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Ultrasound-promoted catalyst-free one-pot four component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones in neutral ionic liquid 1-butyl-3-methylimidazolium bromide

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ABSTRACT

A catalyst-free one-pot four component methodology for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones under ultrasonic irradiation at room temperature using 1-butyl-3-methylimidazolium bromide, [Bmim]Br, as a neutral reaction medium is described. A broad range of structurally diverse aldehydes (aromatic aldehydes bearing electron withdrawing and/or electron releasing groups as well as heteroaromatic aldehydes) were applied successfully, and corresponding products were obtained in good to excellent yields without any byproduct.

1. Introduction

The efficient high-throughput synthesis of organic compounds is one of the most important objectives in modern drug discovery. Organic reactions should be fast and facile, and the target products should be easily separated and purified in high yields. From this point of view, there is much interest in the implementation of new processes and new synthetic strategies. In this regard, nonclassical methods, microwave-assisted synthesis, ultrasonic irradiation, and supercritical fluids, find application as appealing methods to achieve these goals [1]. Ultrasonic activation, based on cavitation effects leading to mass transfer improvement, is widely used today to promote numerous organic reactions [2]. A survey of literature shows that the synthesis of heterocyclic compounds has been accelerated by ultrasound irradiation. Compared with traditional methods, this technique is more convenient and easily controlled and is more appropriate in the consideration of green chemistry concepts [3]. In this way, Cella and Stefani have recently published an important review concerning to the use of ultrasound in heterocyclic chemistry [4]. Ultrasound irradiation have also been used for the synthesis of a wide variety of heterocycles such as tetrahydropyrimidines [5], 4*H*-benzo[*b*]pyran derivatives [6], 1,8-dioxooctahydroxanthene derivatives [7], 1,5-benzodiazepines [8], pyrido[2,3-*d*]pyrimidine derivatives [9], 3,4-dihydropyrimidin-2-ones [10], 1,3,5-thiadiazole and bi(1,3,5-thiadiazole) [11], benzoacridinones [12], 2-(3,5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazoles [13]. In all cases, the reactions occurred under mild conditions with good to excellent yields and in a few minutes.

In the other hand multi-component reactions (MCRs) play an important role in combinatorial chemistry because of the ability to synthesize target compounds with greater efficiency and atom economy by generating structural complexity in a single step from three or more reactants. Moreover, MCRs offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions [14].

Moreover one of the most important aspects in green chemistry is the use of ionic liquids (ILs) as greener solvents in organic reactions that is in combination with some advantages such as control of product distribution [15], enhanced rate [16] and/or reactivity [17], ease of product recovery [18], catalyst immobilization [19], and recycling [20]. Since ILs are neither completely nonvolatile nor non-flammable, use of ILs omits the risk of combustion by replacement of volatile organic compounds widely used as solvents in organic reactions.

In combination with the use of ILs in organic transformations, catalyst-free methodologies for the synthesis of organic compounds have attracted much interest because of their ease of experimental procedures as well as workup, low cost, possibility of using acid or base sensitive substrates, and environmentally

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benign nature [21]. Many organic transformations were studied under catalyst-free conditions such as synthesis of 2-amino thiazols,[22] N-benzyloxycarbonylation of amines,[23] synthesis of benzoic and benzyl esters,[24] gembisillylation of carboxylic acids,[25] synthesis of polyorganosyloxanes [26] and one-pot four component synthesis of poly substituted imidazoles [27].

Nitrogen heterocycles containing a phthalazine moiety are important because they show biological and pharmacological activities such as anticonvulsant, cardiotonic, and vasorelaxant, and also unique electrical and optical properties [28]. Despite many methods being available for the synthesis of phthalazine derivatives,[29–33] their broad utility has accentuated the need to develop new synthetic routes for these compounds. Recent protocols have employed three-component condensations of aldehydes and dimedone (5,5-dimethylcyclohexane-1,3-dione) with 2,3-dihydro-1,4-phthalazinedione (phthalhydrazide) and/or one-pot four component reaction between aldehydes and dimedone (5,5-dimethylcyclohexane-1,3-dione), hydrazinium hydroxide and phthalic anhydride using various catalytic systems such as *p*-toluenesulfonic acid (*p*-TSA) [34a], H_2SO_4 [34b], heteropoly acids (HPAs) [34c], starch sulfate [35a], $CeSO_4{\cdot}4H_2O$ [35b] and silica supported poly phosphoric acid [35c]. These protocols have limitations such as the formation of by-products and the use of toxic organic solvents, acidic conditions, large amounts of catalyst, and tedious work-up procedures. According to the principle of safe chemistry, synthetic methods should be designed to use substances that exhibit little or no toxicity to human health and the environment [36].

As a part of our continuing studies in developing efficient catalyst-free synthetic methodologies in organic preparations,[27,37] we found that synthesis of 2*H*-indazolo [2,1-*b*] phthalazine-triones *via* a one-pot four component reaction can be efficiently achieved without any catalyst with the use of neutral ILs under ultrasonic irradiation at room temperature.

