

Acetonitrile-H₂O₂/(NH₄)₂CO₃: A Good medium for a facile and green synthesis of benzalazines via self-condensation reaction of benzaldehyde derivatives

Ali Reza Molla Ebrahimlo* and Karim Nazarlou

Department of Chemistry, Islamic Azad University, Khoy Branch, P.O. Box 58168-44799, Khoy, Iran

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Abstract: A facile and useful method for synthesis of benzalazines was introduced in this work. The reaction of synthesis of the relevant azines is carried out in the presence of acetonitrile-H₂O₂/(NH₄)₂CO₃ without using hydrazine. This reaction affords symmetrical azines in excellent yields with high purity. Products were characterized by the Common techniques (infrared, ¹H NMR and melting point).

Keywords: Acetonitrile; benzalazines; benzaldehyde derivatives; green synthesis. © 2018 ACG Publications. All rights reserved.

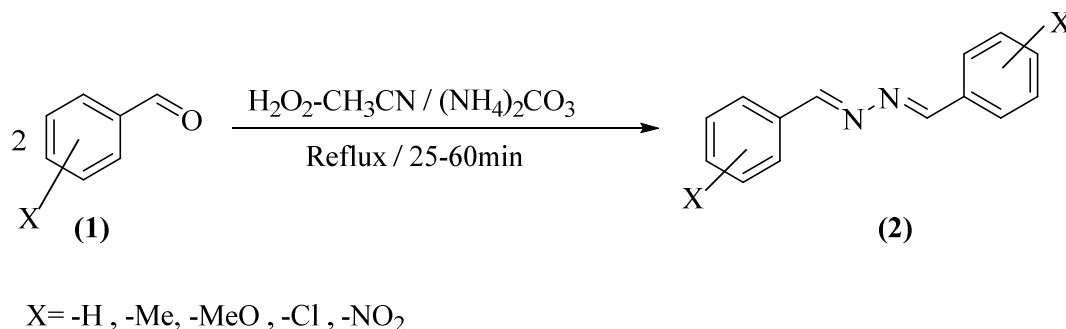
1. Introduction

Benzalazines, azines with N-N bond, are very useful in organic synthesis. The benzalazines are an important class of organic compounds because many compounds of pharmacological interest can be synthesized from them¹. Benzalazine derivatives display significant biological properties and are important for the synthesis of drug². Other applications of benzalazines include possible nonlinear optical materials³ and conducting polymers (polyazines)⁴.

2. Background

Benzalazines and their derivatives are widely used as reagents in organic synthesis and in various reactions, benzalazines are used to synthesize heterocyclic compounds such as 1,2,4-triazoles⁵, 1,2,4-triazines⁶, and benzoxazepines⁷. Several synthetic methods have been reported to synthesize benzalazines including reaction of hydrazine hydrate with benzaldehyde derivatives⁸⁻¹⁰. In some methods, hydrazine salts have been used to perform the reaction¹¹. Other methods involve treatment of benzaldehydes with carbamic acid¹², air oxidation of ammonium salts and benzyldrazones in DMSO¹³. Also, symmetrical and unsymmetrical benzalazines have been synthesized by the condensation of aldehydes or ketones with hydrazine in ethanol solution under reflux conditions¹⁴. On these bases, the aim of our work has been the facile and safe synthesis of benzalazine, therefore, We report herein our progress toward the establishment of a new protocol for preparation of these compounds without using hydrazine. The general reaction is illustrated in scheme 1.

* Corresponding author: mollaebrahimilo@yahoo.com



Scheme 1. Synthesis of benzalazine derivatives without using hydrazine

3. Experimental

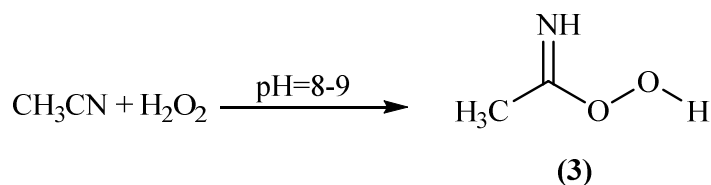
All substrates and reagents were obtained from commercial sources of the highest quality and were used without further purification. The products were characterized by a comparison with authentic samples (melting points) and their ¹H NMR or FT-IR spectra. Melting points were determined on an Electrothermal 9200 apparatus. ¹H-NMR (400 MHz) spectra were recorded on a BRUKER spectropin Avanc spectrometer in CDCl₃ and DMSO-d₆ with tetramethylsilane as internal standard. FT-IR spectra were recorded on a Thermo Nicolet (Nexus 670) and BRUKER (Vector 22), FT-IR spectrometer measured as KBr disks. All yields refer to isolated products.

