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Novel Three-Step Synthesis of Imidazo[1,2-c]quinazoline-5(6H)-thione Derivatives

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Abstract

A novel synthesis of Iimidazo[1,2-c]quinazoline-5(6*H*)-thione framework was developed through a three-step reaction starting from benzil. The resulting (2-nitrophenyl)-4,5-diphenyl-1*H*-imidazole from the reaction of benzil and different 2-nitrobenzaldehyde, reduction of nitro group and then cyclization reaction with carbon disulfide (CS_2). All steps were carried out under easy and user-friendly conditions in short time without using expensive catalysts or reagents.

Keywords: Iimidazo[1,2-*c*]quinazoline-5(6*H*)-thione; Heterocycles; 2-Nitrobenzaldehydes; Carbon disulfide (CS_2).

Introduction

A literature survey revealed that quinazolinones show antihypertonic, antirheumatic, antianaphylactic, antiasthmatic, tranquilizing, neurostimulating, and benzodiazepine binding activity [1,2]. For example, 3-substituted quinazolinones, such as SGB-1534 [3] and ketanserin have been found to have antihypertensive activities mediated via α-adrenoceptor and serotonic receptor antagonism, respectively. Addition of (2-methoxyphenyl)piperazine side chain at the 2- or 3-position of the angular tricyclic 2,3-dihydroimidazo[1,2-*c*]quinazoline ring system of SGB-1534 resulted in the formation of potent antihypertensive agents, such as 2-[[4-(2-methoxyphenyl)- piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one and 3-[[4-(2-methoxy phenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one that selectively antagonized the α1-adrenoceptor (Fig. 1) [4].

The imidazo[1,2-*c*]quinazolinone ring system can generally be prepared by the reaction of α-aminoketones with 2-isocyanatobenzonitrile [7], α-aminocarboxylic esters with 2-isocyanatobenzonitrile [8], 2-(2-nitrophenyl)-1*H*-imidazoles with triphosgene [9]. Cyclocondensations of 2-isothiocyanatobenzonitrile (ITCB) with α-aminoketones [10], enzymatic cyclizations mediated by ultrasonically stimulated baker's yeast [11], sequential Sonogashira and Suzuki-Miyaura and one-pot two-step Sonogashira/Stille cross-coupling reactions [12], and reductive cyclization of 2-(2-nitrophenyl)-1H-imidazoles with isothiocyanates or isocyanates mediated by $SnCl_2$ [13] are reported. Chern *et al*. also reported the synthesis of imidazo[1,2-*c*]quinazolinone derivatives based on cyclocondensations with NBS [14].

However, these methods suffer from some disadvantages, such as drastic conditions, unsatisfactory yields, long reaction time, high temperature, complex manipulation, and inaccessible starting materials. Therefore, we became interested in developing a convenient synthetic methods for the preparation of imidazo[1,2-*c*]quinazolinone derivatives.

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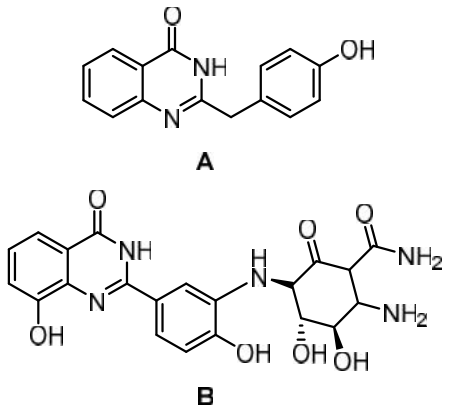


Figure 1. Some biologically active quinazolinones.

In recent years, our interest has been focused on the usage of $SnCl_2$ reagent. It has previously reported the synthesis of 2-aryl-2*H*-indazoles, 1-hydroxy quinazolinones [15], respectively mediated by $SnCl_2$ reagent. As our earlier works goes, herein, we will describe a new approach to synthesize imidazo[1,2-*c*]quinazolinone derivatives by treating 2-(2-nitrophenyl)-1*H*-imidazoles with isothiocyanates or isocyanates mediated by $SnCl_2$.

