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ONE-POT, MULTICOMPONENT SEQUENTIAL SYNTHESIS OF BENZOTHIAZOLOQUINAZOLINONES

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Benzothiazolo[2,3-b]quinazolin-1-ones have been synthesized by a multicomponent reaction of substituted 2-aminobenzothiazoles with cyclic β-diketone and aromatic aldehydes in the presence of absolute ethanol. The structures of the synthesized benzothiazoloquinazolinones have been characterized by elemental analysis and spectral studies.

Keywords: 2-Aminobenzothiazoles; benzothiazoloquinazolinones; CDK and GSK-3 inhibitors; quinazolines; thiazoloquinazolines

INTRODUCTION

The synthesis of fused heterocycles has attracted considerable interest in heterocyclic chemistry because the fusion of biodynamic heterosystems has proved to be a very attractive and useful for the design of new molecular frameworks for potential drugs of varying pharmacological activities. There has been increasing interest in the chemistry of quinazolines[1,2] because the quinazoline heterocyclic system is a building block in many natural and synthetic products that exhibit a wide variety of biological and pharmacological activities.[3] Quinazolines have been reported to exhibit anticonvulsant, antibacterial, antidiabetic, and anticancer activities. Benzothiazole has also been an interesting heterocyclic system in drug research on account of the significant biological activities of its fused derivatives.[4] Thiazoloquinazolines, incorporating both biodynamic heterosystems thiazole and quinazoline, have shown significant activity against cancer.[5] Thiazoloquinazolines have also been identified as cyclin dependent kinase (CDK) and glycogen synthase kinase-3 (GSK-3) inhibitors.[6]

RESULTS AND DISCUSSION

The methods reported in the literature[7] for the synthesis of thiazoloquinazolines, irrespective of positions of attachment of both the heterocyclic systems, involve multiple steps in which the formation of thiazole ring before the quinazoline ring induced low subsequent reactivity. Thiazoloquinazolines prepared by reaction of

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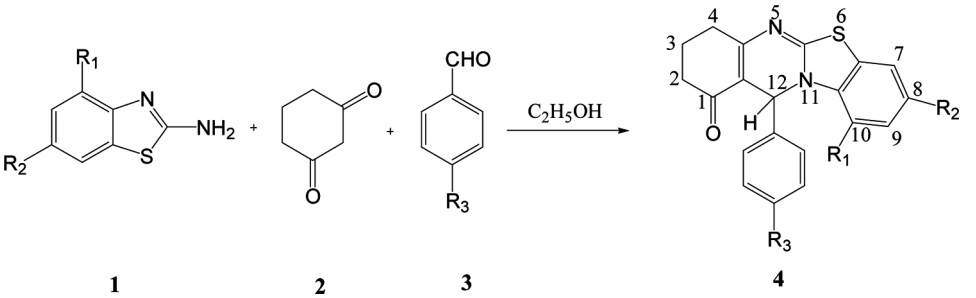
2-aminobenzylamine with aromatic amine and then with 2-mercaptopropionic acid also involve multistep reactions. In continuation of our research program on the synthesis of nitrogen- and sulfur-containing novel heterocycles[8] of pharmaceutical interest and in view of the simplicity of multicomponent reactions and their potential to introduce considerable structural diversity,[9] we have synthesized benzothiazolo[2,3-b]quinazolinones, incorporating two biodynamic heterocyclic systems, by a simple and efficient multicomponent reaction. The reaction involves a three-component cyclocondensation of 2-aminobenzothiazole with cyclic β-diketone and an aromatic aldehyde in the presence of absolute ethanol (Scheme 1).

The reaction is believed to proceed with Knoevenagal condensation between cyclic β-diketone and an aromatic aldehyde in the initial step to form an α,β-unsaturated ketone, which undergoes Michael-type addition with the nucleophilic endocyclic nitrogen of 2-aminobenzothiazole under reflux. The adduct formed is then cyclized intramolecularly with the loss of water molecule to provide benzothiazolo[2,3-b]quinazolinones. These reactions have taken place in one flask in a domino manner, and the enone system generated in situ immediately undergoes Michael-type addition with 2-aminobenzothiazole and subsequent cyclization. The structures of the synthesized compounds were confirmed by their elemental analysis and spectral studies. The regioselectivity of the process has also been confirmed by theoretical studies that show the endocyclic nitrogen is more nucleophilic than the amino group. The possibility of formation of the isomeric product involving nucleophilic attack of exocyclic amino group has been completely discarded.

Infrared (IR) spectra of all the synthesized compounds exhibit an intense carbonyl absorption band in the region 1680–1660 cm^{-1}. The absorption band in the region 1620–1604 cm^{-1} in the IR spectra of all the compounds indicated the presence of C=N bonds. Two absorption bands corresponding to asymmetric and symmetric stretching vibrations of the $–NH_2$ group, which were present in the IR spectra of 2-aminobenzothiazoles, are absent in the IR spectra of the synthesized compounds. ^1H NMR spectra of the synthesized compounds showed a multiplet in the region δ 7.16–7.54 ppm due to aromatic protons. The singlet in the region δ 6.47–6.58 ppm was assigned to the aliphatic proton (12-H).The singlet observed in the region δ 3.73–3.77 ppm was attributed to the methoxy protons, whereas the methyl protons resonate as a singlet in the region δ 2.34–2.36 ppm in the ^1H NMR spectra of thiazoloquinazolinones containing $–OCH_3$ and $–CH_3$ groups at position 10. The multiplets observed in the regions δ 2.00–2.05 ppm and δ



1 2 3 4

Scheme 1.

