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Catalyst-free sonosynthesis of highly substituted propanamide derivatives in water

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ABSTRACT

A clean, rapid and energy-efficient approach to catalyst-free one-pot synthesis of highly substituted propanamide derivatives in water was developed utilizing of the ultrasonic irradiation. The method has been successful in achieving the green chemistry objective. A catalyst-free operation, an energy efficient protocol using ultrasound irradiation instead of conventional heating or stirring and use of water as a non-hazardous, inexpensive and readily available solvent in the one-step reaction against sequential reaction steps thus combining the features of both economic and environmental advantages.

1. Introduction

Within the previous decade, isocyanide based multicomponent reactions (IMCRs) gained significant interest in the scientific association as an effective, appropriate, time-saving, and atom-economical procedure to quickly produce chemical diversity. IMCRs are easily accomplished using variety available starting materials and tolerate a variety range of functional groups. Variations on starting materials and subsequent transformations provide access to a fairly large number of incomparable structures that would differently need long preparations [1–5]. One-pot MCRs often shorten reaction periods, giving the superior totally chemical yields than multiple-step syntheses and hence can decrease the usage of energy and manpower. MCRs are useful for the expedient creation of chemical libraries of drug-like compounds with excellent levels of molecular complexity and variety, therewith simplifying identification/optimization in drug discovery programs [6–10]. Therefore, the design of new MCRs with green procedure has attracted great attention, especially in the areas of drug discovery, organic synthesis and material science [11–15]. Moreover, improving already known MCRs also is of substantial interest in current organic synthesis [16].

Ultrasound irradiation has been established as a significant technique in synthetic organic chemistry. It has been used as an efficient heating source for organic reactions. Shorter reaction time is the main advantage of ultrasound-assisted reactions. Simple experimental method, very high yields, improved selectivity and clean reactions of many ultrasound-induced organic transformations presents extra facilities in the field of synthetic organic chemistry [17–19]. The beneficial effects of ultrasound irradiation are performing a developing role in flow chemistry, particularly in cases where classical procedures need drastic condition for prolonged reaction times [20]. During the dilution cycle in the cavitation proceeding, the molecules of the liquid are isolated, producing bubbles that further collapse in the compaction cycle. These quick and severe implosions produce short-lived areas with temperatures of roughly 5000 °C, pressures of about 1000 atm and heating and cooling rates above 10 billion °C/s. Such localized hot spots can be thought as micro reactors [21–23]. This process has been assumed as a clean and beneficial protocol in organic synthesis compared with classical methods and the procedure is in general, more convenient [24].

The "greening" of chemical proceedings has become a main subject in industry and academia. The search for another reaction media to substitute flammable, volatile and often toxic solvents generally utilized in organic synthetic methods is a significant aim of the extension of green chemical processes [25–26]. From both the environmental and economic viewpoints, utilizing aqueous media to accomplish organic reactions has absorbed

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potent interest, since water is presumed to be the most environmentally acceptable, safe and cheap solvent [27]. In addition, using water as the solvent generally means easier work-up because most organic compounds are lipophilic and are easily separated from aqueous media [28].

In our previous work we have studied the multicomponent reactions leading to one-pot synthesis of γ-Iminolactone derivatives in water [29] and rapid catalyst-free one-pot three component synthesis of 2,5-dihydro-5-imino-2-methylfuran-3, 4-dicarboxylate derivatives under ultrasound irradiation [30]. Herein, as section of our program proposed at extending novel isocyanide-based multi-component reactions [31–34] and exploring the chemistry of our synthetic active ketones [43,44] and also according to burgeoning interest of the synthesis and study of highly congested propanamide derivatives in various pharmaceutical investigations [35–39], we wish to report for the first time, a novel one-pot three-component synthesis of substituted propanamide derivatives **4** and **5** from three-component reaction of an isocyanide (*tert*-butyl isocyanide, cyclohexyl isocyanide and 1,1, 3,3-tetramethylbutyl isocyanide) **1** carboxylic acids ((*E*)-cinnamic acids and aromatic carboxylic acids **2** and 2-oxopropyl benzoate **3** in water as a solvent (Scheme 1).

2. Experimental section

2.1. General remarks

Starting materials were received from Merck (Germany) and Fluka (Switzerland) and were utilized without additional purification. The procedures used to pursue the reactions are TLC and NMR TLC and NMR showed that there is no side product. ^{1}H- and ^{13}C NMR spectra were measured ($CDCl_3$) with a BRUKER DRX-400 AVANCE spectrometer at 400.0 and 100.0 MHz, respectively. IR spectra were gagged on a Jasco 6300 FTIR spectrometer. Sonication was performed in Bandelin SONOPULS ultrasonic homogenizers (made in Germany) with 20 kHz processing frequency, a nominal power 250 W and uniform sonic waves. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. 2-Oxopropyl benzoate **3** was prepared based on known procedure [43].

2.2. Classical procedure for the synthesis of propanamide derivatives (4 and 5)

To a stirred solution of carboxylic acid (**2**) (1 mmol) and 2-oxopropyl benzoate (**3**) (1 mmol) in water (7 mL), isocyanide (**1**) (1 mmol) was added (5 mL) at room temperature. The mixture was stirred for 24 h. The solvent was eliminated under decreased pressure, and the products were generated without any purification (**4** and **5**).