Materials and Methods

General

Commercially available reagents were used without further Purification. Melting points were measured with a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker FT-400, 500, using TMS as an internal standard. IR spectra were obtained with a Shimadzu 470 spectrophotometer (KBr disks). MS were recorded with an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed with an Elementar Analysen system GmbH Vario ELCHNS mode.

General Procedure for the synthesis of imidazo[1,2-c]quinazoline-5(6H)-thione derivatives:

A mixture of 2-(4,5-diphenyl-1*H*-imidazol-2-yl)aniline derivatives (2 mmol), carbon disulfide (CS_2) (5 mmol), and potassium hydroxide (KOH) (2 mmol) in EtOH (10 mL) was heated at reflux for 3-5 h. After completion of the reaction (checked by TLC), the reaction mixture was cooled down to room temperature, poured in ice-cold water, and the white precipitates were filtered off and recrystallized from EtOH to give pure produts.

2,3-diphenylimidazo[1,2-c]quinazoline-5(6*H*)-thione (5a): ^{1}HNMR (500MHz, DMSO-d_6): δ = 9.07 (1H, s), 8.54 (1H, d, *J* = 8.0 Hz), 8.43 (1H, d, *J* = 8.0 Hz), 8.09 (1H, t, *J* = 7.5 Hz), 7.98 (1H, d, *J* = 7.5 Hz), 7.67-7.72 (4H, m), 7.55-7.61 (3H, m), 7.33-7.40 (3H, m) ppm; ^{13}CNMR (125MHz, DMSO-d_6): δ = 159.8, 139.8, 137.9, 134.6, 133.1, 131.9, 130.9, 130.8, 129.5, 129.2, 128.9, 128.5, 128.2, 128.1, 127.8, 124.0, 121.2, 116.3 ppm.

2,3-bis(4-methoxyphenyl)imidazo[1,2-*c*]quinazoline-5(6*H*)-thione (5b): ^{1}HNMR (500MHz, DMSO-d_6): δ = 9.11 (1H, s), 8.51 (1H, d, *J* = 7.5 Hz), 8.05 (1H, d, *J* = 7.5 Hz), 8.06 (1H, t, *J* = 7.5 Hz), 7.94 (1H, t, *J* = 7.5 Hz), 7.65 (2H, d, *J* = 8.5 Hz), 7.58 (2H, d, *J* = 8.5 Hz), 7.14 (2H, d, *J* = 8.5 Hz), 6.94 (2H, d, *J* = 8.5 Hz), 3.87 (3H, s), 3.77 (3H, s) ppm; ^{13}CNMR (125MHz, DMSO-d_6): δ = 159.7, 159.2, 139.5, 137.9, 134.4, 132.2, 131.5, 130.6, 129.4, 129.0, 125.5, 122.9, 121.1, 120.1, 116.2, 114.5, 114.2, 114.0, 55.3, 55.1 ppm.

9-methoxy-2,3-diphenylimidazo[1,2-*c*]quinazoline-5(6*H*)-thione (5c): ^{1}HNMR (500MHz, DMSO-d_6): δ = 9.00 (1H, s), 7.98-8.04 (2H, m), 7.66-7.71 (3H, m), 7.53-7.60 (3H, m), 7.48 (2H, dd, *J* = 8.0, 1.5 Hz), 7.35-7.40 (3H, m), 4.09 (3H, s) ppm, ^{13}CNMR (125MHz, DMSO-d_6): δ =159.7, 159.0, 152.3, 154.2, 139.9, 135.9, 133.0, 130.6, 129.1, 128.8, 128.4, 128.1, 127.8, 117.4, 113.6, 111.8, 105.4, 56.4 ppm.

9-methoxy-2,3-bis(4-methoxyphenyl)imidazo[1,2-c]quinazoline-5(6*H*)-thione (5d): ^{1}HNMR (500MHz, DMSO-d_6): δ = 8.63 (1H, s), 7.96-8.03 (2H, m), 7.64 (2H, d, *J* = 9.0 Hz), 7.57 (2H, d, *J* = 9.0 Hz), 7.46 (1H, d, *J* = 8.0 Hz), 7.13 (2H, d, *J* = 9.0 Hz), 6.94 (2H, d, *J* = 9.0 Hz), 4.09 (3H, s), 3.87 (3H, s), 3.78 (3H, s) ppm; ^{13}CNMR (125MHz, DMSO-d_6): δ = 159.7, 159.2, 156.5, 139.5, 135.7, 132.0, 131.4, 131.1, 129.5, 128.9, 128.4, 125.4, 122.9, 120.2, 117.3, 114.4, 113.9, 111.9, 111.5, 56.4, 55.2, 55.0 ppm.

