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Glycerol based ionic liquid with a boron core: A new highly efficient and reusable promoting medium for the synthesis of quinazolinones

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ABSTRACT

A highly efficient and environmental benign procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via the condensation of carbonyl compounds with 2-aminobenzamide using a glycerol based ionic liquid with a boron core as a new and reusable promoting medium is described. A broad range of substrates including aldehydes and ketone were condensed with 2-aminobenzamide. All reactions are completed in short times and the products are obtained in good to excellent yields. The reaction medium could be recycled and reused several times without any loss of efficiency. Moreover, presented procedure has been applied successfully for the synthesis of some novel bis(pyrazolinone) derivatives.

1. Introduction

One of the most important classes of nitrogen heterocycles is quinazoline and its derivatives that have recently been evaluated as antagonists of various biological receptors, such as 5-HT5A related diseases [1], calcitonin generelated peptide [2], and vasopressin V3 receptors [3]. Between various kinds of quinazoline derivatives, 2-substituted quinazolines show important biological activities such as anti-inflammatory [4], antihypertensive [5], anticancer [6], antitumor [7], and antibacterial [8]. Methaqualone (Fig. 1) is an anti-malarial drug [9a] and currently being used for the assessment of the abuse liability of sedative hypnotic drugs [9b]. Tiodazosin (Fig. 1), a hybrid of quinazoline and [1,3,4]-oxadiazole heterocycles has been marketed as antihypertensive agent [9c,d].

Based on the above facts, the synthesis of quinazoline derivatives is currently of great interest in organic synthesis. The most popular method for the synthesis of 2-sustituted quinazolines is based on the condensation of 2-aminobenzamide with aromatic aldehydes catalyzed by NH_4Cl, $AlCl_3/ZnCl_2$, *p*-TSA, other Lewis acids, and asymmetric Brönsted acids [10] or one-pot condensation of isatoic anhydride and amines with aldehydes in organic solvents [11].

Moreover, reductive condensation of 2-nitrobenzamide and aldehydes or ketones was also reported in the presence of low valence titanium [12].

Most of these methods have certain limitations such as tedious processes, long reaction times, harsh reaction conditions, application of volatile organic solvents, toxic reagents, non-reusability of the catalyst and low yields of products.

Nowadays, more severe legislation and restrictions are ordained in order to reduce of the environmental impact of man-made chemicals. In this context, the ability of ionic liquids (ILs) as new reaction media, to provide the requirements of environmental sustainability is remarkable. The most important advantage of ILs is their lack of vapor pressure relative to the traditional volatile molecular solvents, that corroborate their efficiency about the incorporation in a sustainable synthesis [17] (Green Chemistry principle 2) [13]. Moreover, their low toxicity and limited environmental persistence (Green Chemistry principles 3 and 10) [13] make them competent solvents for sustainable chemical processes. Another feature of ionic liquids is their ability to be reused many times. Over the last few years, there have been several reviews published in which ionic liquids occupied a central theme [14].

Glycerol, an organic liquid molecule that forms from the alkaline hydrolysis of fats has gained special attention because of its unique chemical and physical properties. Nowadays, this material is obtained as a by-product of biodiesel synthesis via the transesterification of seed oils with methanol. Glycerol is a green and biodegradable compound. Moreover, this material is non-volatile under normal atmospheric pressure and has a high boiling point. Besides, it is a nontoxic

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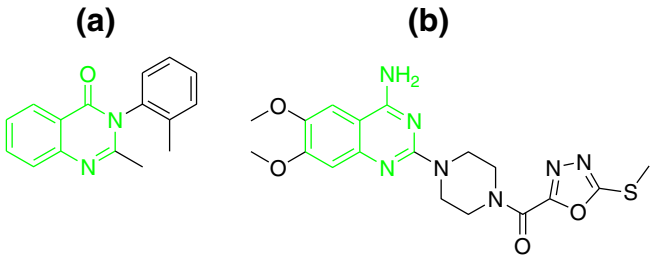


Fig. 1. Chemical structures of (a) Methaqualone and (b) Tiadazosin.

(LD_{50} (oral rat) = 12,600 mg kg^{-1}) material that is used widely in cosmetics such as face masks, skin creams, tooth paste etc.

In addition, boron is present in many foods and drinking water supplies. Estimated human consumption of boron in the U.S. diet ranges from 0.02 mg boron/day to more than 9 mg boron/day with an estimated average intake of 1.17 mg boron/day for men and 0.96 mg boron/day for women. Recent evidence has suggested that boron may be an essential micronutrient. The US EPA considers boric acid to be low in acute toxicity based on studies in rats with an oral LD_{50} of 3450 mg kg^{-1} for male rats and 4080 mg kg^{-1} for female rats.

Considering the biological importance and pharmaceutical applications of quinazolines and green behaviors of glycerol and importance of its derivatives in the development of more environmental benign organic procedures, and along with our previous studies on the application of glycerol and its derivatives in organic synthesis [15], herein we report the application of a glycerol based ionic liquid with a boron core as a highly efficient biodegradable and reusable promoting medium for the synthesis of quinazolinone derivatives (Scheme 1).