3.1. General Procedure for the Green Synthesis of Benzalazine Derivatives 2a-h

A mixture of the aldehyde (1 mmol), ammonium carbonate (0.5 mmol) and 30% hydrogen peroxide (0.5 mmol) dissolved in acetonitrile (5 ml) and the reaction mixture was refluxed. The completion of the reaction was monitored by thin layer chromatography (TLC) (ethyl acetate/n-hexane 3:7). After the completion of the reaction, the reaction mixture was left to cool to room temperature and resulting precipitate was collected by suction filtration, then was washed with water, and dried under vacuum. The dried yellow solid was recrystallized from ethanol to afford the desired product as yellow crystals.

4. Present Study

Due to the fact that hydrazine is a highly reactive and toxic compound. Therefore, its maintenance in the laboratory is very difficult, it is important to eliminate this compound in reactions and to replace it with another reagent or a method for producing hydrazine during the reaction. Accordingly, many efforts have been made to modify reactions that are used hydrazine as a reagent. We conceived that various benzalazine can be synthesized from the condensation reaction between two moles of aromatic aldehydes in the presence of acetonitrile-H₂O₂/(NH₄)₂CO₃. In order to determine the optimal reaction conditions, we screened different conditions of this reaction with ammonium salts (table 1) using benzaldehyde as a model compound. From the results of Table 1, decrease of the yield in the ammonia solution, due to the oxidation of the benzaldehyde derivatives in alkaline solution that the major products are related benzoic acids. Also, High efficiency in acetonitrile indicates the importance of solvent in this reaction. As the reaction proceeds very slowly in the absence of acetonitrile, with very low yield, acetonitrile reacts with Hydrogen peroxide under controlled pH conditions to generate what is felt to be a peroxy-carboximidic acid intermediate (3) (Scheme 2)¹⁵. It reacts rapidly with benzaldehyde derivatives in presence ammonium carbonate and produces benzalazine in subsequent steps.

**Scheme 2.** Formation of peroxy carboximidic acid intermediate

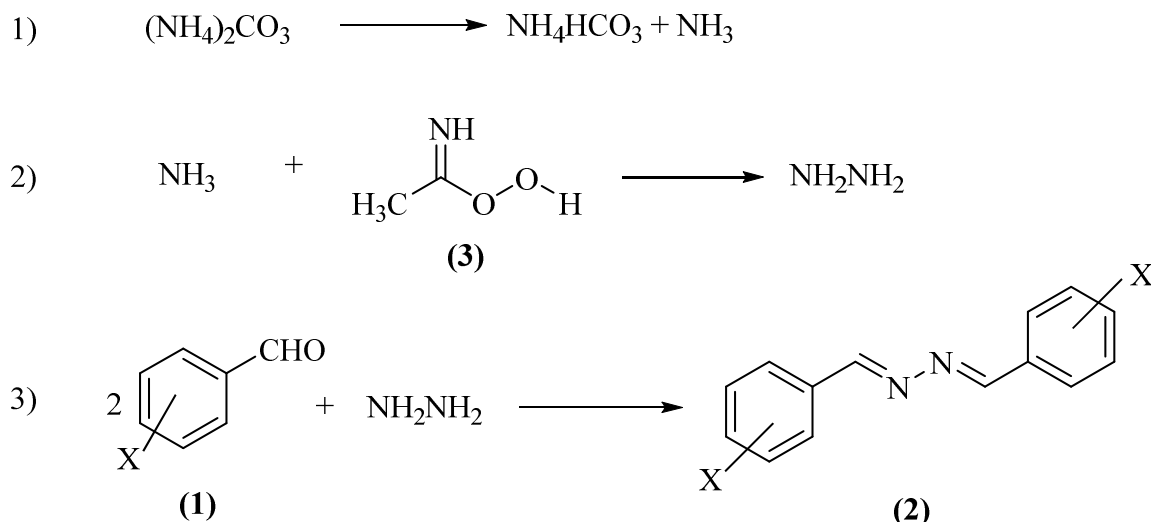
Thus, we have found that acetonitrile and ammonium carbonate would be respectively, suitable solvent and ammonium salt for this reaction.