2,3-bis(4-methoxyphenyl)-[1,3]dioxolo[4,5-g]imidazo [1,2-c]quinazoline-5(6*H*)-thione(5e): ^{1}HNMR (500MHz, DMSO-d_6): δ = 8.86 (1H, s), 7.81 (1H, s), 7.62 (1H, d, *J* = 8.5 Hz), 7.54 (1H, d, *J* = 8.5 Hz), 7.12 (2H, d, *J* = 9.0 Hz), 6.93 (2H, d, *J* = 9.0 Hz), 6.37 (2H, s), 3.86 (3H, s), 3.77 (3H, s) ppm; ^{13}CNMR (125MHz, DMSO-d_6): δ = 159.6, 159.2, 152.9, 154.0, 139.7, 135.3, 132.3, 132.1, 129.0, 125.7, 122.0, 120.4, 114.4, 113.9, 113.6, 106.6, 103.4, 97.6, 55.2, 55.1 ppm.

2,3-diphenyl-[1,3]dioxolo[4,5-*g*]imidazo[1,2-*c*]quinazoline-5(6*H*)-thione (5f): ^{1}HNMR (500MHz, DMSO-d_6): δ = 9.17 (1H, s), 7.79 (2H, s), 7.66 (2H, d, *J* = 7.5 Hz), 7.62 (2H, d, *J* = 7.5 Hz), 7.53-7.58 (3H, m), 7.32-7.37 (3H, m), 6.35 (2H, s) ppm; ^{13}CNMR (125MHz, DMSO-d_6): δ = 153.0, 150.5, 140.0, 135.4, 133.2, 132.6, 130.7, 129.5, 129.0, 128.9, 128.4, 128.3, 128.2, 128.0, 127.8, 123.0, 113.7, 106.6, 106.3, 103.4, 97.7 ppm.

9-chloro-2,3-diphenylimidazo[1,2-*c*]quinazoline-5(6*H*)-thione (5g): ^{1}HNMR (500MHz, DMSO-d_6): δ = 9.14 (1H, s), 8.47 (1H, s), 8.42 (1H, d, *J* = 9.0 Hz), 7.95 (1H, d, *J* = 9.0 Hz), 7.65 (2H, d, *J* = 8.5 Hz), 7.57 (2H, d, *J* = 8.5 Hz), 7.14 (2H, d, *J* = 8.5 Hz), 6.94 (2H, d, *J* = 8.5 Hz), 3.87 (3H, s), 3.78 (3H, s) ppm; ^{13}CNMR (125MHz, DMSO-d_6): δ = 159.8, 159.3, 140.0, 138.7, 136.3, 132.0, 131.5, 130.8, 128.9, 125.3, 123.2, 120.1, 119.8, 117.4, 114.4, 114.0, 55.2, 55.1 ppm.

9-chloro-2,3-bis(4-methoxyphenyl)imidazo[1,2-*c*]quinazoline-5(6*H*)-thione (5h): ^{1}HNMR (500MHz, DMSO-d_6): δ = 9.01 (1H, s), 8.44 (1H, d, *J* = 2 Hz), 8.40 (1H, d, *J* = 9.0 Hz), 7.93 (1H, dd, *J* = 8.5, 2.0 Hz), 7.63 (2H, d, *J* = 8.5 Hz), 7.56 (2H, d, *J* = 8.5 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 6.92 (2H, d, *J* = 8.5 Hz), 3.87 (3H, s), 3.77 (3H, s) ppm; ^{13}CNMR (125MHz, DMSO-d_6): δ = 159.8, 159.2, 140.0, 138.7, 136.2, 132.0, 131.5, 130.7, 130.3, 128.9, 125.2, 123.2, 120.1, 119.8, 117.4, 114.4, 113.9, 55.2, 55.0 ppm.

