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Short Note

Methyl 2-((3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetate

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Abstract: A green synthetic procedure was developed for the two-step synthesis of methyl 2-((3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetate from anthranilic acid, using two green chemistry approaches: utilization of the DES and microwave-induced synthesis. The first step includes a synthesis of 2-mercapto-3-(3-methoxyphenyl)quinazolin-4(3*H*)-one which was performed in choline chloride:urea DES. In the second step S-alkylation of 2-mercapto-3-(3-methoxyphenyl)quinazolin-4(3*H*)-one was performed in a microwave-induced reaction. The desired compound was successfully obtained in a yield of 59% and was characterized by different spectral methods.

Keywords: quinazolinone; green chemistry; alkylation

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1. Introduction

Quinazolinones are fused heterocyclic compounds, which have been proven to be excellent scaffolds in pharmaceutical and medicinal chemistry. Their potential to act as excellent antibacterial [1,2], antiviral [3], anticancer [4–6], enzyme inhibitory [7–9], anti-HIV [10–12] and other biologically active agents depends on their structure, which can be altered using different synthetic approaches. A high potential for pharmaceutical and medicinal uses inspires researchers to synthesize different quinazolinone analogues to enhance the biological activity. The most common approach to synthesize quinazolinone derivatives is the Niementowski reaction of anthranilic acid derivatives and amides (Figure 1) [13,14]. Today, many different modifications to the initial reaction path have been employed, using formic acid or different amines instead of amides [15], microwave induced synthesis using formamide [16–18], aniline thiocarbamate salts [19], and isatoic anhydride, phenyl hydrazine and 2-nitrobenzaldehyde with $SrFe_{12}O_{19}$ nanoparticles as catalyst [20].

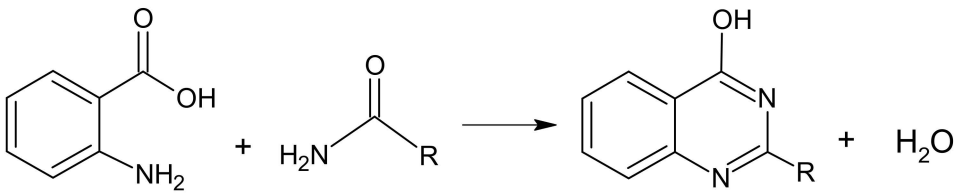

Figure 1. Niementowski synthesis of quinazolinones [13].

2-Mercapto quinazolinones have also proven to be excellent scaffolds for further synthesis of different derivatives. Their synthesis usually proceeds from anthranilic acids and isothiocyanates using different catalysts and conditions [21–24]. Our investigation showed that those derivatives could be easily synthesized in deep eutectic solvents (DESs) with no catalysts applied, where DESs were combined with microwaves or ultrasound [25]. Alkylation of such compounds usually proceeds in the reaction of 2-mercapto quinazolinones, alkylation agent and potassium carbonate in different solvents and conditions. El-Azab

et al. refluxed the reaction mixture in acetone for 20 h [22], or stirred the mixture at room temperature [26], while Khalil (2005) used tetrabutylammonium bromide as a catalyst to perform the alkylation [27]. Green chemistry methods could find their application in this manner, thus reducing the reaction time, increasing the yields and minimizing the postsynthetic procedures. The application of DESs instead of harmful volatile organic solvents with no need of catalysts has already been shown to be very effective in the synthesis of 2-mercaptoquinazolinones [25,28]. DESs are environmentally friendly mixtures of non-toxic compounds showing a high melting point depression compared to the individual components [29–32], prominently used these days for different chemical processes [31,33]. Furthermore, microwave-induced synthesis has proven to be one of the most efficient methods in synthetic chemistry owing to its increased product yields, short reaction times and low energy consumption [34].

Modern demands for the utilization of environmentally friendly approaches in chemical processes have led us to investigate synthetic paths to obtain valuable quinazolinone derivatives.

2. Results and Discussion

The green chemistry approach in this research resulted in the efficient synthesis of the desired quinazolinone derivatives. A series of desired derivatives was synthesized yielding some new compounds, methyl 2-((3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetate being one of them. These compounds in general are valuable starting materials for the synthesis of different heterocyclic compounds with potential biological activity.

The synthesis started with the formation of 2-mercapto-3-(3-methoxyphenyl)quinazolin-4(3*H*)-one (**1**) which was synthesized from anthranilic acid and 3-methoxyphenyl isothiocyanate (Figure 2) in choline chloride:urea (1:2) DES at 80 °C as described in our previous work [25]. This paper [25] describes the whole process of reaction optimization using different DESs with choline chloride: urea DES showing the best results.