2. Method and material

Reagents and solvents were purchased from Merck, Fluka or Aldrich. The IL was prepared according to the reported method [16]. 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 a δ value against tetramethylsylane as the internal standard and *J* values are given in Hz. Microanalysis was performed on a Perkin-Elmer 240-B microanalyzer. All experiments performed in this work were repeated three times. The yield reported represents the average of the values obtained for each reaction.

3. Experimental

3.1. General procedure for the synthesis of H[Gly_2B]

Boric acid (61.83 g, 1 mol) and glycerol (190 g, 2 mol) were added to a 1 L flask containing toluene (500 mL) and the mixture was stirred at 110 °C for 4 h. During this time, the byproduct water was removed by azeotropic distillation. After this time, toluene was evaporated under reduced pressure and glyceroboric acid was obtained as a colorless viscous liquid [16].

3.2. General procedure for the synthesis of quinazolinones

2-Aminobenzamide (1 mmol) were added to the mixture of carbonyl compound (1 mmol) in H[Gly_2B] (0.5 g) in a 25 mL pyrex flask connected to a condenser and the resulted mixture was stirred magnetically for the appropriate time (Table 1) at 60 °C. The reactions were followed by thin layer chromatography (TLC) using hexane/ethyl acetate (3:1) as a mobile phase. After completion of the reaction, water (20 mL) was added and stirred magnetically for 5 min. Insoluble crude products were filtered and recrystallized from EtOH. To recover the H[Gly_2B], after the isolation of insoluble products, water was evaporated, and the remaining viscous liquid was washed with methyl *tert*-butyl ether (5 mL) and dried under reduced pressure. As H[Gly_2B] is too hydrophilic, in order for the complete removal of water, an additional lyophilization step was run. For this, recovered H[Gly_2B] was frozen in liquid nitrogen and lyophilized to near-dryness over 2 days [20]. (H[Gly_2B] was recovered in 98% yield).

3.3. Selected spectral data

3.3.1. 1′H,2H-spiro[acenaphthylene-1,2′-quinazoline]-2,4′(3′H)-dione (compound 3x)

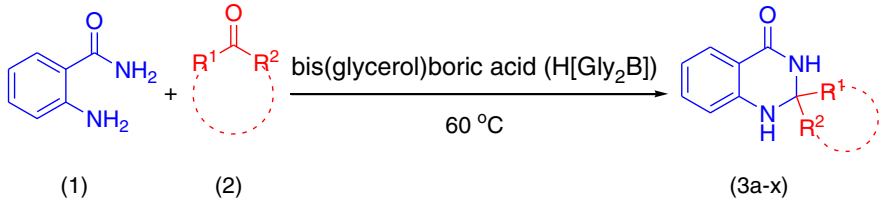
White powder (m.p. = 295–297 °C), υ_{max} (KBr):,3470, 3340, 3025, 2960, 1710 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 6.95–7.03 (m, 2H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.47–7.51 (m, 3H), 7.71 (d, *J* = 7.3 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 8.09–8.18 (m, 2H), 9.5 (s, 1H), 10.8 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 104.0, 113.5, 115.8, 116.5, 120.9, 124.8, 125.9, 127.3, 128.8, 128.9, 129.3, 129.9, 131.8, 132.5, 133.1, 143.1, 147.5, 165.9, 198.8. Anal. Calcd for $C_{19}H_{12}N_2O_2$: C, 75.99; H, 4.03; N, 9.33%; found: C, 75.91; H, 4.09; N9.41%.

3.3.2. Bis(spiro-quinazoline) (compound 3y)

White powder, mp: > 300 °C, υ_{max} (KBr): 3450, 3390, 3020, 2975, 1700, 1650 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 1.09 (m, 4H), 1.47 (m, 4H), 6.8 (t, *J* = 7.5 Hz, 2H), 7.08 (d, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H), 9.8 (s, 2H), 10.7 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 21.8, 81.7, 112.5, 115.7, 116.8, 127.5, 132.9, 147.1, 166.6. Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08%; found: C, 69.01; H, 5.83; N, 16.01%.

3.3.3. Ethyl 2-(2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)acetate (compound 11a)

White powder, m.p. = 227–229 °C, υ_{max} (KBr): 3420, 3395, 3017, 2950, 1705, 1675 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 0.97 (t, *J* = 7.8 Hz, 3H), 1.12 (s, 3H), 2.56 (d, *J* = 15.5 Hz, 1H), 2.68 (d, *J* = 15.5 Hz, 1H), 3.71 (m, 2H), 6.83 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.76 (d, *J* = 7.3 Hz, 1H), 9.15 (s, 1H), 10.31 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 14.6, 24.7, 45.5, 62.7, 73.4, 112.1, 116.3, 117.2, 128.5, 132.3, 147.3, 164.3, 171.9.



Scheme 1. Synthesis of quinazolinone derivatives using H[Gly_2B] as a highly efficient and reusable promoting medium.