Results and Discussion

Due to the importance of heterocycles [16-21], we were encouraged to design a novel strategy for the synthesis of imidazo[1,2-*c*]quinazoline-5(6*H*)-thione utilizing benzil. For this purpose, we outlined a synthetic route in three steps for the preparation of the above mentioned compounds (Scheme 1).

In the first step of our synthetic scheme consisted on various imidazole derivatives by our green reaction of benzil and various 2-nitrobenzaldehydes and ammonium acetate in acetic acid at reflux conditions [22].

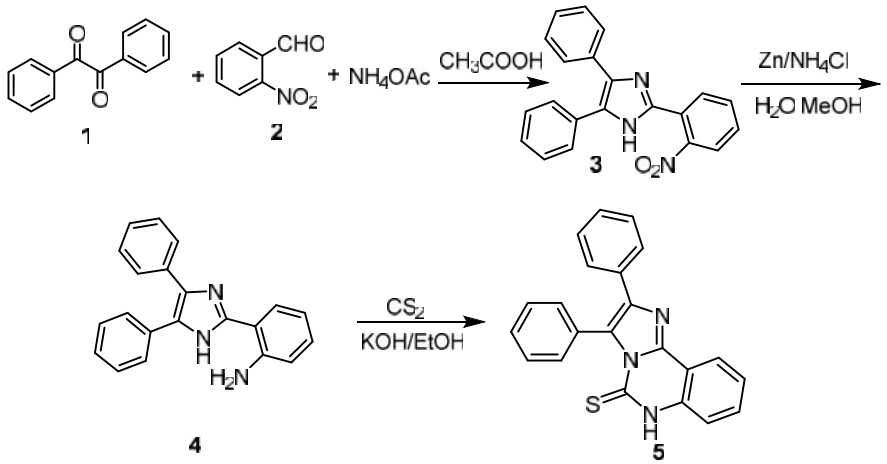
In second step of our synthetic scheme consisted in preparing the 2-(4,5-diphenyl-1*H*-imidazol-2-yl)aniline derivatives. Literature survey shows that there are various procedures for the one-pot three-component synthesis of imidazoles starting from benzil, ammonium acetate and 2-nitrobenzaldehydes [23]. For this purpose, benzil, ammonium acetate and 2-nitrobenzaldehydes were reacted in acetic acid as solvent at reflux conditions for 6 h. after the reaction completion, pouring the reaction mixture on ice resulted in precipitating the desired product with no need to more tedious purification steps (Scheme 1).

In the third step, reduction of nitro group in compounds gave 2-(4,5-diphenyl-1*H*-imidazol-2-yl)aniline. It should be noted that the best reaction conditions for reducing of NO_2 group was obtained using mixture of Zn powder, ammonium chloride (NH_4Cl) in MeOH/H_2O, at room temperature.

Finally, the products were obtained easily by heating the mixture of 2-(4,5-diphenyl-1*H*-imidazol-2-yl) anilines and excess amount of carbon disulfide (CS_2) in the presence of potassium hydroxide (KOH).

