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ORIGINAL ARTICLE

Microwave-assisted intermolecular aldol condensation: Efficient one-step synthesis of 3-acetyl isocoumarin and optimization of different reaction conditions

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Abstract This paper describes the optimization and comparison of conventional and microwave-assisted methods for efficient, cheap, one-pot, and straightforward synthesis of isocoumarins under mild reaction conditions. On this basis of this aim, synthesis of 3-acetyl isocoumarin from 2-formylbenzoic acid with mono-chloroacetone was chosen as a model reaction. Afterward, four different methods conventional (Method A), microwave open vessel (Method B), microwave sealed vessel (Method C), and microwave closed system (Method D) were used methodologically to determine best experimental conditions for each of these methods in this model reaction. The results revealed that developed Methods A, C and D could be used successfully under solvent-free conditions with good yields (84–87%) for the future efficient, one-pot synthesis of isocoumarins. This paper is also a first for characterizing 3-acetyl isocoumarin by using ATR, ^{1}H NMR, ^{13}C NMR and GC–MS.

1. Introduction

Isocoumarins form an important part of natural lactones, many natural products, and pharmacological substances. They display a broad range of biological activities, including antifungal (Engelmeier et al., 2004; Hussain et al., 2009; Zhang et al., 2008), antimicrobial (Yoshikawa et al., 1994) anti-inflammatory, (Matsuda et al., 1999), antitumor (Agata et al., 2004; Kawano et al., 2007; Lim et al., 2003), anti-allergic (Kam et al., 1988), herbicidal (Kurume et al., 2008; Matsuda et al., 2008), and many others (Heynekamp et al., 2008; Kam et al., 1994). Depending on their broad range of biological activities,

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isocoumarins play a major role in the synthesis of various important pharmaceutical compounds as synthetic precursors and intermediates. Their such properties also make isocoumarins a focal point for inhibition studies such as DNA helicase inhibition (heliquinomycin) (Chino et al., 1998), β-amyloid peptide production inhibition (Bihel et al., 2003), and protease inhibition (Bihel et al., 2003; Harper and Powers, 1984). Due to these properties and wide range of applications, several synthetic routes and methods have been developed for the synthesis of isocoumarins and the attempts are still continuing. Consequently, isocoumarin synthesis has received much attention for developing efficient, more improved, and cheaper methods. Thus, a considerable scope for isocoumarin synthesis has emerged in time.

Microwave irradiation could be an alternative to many classical reactions with some advantages such as having better yields, shorter reaction times, and fewer by products (Kappe, 2004; Kim et al., 2009; Sinnwell and Ritter, 2007; Zhang et al., 2010). In addition, the amount of solvents, wasteful by products and reagents can also be minimized or even disappeared by microwave heating. These advantages of microwave irradiation are considered to be stemmed from microwave effect or thermal effect, which are the consequences of dielectric constant of used solvent. Thus, depending on the reaction conditions (ambient pressure, temperature, and superheating of solvent), reaction proceedings could be accelerated and the desired reactions, products, and yields that could not be succeeded by conventional synthesis methods, could be achieved by microwave (Iannelli et al., 2005; Kappe, 2004). However, it should be noticed that the microwave assisted synthesis is not a complete alternative for the conventional synthesis. In the last decade, 3-substituted isocoumarins with no substituent at the 4th position or substituent with halides (H, Br, I, etc.) were synthesized mainly by traditional (Bovicelli et al., 1999; Hussain et al., 2001; Mal et al., 2000) or transitional metal catalyzed reactions (Bellina et al., 2000; Liao and Cheng, 1995; Wang and Shen, 1998). Although these methods are useful and effective for the synthesis of isocoumarins, no method has been developed under solvent-free conditions for both microwave irradiation and conventional synthesis comparatively up to now.

The purpose of this study was to develop and compare efficient, cheap, one-pot and straightforward various microwave and conventional synthesis methods for isocoumarins under mild reaction conditions. For this aim, the reaction of starting material 2-formylbenzoic acid with monochloro acetone for the synthesis of 3-acetyl isocoumarin, which is the product of an intermolecular aldol condensation, was chosen as model reaction. Indeed, the main deterministic reason behind this selection was the insufficient number of present work and synthetic approach available in the literature for this molecule.