2.3. Ultrasound-promoted synthesis of propanamide derivatives (4 and 5)

The carboxylic acid derivative (**2**) (1.0 mmol), 2-oxopropyl benzoate (**3**) (1 mmol), isocyanide (**1**) (1 mmol) and water (7 mL) were added into a 25 mL round bottomed flask. The reaction mixture was sonicated under 100 W for the period of time (the reaction was monitored by TLC). The solvent was eliminated under decreased pressure, and the products were generated without any purification (**4** and **5**). The authenticity of the samples (**4a–4i** and **5a–5i**) was established by their ^{1}H NMR, ^{13}C NMR, FT-IR, elemental analyses and MS. The characterization data of the compounds are given below:

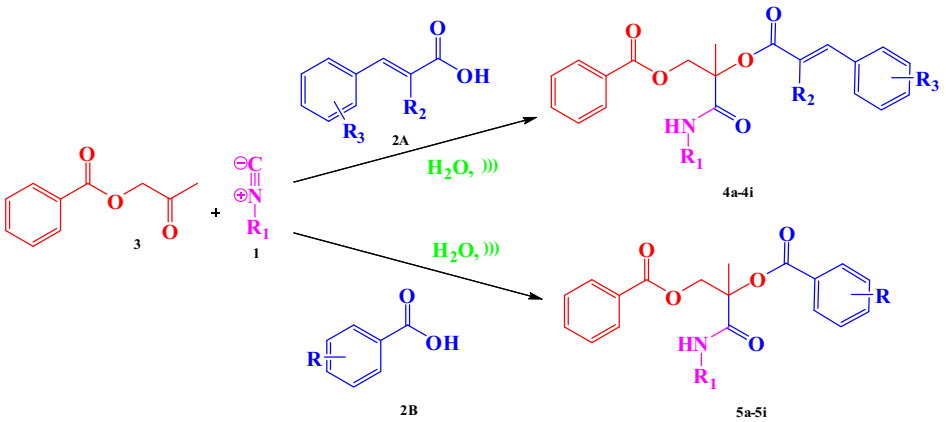
2.4. Spectral data of products

2.4.1. (E)-3-(cyclohexylamino)-2-methyl-3-oxo-2-(3-p-tolylacryloyloxy)propyl benzoate (**4a**)

Yellow oil, yield (92%); IR: 3372.22, 2931.98, 2854.87, 1723.94, 1660.40, 1634.45, 1451.02, 1112.58, 711.79 cm^{-1}, ^{1}H NMR($CDCl_3$) δ:1.16–1.92 (m, 5CH_2 of cyclohexyl), δ = 1.83 (s, 3H, CH_3), δ = 2.38 (s, 3H, CH_3 (4-methyl on phenyl)), 3.82–3.90 (m, 1H, CH–N), δ = 4.75 and 5.05 (AB-quartet, 2H, $^2J_{HH}$ = 11.6 Hz, CH_2CO_2Ph), 6.28 (d, 1H, NH),6.41 (d, 1H, $^3J_{HH}$ = 16 Hz, CH=C*H*), δ = 7.19–8.03 (m, C=C*H* and aromatic protons of phenyls).^{13}C NMR ($CDCl_3$) δ: 20.04 (CH_3), 21.53 (CH_3 (4-methyl on phenyl)), 24.79 (2 CH_2(β) of cyclohexyl), 25.49 (1 CH_2(γ) of cyclohexyl), 32.99 (2 CH_2(α) of cyclohexyl), 48.33 (CH–N), 66.45 (*C*H_2CCH_3), 82.26 (*C*CH_3), 116.41 and 146.27 (CH=CH), 165.13, 165.66, 169.34 (3C=O), 128.28, 128.40, 129.67, 129.71, 131.24, 133.21, 141.29 (9 CH and 3 C aromatic). Anal. calc. for $C_{27}H_{31}NO_5$ (449.54): C 72.14, H 6.95, N 3.12; Found: C 72.18, H 6.97, N 3.09.

2.4.2. (E)-3-(cyclohexylamino)-2-(3-(4-fluorophenyl)acryloyloxy)-2-methyl-3-oxopropyl benzoate (**4b**)

Yellow oil, yield (95%); IR: 3331.47, 2933.60, 2855.71, 1723.94, 1661.55, 1634.45, 1451.28, 1112.58, 712.44 cm^{-1}, ^{1}H NMR($CDCl_3$) δ:1.15–1.93 (m, 5CH_2 of cyclohexyl), δ = 1.82 (s, 3H, CH_3), 3.81–3.90 (m, 1H, CH–N), δ = 4.73 and 5.04 (AB-quartet, 2H, $^2J_{HH}$ = 11.6 Hz, CH_2CO_2Ph), 6.24 (d, 1H, NH), 6.37 (d, 1H, $^3J_{HH}$ = 16 Hz, CH=C*H*), δ = 7.29–8.03 (m, C=CH and aromatic protons of phenyls). ^{13}C NMR ($CDCl_3$) δ: 20.00 (CH_3), 24.79 (2 CH_2(β) of



Scheme 1. Synthesis of highly substituted propanamide derivatives in water.