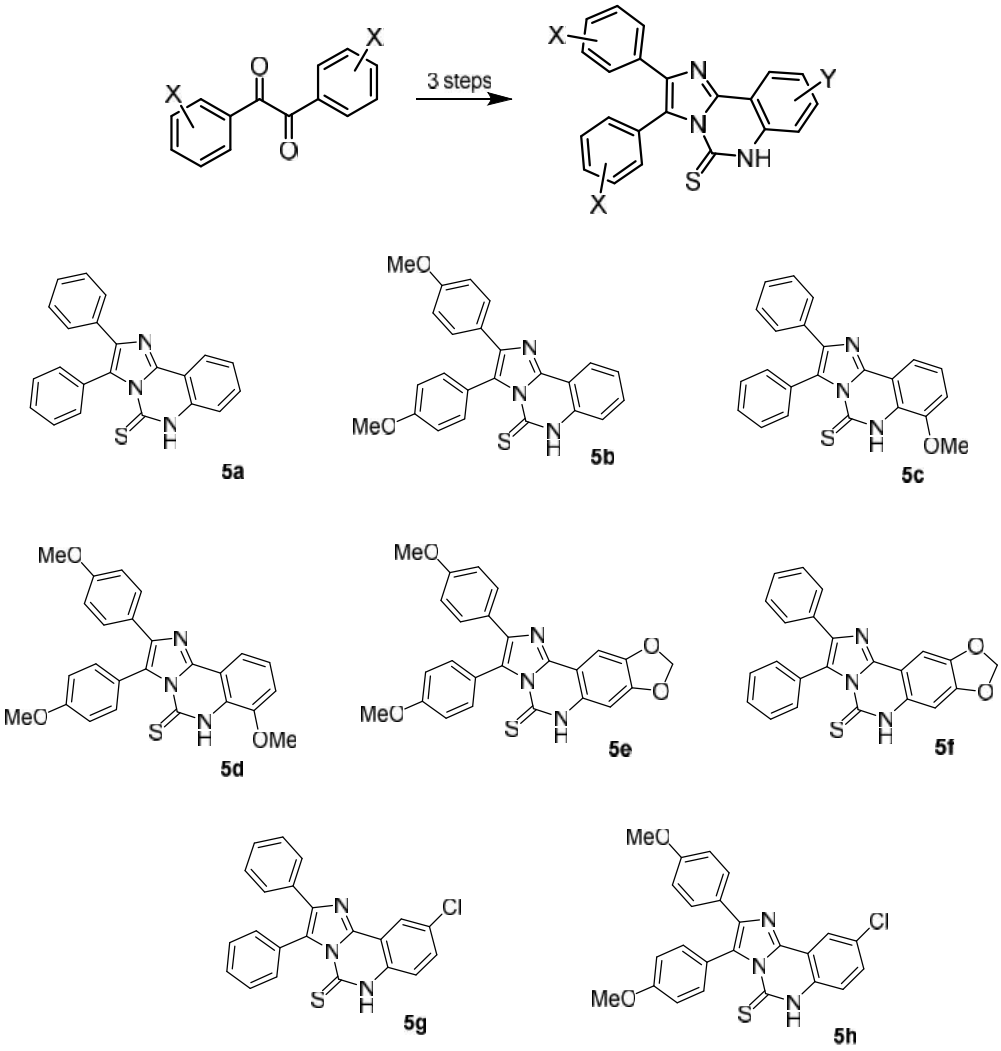
The structures of all products were confirmed on the basis of ^{1}H, and ^{13}C NMR spectra. For instance, ^{1}H NMR spectrum of 2,3-diphenylimidazo[1,2-*c*]quinazoline-5(6*H*)-thione consisted of a singlet signals at 9.06 for the protons of NH. The 14 protons associated with the aromatic rings were observed around 6.71-8.01 ppm. As expected, the ^{13}C spectrum exhibited 18 distinct resonances. A signal at 159.8 is related to thiourea carbon. Seventeen signals related to aromatic carbons were observed around 113.0-142.5.

As can be seen in Table 1, we could synthesize various imidazo[1,2-*c*]quinazoline-5(6*H*)-thione derivatives through the described method. It is worth mentioning that all 2-nitrobenzaldehysed showed good reactivity and all of corresponding products tolerated reduction reaction and also cyclization reaction with CS_2. It should be noted that different electron-donating



Scheme 1. Synthesis of fused Imidazo[1,2-*c*]quinazoline-5(6*H*)-thione

Table 1. Synthesis of fused Imidazo[1,2-*c*]quinazoline-5(6*H*)-thione derivatives.



and electron-withdrawing substituents on either para or ortho positions of aromatic rings did not show remarkable differences in the yield of products and reaction times.

Conclusion

In summary, we have developed a novel and efficient three-step synthesis of fused imidazo[1,2-*c*]quinazoline-5(6*H*)-thione derivatives starting from benzil as an available starting material, in moderate to good yields. All three steps included easy and user friendly procedures which did not diminish yields of products significantly. All steps were done without using expensive catalyst and reagents in short time. Noticing that synthesis and biological evaluation of the title compounds have not been investigated, we hope that the described strategy for the synthesis of these potentially bioactive products can open a new horizon for organic and medicinal chemists. These compounds may possess cytotoxic activities.

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