The first attempt to develop a synthetic method for 3-acetyl isocoumarin was pioneered by Kanevskaya et al. (1953), Kanevskaya and Shemyakin (1932) in the beginning of 1930s. This study reported the two-step synthesis of 3-acetyl isocoumarin. The first step is the condensation of the 2-formylbenzoic acid potassium salt (alkali metal salt) with mono-chloroacetone (halogenated methyl ketone) to give esters. These esters are cyclized when heated with an organic base piperidine yielding 3-acetyl isocoumarin. Several decades later, in 2008, this attempt was followed by using a different method just by Ishchenko et al. (2008) for 3-substituted isocoumarin derivatives. In their study, a convenient one-step method for the synthesis of 3-oxohetarylisocoumarins, by cyclization of 2-formylbenzoic acid and heterocyclic α-haloketones with triethylamine as a base was developed. Afterward, a little effort has been conducted in the literature for the synthesis of 3-acetyl isocoumarin. It seems to be synthesized on demand from only one commercial source (http://www.daybiochem.com, 2015) with no explicit synthetic route. In this point, lack of sufficient and validated synthesis methods for 3-acetyl isocoumarin in the literature has attracted our interest. Thus, we have canalized our method development studies on the synthesis of isocoumarins by selecting this molecule as a model.

Methodologically, four different methods were used for the model synthesis of 3-acetyl isocoumarin. These were conventional (Method A), microwave open vessel (Method B), microwave sealed vessel (Method C), and microwave closed system (Method D) methods. Factors affecting the reaction conditions for all the methods were considered as solvent type, temperature, used base and reaction time except for heating sources, which are microwave and conventional. Therefore, reactions were optimized under different series of experimental trials, and best reaction conditions were determined. Interestingly, solvent-free conditions have been considered for both conventional and microwave methods, as well. In this way, the source of microwave effect was investigated.

In this study, we have presented mild and efficient novel synthesis methods using microwave and conventional methods comparatively for the synthesis of 3-acetyl isocoumarin. In this way, the best synthetic conditions for the 3-acetyl isocoumarin, which could be used as a backbone in the role of precursor or reaction intermediate in the synthesis of numerous pharmaceutically active agents, were optimized. These methods can also be used as general synthetic routes leading to the synthesis of substitute isocoumarins and derivatives in future studies.

2. Result and discussion

Our aim was to develop one-step, efficient, cheap methods for the synthesis of 3-substituted isocoumarins using conventional and microwave conditions comparatively. To perform this aim, reaction of 2-formylbenzoic acid (**1**) with monochloroacetone (**2**) was chosen as a model reaction to synthesize 3-acetyl isocoumarin (**3**) (Scheme 1). For this model reaction, four different types of methods were used. These methods were Methods A, B, C and D. Indeed, Method A was conventional and the other methods B, C and D were the microwave-assisted synthesis methods. While factors affecting the reaction conditions were considered as the presence or absence (solvent-free) of any solvent, type of solvent, base, temperature, time for Method A, power (watt) at different temperatures was also regarded as a significant influential parameter for Methods B, C and D.

In the experiments, ethanol (EtOH) was used as polar protic solvent whereas acetone and dimethylformamide (DMF) were used as polar aprotic solvents. In addition, solvent-free conditions and influence of the type of used base on the reactions were also investigated. Thus, potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), and Trimethylamine (TEA) were used as different types of bases during experiments. In this way, polar and nonpolar reaction conditions for Methods A, B, C and D were optimized by performing different series of experimental trials for each factor. As a result, optimum reaction conditions for the methods were determined and described in detail as follows.

2.1. Conventional synthesis of 3-acetyl isocoumarin

2.1.1. Method A: conventional synthesis

We started to investigate optimum reaction conditions for the synthesis of 3-acetyl isocoumarin with the traditional approach, Method A, comprising of conventional heating. Primarily, pre-experiments were conducted and repeated under different series of trials for various temperatures, time, base, and solvents. The optimization results for Method A are summarized in Table 1. As shown in Table 1, compound **3** could be

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