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One-pot multicomponent synthesis hexahydroquinoline derivatives in Triton X-100 aqueous micellar media

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ABSTRACT

A facile and efficient synthesis of hexahydroquinoline derivatives (**5a–o**) was reported via a four-component condensation reaction of aldehydes, dimedone, methyl aceto acetate and ammonium acetate in the presence of Triton X-100 in water at room temperature. The use of just 20 mol % of Triton X-100 in water solvent is sufficient. The FT-IR, ^{19}F NMR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis confirm the structure of the compounds.

1. Introduction

Multicomponent reactions (MCRs) have drawn great interest enjoying an outstanding status in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity [1]. Such processes are of great interest in diversity-oriented synthesis, especially to generate compound libraries for screening purposes. The Hantzsch reaction [2], and its products 1,4-dihydropyridines (DHP) have attracted immense attention of synthetic chemists due to their pharmacological properties [3,4].

In addition, the dihydropyridine unit has been widely employed as a hydride source for reductive amination [5]. Despite the potential importance of 1,4-dihydropyridyl compounds from a pharmaceutical, industrial, and synthetic point of view [6–8], polyhydroquinoline compounds not only attract the attention of chemists to synthesize but also represent an interesting research challenge. The classical methods involve the three-component condensation of an aldehyde with ethyl acetoacetate, and ammonia in acetic acid or in refluxing alcohol [9–11]. However, these methods suffer from drawbacks such as a long reaction time, use of large quantities of organic solvents, lower product yields or harsh refluxing conditions. In recent years, several new efficient methods for the synthesis of polyhydroquinoline derivatives, which include the use of microwaves, [12] autoclave, [13] ionic liquids, [14] iodine, [15] metal triflate, [16] cerric ammonium nitrate, [17] L-proline, [18] PTSA-SDS, [19] BINOL-phosphoric acid, [20] $Hf(NPf_2)_4/C_{10}F_{18}$, [21] and TFE [22], ionic liquids [23], the use of microwaves [24], refluxing at high temperature [25], grinding [26], Bu4NHSO4 [27], HY-zeolite [28], L-proline [29], silica-supported acids [30], TMSCl–NaI [31], boronic acids [32], metal triflates [16], cerric ammonium nitrate (CAN) [33], baker's yeast [34], and p-TSA [35], or ZnO-nanoparticles [36].

In continuation of our studies in developing cheap and environmentally benign methodologies for organic synthesis, we turned our attention towards the synthesis of

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hexahydroquinoline derivatives. The non-ionic surfactant Triton X-100 (TR) is one of the most commonly used detergents in biochemistry as solubilizer with a wide range of applications to biological systems [37]. Solubilization of lipid membranes triggered by Triton X-100 is a well-described phenomenon. It is also used as an emulsifier, and complexing agent in both aqueous and non-aqueous media. Non-ionic surfactants have the tendency to adsorb at interfaces and to form micelles beyond their critical micelle concentration (CMC) similar to ionic surfactants [38]. However, the advantage of non-ionic surfactants (Triton X-100) is the absence of the electrical double layer as formed by the ionic surfactants. Consequently, non-ionic surfactants are desirable model adsorbents for interfacial processes. Therefore, we decided to exploit these properties of non-ionic surfactant for organic reaction. We report herein a practical synthesis of hexahydroquinoline derivatives in Triton X-100 aqueous micellar media at room temperature.

2. Results and discussion

We carried out the four-component coupling reaction of dimedone, aldehyde, acetoacetic ester, and ammonium acetate using Triton X-100 in water solvent (Scheme 1).

Initially, we screened various conditions for the one-pot four-component reaction of benzaldehyde, dimedone, acetoacetic ester, and ammonium acetate as a model reaction in methanol at room temperature. In polar solvents like methanol, ethanol, DMF, tetrahydrfuran, acetonitrile and DMSO product **5a** was obtained in higher yields. However, in a non-polar solvent such as dichloromethane, product **5a** were obtained in poor yield. When the reaction was carried out under solvent free condition at room temperature and 60 °C, we found 21% and 53% product **5a**. Also, when benzaldehyde, dimedone, acetoacetic ester, and ammonium acetate were stirred at room temperature without water, using water as solvent and Triton X-100 (20 mol %) as a surfactant the yield of **5a** was improved (entry 11, 12, Table 1). However, it was found that the amount of Triton X-100 ($C_{14}H_{22}(C_2H_4O)_n$) where $n = 9–10$, influenced the yield of **5a**.

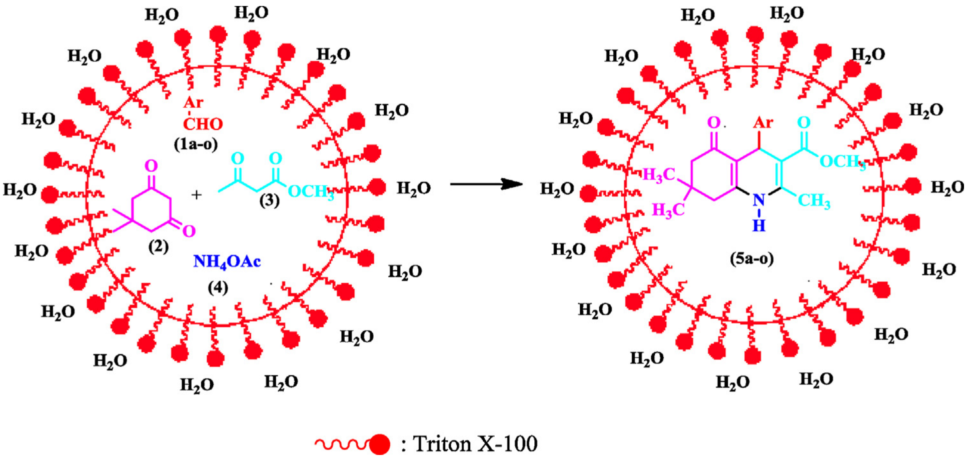
We studied the role of catalyst concentration on the model reaction **5a**. We have varied the catalyst concentration to 0, 1, 5, 10, 20 and 25 mol %. The result revealed that, when the reaction was carried out in the presence of 0, 1, 5 and 10 mol % of catalyst it gave lower yield of product even after prolonged reaction time. At the same time when the concentration of catalyst was 20 mol % we achieved an excellent yield of product in a short span. Even after increasing the catalyst concentration above 20 mol % the yield of the products did not improve. So, it is established that the 20 mol % of catalyst is sufficient to catalyst and bring it to completion. The results are listed in Table 2.

In order to determine the scope of this reaction, we have synthesized differently substituted hexahydroquinoline by varying differently substituted aldehydes (**1a–o**) including both electron-donating and electron-withdrawing groups. It is observed that the reaction gave good yields of products with faster reaction rate when the aldehyde bearing electron-withdrawing group is used compared to the aldehydes with electron-donating groups. The corresponding results are tabulated in Table 3.

3. Conclusion

In summary, we have described herein an efficient methodology for Hantzsch reaction using various electronically and structurally divergent aldehydes to give the product in excellent isolated yields. In contrast to the existing methods using potentially hazardous catalysts/additives, this new method offers the following competitive advantages:

- avoiding the use of any base, metal or Lewis acid catalyst;
- short reaction time;
- ease of product isolation/purification by non-aqueous work-up;
- high chemo selectivity;
- no side reaction;
- low costs and simplicity in process and handling.



Scheme 1. Triton X-100 catalyzed condensation of dimedone, aldehydes, methyl acetoacetate and ammonium acetate.