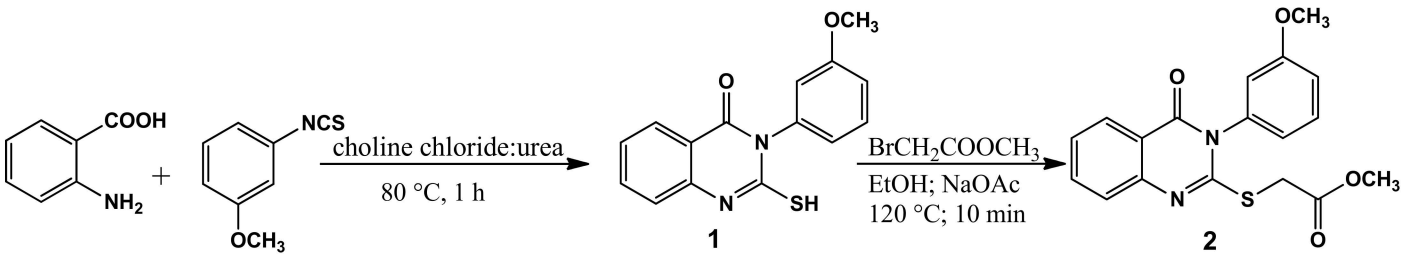

Figure 2. Synthetic path for 2-((3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetate.

The next step was the synthesis of methyl 2-((3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetate (**2**). A reaction mixture of 2-mercapto-3-(3-methoxyphenyl) quinazolin-4(3H)-one (**1**), methyl bromoacetate and sodium acetate in ethanol was heated under microwaves at 120 °C for 10 min. This reaction was fast, yielding 59% of the final product. 2-((3-(3-Methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetate was characterized by different spectral methods. ^{1}H NMR spectra showed characteristic peaks for 3-OCH_3 phenyl group at 3.79 ppm and ester –OCH_3 group at 3.69 ppm. Methylene group was characterized by the peak of 4.01 ppm, while the aromatic protons were found at 7.04–8.08 ppm. ^{13}C NMR spectra also showed characteristic peaks for methylene group at 34.17 ppm, 3-OCH_3 phenyl group at 55.50 ppm and ester –OCH_3 group at 52.34 ppm (Figures S1–S3). A structure was additionally confirmed with mass spectra showing a molecular ion m/z 357.12. This green chemistry method was efficient and successful in the synthesis of the desired compound since this reaction usually takes a longer time and reflux conditions to occur. Nguyen et al. (2019) performed a similar reaction in DMF by refluxing the mixture for 5 h [24], while Khalil (2008) stirred the mixture at room temperature for 2–4 h [27] and El-Azab et al. (2020) performed the alkylation for up to 13 h [26].

3. Materials and Methods

Chemicals were purchased from commercial suppliers and used without purification. Choline chloride (99%) and anthranilic acid (98+%) were purchased from Acros Organics (Geel, Belgium), urea (p.a.) was purchased from Gram Mol. 3-Methoxyphenyl isothiocyanate (98+%) was purchased from Maybridge (Maybridge Chemical Company Ltd., Altrincham, UK). TLC was used for monitoring the reaction using aluminium plates which were silica gel coated with fluorescent indicator F254 (Kieselgel 60). Benzene: acetic acid: acetone (8:1:1) was used as a solvent. HP-UVIS cabinet (Biostep GmbH) was used to monitor the plates under UV light at 254 and 365 nm. The melting point was determined using capillary Electrothermal IA9100 digital melting point apparatus (Electrothermal Engineering Ltd., Rochford, UK). ^{1}H and ^{13}C NMR spectra were recorded on Bruker 600 MHz spectrometer (Bruker Biospin, Rheinstetten, Germany) at 298 K in dimethylsulfoxide (DMSO-d_6). Mass spectra were recorded on an LC/MS/MS API 2000 (Foster City, CA, United States). The synthesis was performed using Milestone flexiWAVE reactor equipped with rotating carousel with 15 positions for PTFE vessels and direct control of the process and temperature (Milestone Srl, Milan, Italy).

A mixture of 2-mercapto-3-(3-methoxyphenyl)quinazolin-4(3*H*)-one (0.5 mmol), methyl bromoacetate (1.2 eq), sodium acetate (0.5 mmol) in 10 mL of ethanol was placed in the PTFE vessel in the rotating carousel and heated under microwaves for 10 min at 120 °C. Upon the completion of the reaction, the solvent was removed under vacuum and water was added to the residual mixture. A crude product was filtered off and washed with water. No further purification was needed. The title compound **2** (59%) was obtained as white powder, with mp 137 °C; R_f 0.75 (benzene/acetone/acetic acid 8:1:1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.08 (1H, dd, J = 7.91, 1.13 Hz, arom.), 7.83 (1H, m, arom.), 7.50 (3H, m, arom.), 7.15 (1H, m, arom.), 7.11 (1H, m, arom.), 7.04 (1H, m, arom.), 4.01 (2H, s, -CH_2-), 3.79 (3H, m, –OCH_3), 3.69 (3H, s, –OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.89, 160.45, 160.00, 156.39, 146.94, 136.68, 134.96, 130.29, 126.57, 126.12, 125.89, 121.36, 119.49, 115.76, 115.62, 115.08, 55.50, 52.34, 34.17; *m/z* 357.12 (M+).

Supplementary Materials: The following can be downloaded online. Figure S1: ^{1}H NMR spectra of 2-((3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetate; Figure S2: Mass spectra of 2-((3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetate; Figure S3: ^{13}C NMR spectra of 2-((3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetate; Molfile of ^{1}H NMR spectra of 2-((3-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetate.

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