Table 1. Optimization of reaction conditions^a

| Entry | Solvent | (NH ₄) ₂ CO ₃ (mmol) | NH ₄ Cl (mmol) | NH ₄ OH 35% (mmol) | Yield ^b (%) |
|-------|---------------------|--|---------------------------|-------------------------------|------------------------|
| 1 | Water | 1mmol | - | - | 25 |
| 2 | Water | - | 1mmol | - | 20 |
| 3 | Water | - | - | 1mmol | 15 |
| 4 | Ethanol | 1mmol | - | - | 65 |
| 5 | Ethanol | - | 1mmol | - | 60 |
| 6 | Ethanol | - | - | 1mmol | 50 |
| 7 | Acetonitrile | 1mmol | - | - | 96 |
| 8 | Acetonitrile | - | 1mmol | - | 90 |
| 9 | Acetonitrile | - | - | 1mmol | 10 |

^a Reactions were carried out with 1 mmol of the benzaldehyde and 1 mmol of 30% aqueous H₂O₂ under reflux ^b Isolated yield

The proposed mechanism of reaction is shown in Scheme 3. The first step involves decomposition of the ammonium carbonate into ammonium bicarbonate and ammonia. Then, the oxidation of ammonia by peroxy carboximidic acid intermediate (**3**) forms hydrazine¹⁶. Finally, the condensation of two molecules of benzaldehyde derivatives (**1**) with hydrazine produced the product (**2**) by loss of two molecules of H₂O. The structures of products (**2a-h**) were deduced by ¹H NMR and FT-IR spectroscopy. The ¹H NMR spectrum of (**2a**) exhibited one singlet, arising from the imine group (δ 8.67 ppm). With regard to IR spectra, the presence of signal around 1600 cm⁻¹ is due to C=N related to the imine group, which confirms the proposed structure. However, the yields of compounds (**2**) using this method are much greater than those obtained by reported methods. The results are shown in Table 2.



Scheme 3. The proposed mechanism for the Synthesis of benzalazine derivatives without using hydrazine

Table 2. Green synthesis of benzalazine derivatives **2a-h** without using hydrazine

| Product ^a | Aldehyde | Time (min) | Yield ^b (%) | Mp (°C) | |
|----------------------|--|------------|------------------------|---------|-----------------------|
| | | | | Found | Reported |
| 2a | C ₆ H ₅ | 40 | 96 | 89-90 | 93-94 ¹¹ |
| 2b | 4-MeC ₆ H ₄ | 60 | 99 | 154-157 | 154-155 ⁹ |
| 2c | 4-MeOC ₆ H ₄ | 60 | 95 | 168-169 | 169-170 ¹¹ |
| 2d | 4-ClC ₆ H ₄ | 40 | 93 | 206-207 | 208-210 ⁹ |
| 2e | 4-NO ₂ C ₆ H ₄ | 25 | 86 | 306-308 | 300-303 ⁹ |
| 2f | 2-MeOC ₆ H ₄ | 60 | 90 | 140-141 | 143 ¹² |
| 2g | 3,4-(MeO) ₂ C ₆ H ₄ | 60 | 89 | 189-190 | 192-193 ⁹ |
| 2h | 3-NO ₂ C ₆ H ₄ | 30 | 90 | 193-194 | 195-196 ¹¹ |

^aAll known compounds were characterized by comparing their spectral data (FT-IR, ¹H-NMR) and physical data with those reported. ^b Isolated yield

5. Conclusion

In this work as a green synthesis, for the synthesis of benzalazines, hydrazine has been removed as a reactive agent, and another reagent for the synthesis of benzalazines has been introduced. This reagent (ammonium carbonate in H₂O₂ / CH₃CN) can make hydrazine during the reaction. Of other advantages of this method are high efficiency and an eco-friendly procedure.

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ORCID Ali Reza Molla Ebrahimlo: [0000-0002-4473-0107](https://orcid.org/0000-0002-4473-0107)Karim Nazarlou: [0000-0002-9538-1795](https://orcid.org/0000-0002-9538-1795)**References**

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