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ORIGINAL ARTICLE

Tandem Knoevenagel–Michael reactions in aqueous diethylamine medium: A greener and efficient approach toward bis-dimedone derivatives

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Abstract Diethylamine catalyzed tandem Knoevenagel–Michael reactions have been carried out in aqueous medium as an efficient, greener and cost effective process for the simple one-pot synthesis of *bis*-dimedone derivatives. Reaction of substituted aromatic aldehyde (1 equiv.) and dimedone (2 equiv.), in the presence of aqueous diethylamine medium at room temperature provides *bis*-dimedone derivatives **3a–n** in excellent yields (87–95%) within a very short reaction time (15–60 min). All the *bis*-dimedone derivatives were obtained in high purity and the products were fully characterized by physical and spectroscopic data. The structures of compounds **3b,c** were elucidated by single crystal X-ray diffraction technique. Compound **3b** crystallizes in the monoclinic

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space group $P\ 21/n$ with $a = 10.2895(9)$ Å, $b = 18.0995(15)$ Å, $c = 15.8615(13)$ Å, $\alpha = 90°$, $\beta = 107.975(2)°$, $\gamma = 90°$, $V = 2809.8(4)$ Å^3, and $Z = 4$. Compound **3c** crystallizes in the monoclinic space group $P\ 21/n$ with $a = 10.2816(16)$ Å, $b = 18.080(3)$ Å, $c = 15.637(2)$ Å, $\alpha = 90°$, $\beta = 107.076(4)°$, $\gamma = 90°$, $V = 2778.6(7)$ Å^3, and $Z = 4$.

The use of inexpensive, eco-friendly and readily available reagents, easy work-up, and high purity products makes the procedure a convenient and robust method for the synthesis of tandem Knoevenagel–Michael adducts.

1. Introduction

In recent, the development of environmentally benign and clean synthetic procedures has become the most desired goal in the field of organic synthesis. Therefore, organic reactions in green solvents have attracted much attention; especially from the viewpoints of green chemistry (Gawande et al., 2013). Green chemistry approaches can lower energy costs, waste chemicals and reduce byproducts. The possibility of carrying out multi-component reactions under green solvents can improve their ecological value (Anastas and Williamson, 1998). Reactions in aqueous media are environmentally safe, devoid of carcinogenic effects due to other solvents have simple work up, and are especially suited for industry (Grieco, 1998; Akbar and Mohammad, 2010). Thus, there is a need for the development of multicomponent reactions (MCRs) in water, without the use of any harmful organic solvents and catalysts.

Knoevenagel condensation is one of the most significant C–C bond constricting method in organic chemistry (Tietze and Beifuss, 1991; Posner, 1986), that involves the reaction of carbonyl compounds with active methylene group in the presence of amines (Knoevenagel, 1894; Knoevenagel, 1896). Combination of this reaction with other reactions in a Domino manner is termed as multicomponent coupling reaction (MCRs) (Bunce, 1995; Tietze and Rackelmann, 2005; Tietze and Brasche, 2006; Hasaninejad et al., 2013a,b). Moreover, MCRs are attractive choice for organic chemists because of operational simplicity, reduced steps for work-up, extraction, purification, and facile automation and minimal waste generation (Zhu and Bienayme, 2005; Nicolaou et al., 2006).

Dimedone (**1**) is one of the most important substrates among the active methylene compounds, having 1,3-dicarbonyl groups flanked by active methylene groups, which can exists in *trans*-enolized tautomer form, stabilized by intermolecular hydrogen bonding network (Mark et al., 2011; Xu et al., 2005). It has been used as a versatile synthetic precursor for the synthesis of several classes heterocyclic and spirocyclic compounds (El Ashry et al., 2009). A number of dimedone derived heterocyclic and non-heterocyclic compounds have been reported in the literature for their biological properties, such as tetrahydrobenzo[*b*]pyrans (Akbar and Mohammad, 2010), fused spiroketal derivatives (Giasuddin Ahmed et al., 2005), *bis*-spiropiperidine derivatives (Atar and Jeong, 2013), 5-aminouracil derivatives (Shaker et al., 2009), triazolo[1,2-*a*] indazole-triones (Nikpassand et al., 2009), fused 1,4-dihydropyridines (Mosaddegh and Hassankhani, 2012), isoquinolines (Ivanov and Nikolova, 2008), spirocarbocycles (Clavier et al., 2012), 9-aryl-1,8-dioxooctahydroxanthene derivatives (Ilangovan, et al., 2012) and others (Al-Majid et al., 2013a,b). Therefore, we employed tandem Knoevenagel–Michael reaction in our ongoing research for the one-pot synthesis of various dimedone derivatives. We report here, diethyl amine catalyzed tandem Knoevenagel–Michael reactions of dimedone with various substituted aromatic aldehyde in aqueous medium as a new, robust, greener and highly efficient procedure for the synthesis of *bis*-dimedone derivatives.

2. Experimental

2.1. General

All the chemicals were purchased from Aldrich, Sigma–Aldrich, Fluka etc, and were used without further purification, unless otherwise stated. All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR Spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer. The NMR spectra were recorded on a Jeol-400 NMR spectrometer. ^{1}H-NMR (400 MHz), and ^{13}C-NMR (100 MHz) were run in either deuterated dimethylsulfoxide (DMSO-d_6) or deuterated chloroform ($CDCl_3$). Chemical shifts (δ) are referred in terms of *ppm* and *J*-coupling constants are given in *Hz*. Mass spectra were recorded on a Jeol JMS-600 H. Elemental analysis was carried out on an Elmer 2400 Elemental Analyzer; CHN mode.

2.2. General procedure (GP1) for Knoevenagel-condensation Michael addition for the synthesis of 3a–n

A mixture of aldehyde **2a**–**n** (1.5 mmol), dimedone **1** (3 mmol, 420 mg), and Et_2NH (1.5 mmol, 155 µl) in 1.5 mL of degassed H_2O was stirred at room temperature for up to 60 min until TLC showed complete disappearance of the reactants. The precipitated product was filtered and washed with ether (3 × 20 mL). The solid was recrystallized from a mixture of CH_2Cl_2/Et_2O to afford pure product **3a–n**.

2.2.1. Diethylammonium-2-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(phenyl)methyl)-5,5-dimethyl-3-oxocyclohex-1-enolate 3a

Pure product **3a** was obtained according to **GP1** as solid (1.26 g, 95%). IR (cm^{-1}): 2955 (s), 1586 (s), 1382 (s), 776 (s), 576 (s), 480 (s); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.95–1.14 (m, 12H, $\mathbf{CH_3}$), 1.18 (t, $J = 6.60$ Hz, 6H, $NHCH_2\mathbf{CH_3}$), 2.31 (s, 8H, $\mathbf{CH_2}$ + $CO\mathbf{CH_2}$), 2.84 (q, $J = 6.60$ Hz, 4H, $NH\mathbf{CH_2}CH_3$), 5.74 (s, 1H, Ph**CH**), 7.01–7.21 (m, 5H. Ar**H**), 8.25 (bs, 1H. $\mathbf{NH_2}$), 13.91 (s, **OH**); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 11.4 ($\mathbf{CH_3}CH_2$

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