2. Methods

2.1. Apparatus and analysis

Reagents and solvents were purchased from Merck, Fluka or Aldrich. The IL was prepared according to the reported method [38]. Melting points were determined in capillary tubes in an electro-thermal C14500 apparatus. The progress of the reaction and the purity of compounds were monitored by TLC analytical silica gel plates (Merck 60 F250). All known compounds were identified by comparison of their melting points and ^{1}H NMR data with those in the authentic samples. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer. Chemical shifts are given as δ values against tetramethylsylane as the internal standard and *J* values are given in Hz. Microanalysis was performed on a Perkin–Elmer 240-B microanalyzer. The ultrasound apparatus was cleaning bath Wiseclear 770 W (Seoul, Korea). The operating frequency was 40 kHz and the output power was 200 W, estimated calorimetrically. The reaction flasks were located in the maximum energy area in the water bath, where the surface of reactants (reaction vessel) is slightly lower than the level of the water, and the addition or removal of water controlled the temperature of the water bath. The temperature of the water bath was controlled at 25–30 °C. All experiments performed in this work were repeated three times. The yield reported represents the average of the values obtained for each reaction.

2.2. General procedure for the synthesis of 2H-indazolo[2,1-b] phthalazine-triones

Dimedone (1 mmol), aromatic aldehyde (1 mmol), hydrazinium hydroxide (1.2 mmol) and phthalic anhydride (1 mmol) were added to [Bmim]Br (0.5 g) in a 25 mL Pyrex flask. The mixture was continuously irradiated for the appropriate time (Table 2) at room temperature. The reactions were followed by thin layer chromatography (TLC) using hexane/ethyl acetate (3:1) as an eluent. The ultrasonic apparatus used showed the temperature automatically so the temperature was controlled and fixed at room temperature by pouring cold water in the bath in the case of any elevation of temperature. After completion of the reaction, water (20 mL) was added and stirred magnetically for 5 min. Insoluble crude products were filtered, dried, and recrystallized from ethanol. To recover the [Bmim]Br, after the isolation of insoluble products, water was evaporated, and the remaining viscous liquid was washed with ethyl acetate (5 mL) and dried under reduced pressure ([Bmim]Br was recovered in 97% yield).

2.3. Selected Spectral data

2.3.1. 3,3-dimethyl-13-phenyl-3,4-dihydro-1H-indazolo[1,2-b] phthalazine-1,6,11(2H,13H)-trione (Compound 5a)

Yellow powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.23 (s, 6H), 2.33 (Distorted AB system, 2H), 3.25 (AB System, *J* = 18.0 Hz, 1H), 3.48 (AB System, *J* = 18.0 Hz, 1H), 6.44 (s, 1H), 7.41–8.42 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 28.2, 28.4, 34.3, 38.0, 50.4, 64.5, 118.6, 127.0, 127.5, 127.7, 128.3, 128.6, 129.1, 133.4, 134.2, 136.3, 150.9, 151.7, 154.2, 156.8, 192.3. Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52%, Found: C, 74.23; H, 5.40; N, 7.61%.

2.3.2. 13-(4-chlorophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo [1,2-b]phthalazine-1,6,11(2H,13H)-trione (Compound 5b)

White powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.21 (s, 3H), 1.23 (s, 3H), 2.33 (Distorted AB System, 2H), 3.26 (AB System, *J* = 18.5 Hz, 1H), 3.44 (AB System, *J* = 18.5 Hz, 1H), 6.45 (s,1H), 7.33–8.42 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 28.3, 28.4, 34.5, 38.1, 50.6, 64.4, 118.2, 127.7, 128.0, 128.4, 128.5, 128.7, 129.0, 133.3, 134.4, 134.6, 134.9, 151.0, 154.2, 156.0, 192.2. Anal. Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89%, Found: C, 67.81; H, 4.77; N, 6.95%.

2.3.3. 13-(4-fluorophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo [1,2-b]phthalazine-1,6,11(2H,13H)-trione (Compound 5d)

Yellow powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.23 (s, 6H), 2.35 (Distorted AB System, 2H), 3.22 (AB System, *J* = 18.5 Hz, 1H), 3.43 (AB System, *J* = 18.0 Hz, 1H), 6.41 (s, 1H), 7.01–8.44 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 28.5, 28.6, 34.8, 38.1, 50.5, 64.2, 115.6, 115.9 (d, $^1J_{C-F}$ = 275 Hz), 118.0, 127.3, 128.0, 128.9, 129.0, 132.4, 133.5, 134.6, 151.1, 152.0, 154.3, 156.0, 192.1. Anal. Calcd for $C_{23}H_{19}FN_2O_3$: C, 70.76; H, 4.91; N, 7.18%, Found: C, 70.82; H, 4.85; N, 7.29%.

2.3.4. 3,3-dimethyl-13-p-tolyl-3,4-dihydro-1H-indazolo[1,2-b] phthalazine-1,6,11(2H,13H)-trione (Compound 5h)

Yellow powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.25 (s, 6H), 2.31 (s, 3H), 2.38 (Distorted AB System, 2H), 3.22 (AB System, *J* = 18.0 Hz, 1H), and 3.45 (AB System, *J* = 18.0 Hz, 1H), 6.43 (s, 1H), 7.16–8.42 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 21.3, 28.5, 28.9, 34.6, 38.1, 50.6, 64.6, 118.3, 127.0, 127.7, 127.9, 128.8, 129.3, 129.5, 133.4, 133.6, 134.2, 138.5, 150.9, 154.3, 156.3, 192.1. Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25%, Found: C, 74.66; H, 5.71; N, 7.39%.

2.3.5. 13-(4-isopropylphenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo [1,2-b]phthalazine-1,6,11(2H,13H)-trione (Compound 5o)

Yellow powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.22 (s, 3H), 1.25 (s, 6H), 1.27 (s, 3H), 2.37–2.38 (Distorted AB System, 2H), 2.89–2.94 (m, 3H), 6.24 (s, 1H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.38 (d,