH[6].

Hydrazones were found to serve as sources of a C-H fragment when reacted with the appropriate substrates[7]. Groziak *et al.*[8] prepared two 2,4-dinitrophenyl-hydrazones from the reaction of (2-formylphenyl)boronic acid with 2,4-dintrophenyl-hydrazine in ethanol and found that the electron deficiency of the starting hydrazine reagent played a key role in determining the structure of the hydrazone isolated and that the water-resistant boronate esters can be hydrolyzed under forcing conditions to the boronic acids.

Hydrazones of sulfate conjugates of 17-oxosteroids (17OS) in urine were prepared by use of dansyl hydrazine in trichloroacetic acid solution and then were separated by liquid chromatogtaphy. The method has several advantages : (1) simple, (2) rapid, (3) shows a good separation of 17-oxosteroids sulfates, (4) superior sensitivity and (5) good reproducibility[9].

Pyridoxal 5′-phosphate, *via* the formation of Sciff's bases, function as a coenzyme in the deamination, transamination, recemization and decarboxylation of amino acids and properties[10].

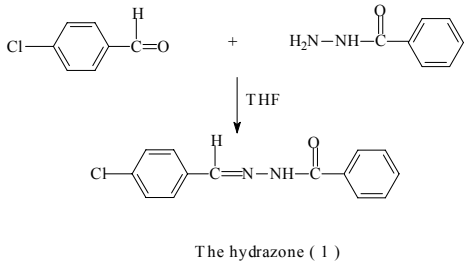
In this paper, a convenient synthesis of a hydrazone (1) and an imine (2) is outlined by a condensation reaction of benzoic acid hydrazide and 2-amino-1-phenyl-ethanol with 4-chlorobenzaldehyde respectively.

Melting points were determined on Gallenkamp melting point apparatus and were uncorrected. The proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained in the identified solvent on a Jeol FX90Q spectrophotometer. The elemental analysis were provided by M.H.W Microanalytical Laboratories (Phoenix AZ, USA).

Synthesis of the hydrazone (1), N-(4-chlorobenzalidine)benzoic acid hydrazide: To a solution of 1.00 g (7.4 mmol) of benzoic acid hydrazide and 1.00 g (7.4 mmol) of 4-chlorobenzaldehyde in 20 mL of a 1:1 THF/absolute ethanol mixture were added two drops of glacial acetic acid. The reaction mixture was heated under reflux for 3 h, then the solution was evaporated to dryness *in vacuo*. The product formed was recrystallized from ethanol to yield 1.50 g (78 % Yield): m.p. 164-165 °C. ^{1}H NMR ($CDCl_3$) δ 9.8 (br, s, 1), 8.2 (d, 2, ArH), 7.7 (d, 2, ArH), 7.4 (s, 5, ArH), 5.2 (s, 1, =CH). Anal. Calcd. for $C_{14}H_{11}N_2OCl$: C, 64.99; H, 4.26; N, 10.83. Found; C, 64.66; H, 4.64; N, 10.91.

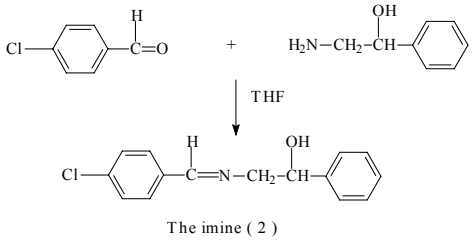
Synthesis of the imine (2), N-(4-chlorobenzalidine)-1-phenylethanolamine: To a solution of 1.00 g (7.4 mmol) of 2-amino-1-phenylethanol and 1.00 g of 4-chloro-benzaldehyde in 20 mL of a 1:1 THF/Absolute ethanol mixture were added two drops of glacial acetic acid. The reaction mixture was heated under reflux for 3 h, then the solution was evaporated to dryness *in vacuo*. The product formed was recrystallized from THF to yield 1.15 g(60 %). m.p. 160-163 °C. ^{1}H NMR ($CDCl_3$) δ 11.3 (s, 1, OH), 8.3 (d, 2, ArH), 7.74 (d, 2, ArH), 7.33 (s, 5, ArH), 5.03 (s, 1, =CH), 2.62 (s, 2, CH_2). Anal. Calcd. for $C_{15}H_{14}NOCl$: C, 69.36; H, 5.39; N, 5.39. Found : C, 69.50; H, 5.28, N, 5.38.

The synthesis of the target compounds **1** and **2** was achieved as shown in **Schemes I** and **II**. Reacting 4-chlorobenzaldehyde with benzoic acid hydrazide gave the hydrazone (**1**) with a yield of 78 %, whereas reacting 4-chlorobenzaldehyde with 2-amino-1-phenylethanol gave the imine (**2**) with a yield of 60 % and the reaction time was 3 h.



The hydrazone (1)

Scheme-I



The imine (2)

Scheme-II

A glance at the chemical literature shows that there is some interest in studying hydrazones and imines since these derivatives have important applications in biological systems.

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