2.22–2.28 ppm were assigned to the two methylene protons at C-4, whereas other multiplets observed in the regions δ 2.52–2.57 ppm and δ 2.59–2.66 ppm were attributed to two methylene protons at C-2. The methylene protons present at C-3 also appeared as multiplets in the region δ 1.44–1.73 ppm. In the ^{13}C NMR spectra of the synthesized benzothiazoloquinazolinones, the δ values of most of the carbon atoms could be determined and assigned to the corresponding carbon atoms.

In conclusion, we have presented a simple and convenient multicomponent one-pot synthesis of biologically and pharmaceutically interesting benzothiazolo[2,3-b]quinazolinones. The present method enables the sequential combination of three reactive components in one pot and efficiently incorporates structural diversity simply by varying the substituent or by slight structural modification in the components involved in the reaction. The structural diversity in molecules makes for effective pharmacophoric interactions with the receptor sites in the biological system.

EXPERIMENTAL

The purities of all the synthesized compounds have been checked by thin-layer chromatography (TLC) using various nonaqueous solvents. The IR spectra were recorded on a Nicolet-Magna Fourier transform (FT)–IR spectrophotometer, model 550, in KBr discs. ^1H NMR spectra have been recorded on a Jeol FX-90 QFT NMR spectrometer at 90 MHz in dimethylsulfoxide (DMSO-d_6)/$CDCl_3$ containing tetramethylsilane (TMS) as an internal standard. Data are presented in Table 1.

General Procedure for the Preparation of Benzothiazolo[2,3-b]quinazolinones

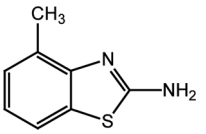
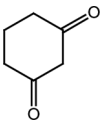
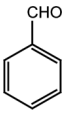
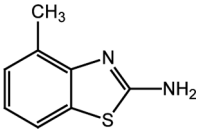
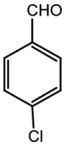
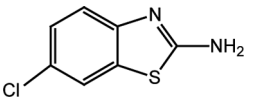
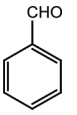
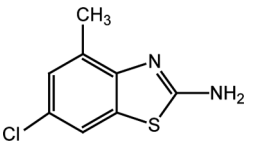
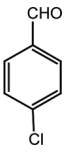
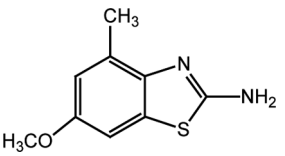
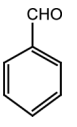
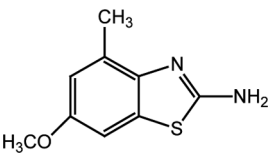
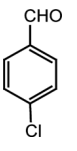
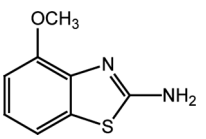
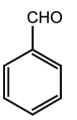
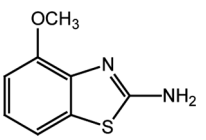
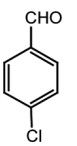
A stirred solution of 2-aminobenzothiazole (0.01 mol), cyclic β-diketone (0.01 mol), and aromatic aldehydes (0.01 mol) in absolute ethanol (20 ml) was refluxed for 30–40 min in a round-bottomed flask fitted with reflux condenser (Scheme 1). The precipitate formed was isolated by filtration. The solid that separated out was washed well with ethanol, dried, and finally crystallized from ethanol.

Selected Data for Benzothiazolo[2,3-b]quinazolinones

Compound 4b. Mp 181–183 °C; FT-IR (KBr): 1665 cm^{-1}(C=O), 1620 cm^{-1} (C=N), 720 cm^{-1} (C-Cl); ^1H NMR (300 MHz, $CDCl_3$): δ 7.18–7.50 (m, 8H), 6.52 (s, 1H), 2.54–2.62 (m, 2H), 2.25–2.34 (m, 2H), 2.03–2.15 (m, 2H), 1.78 (s, 3H); ^{13}C NMR δ (75 MHz, $CDCl_3$): 26.4, 30.2, 40.1, 49.7, 54.1, 116.6, 120.6, 121.4, 122.8, 126.5, 127.0, 127.4, 128.2, 130.2, 140.4, 144.9, 145.2, 163.8, 194.6. Anal. calcd. $C_{21}H_{17}ClN_2OS$: C, 62.22; H, 4.50; N, 7.35. Found: C, 65.85; H, 4.99; N, 7.33.

Compound 4h. Mp 194–196 °C; FT-IR (KBr): 1680 cm^{-1}(C=O), 1616 cm^{-1} (C=N), 712 cm^{-1} (C-Cl); ^1H NMR (300 MHz, $CDCl_3$): δ 7.18–7.74 (m, 8H), 6.53 (s, 1H), 3.77 (s, 3H), 2.54–2.63 (m, 2H), 2.25–2.32 (m, 2H), 2.01–2.12 (m, 2H), 1.78 (s, 3H); ^{13}C NMR δ (75 MHz, $CDCl_3$): 29.3, 39.6, 48.6, 53.5, 166.4, 117.6, 118.3, 122.3, 127.4, 128.6, 134.5, 149.2, 154.6, 162.2, 194.3. Anal. calcd. $C_{21}H_{17}ClN_2O_2S$: C, 63.22; H, 4.79; N, 7.01. Found: C, 63.55; H, 4.32; N, 7.06.

Table 1. Reaction of 2-aminobenzothiazoles with cyclic β-diketone and aromatic aldehydes

2-Aminobenothiazol	Cyclie β-diketone	Aldehyde	Product	Mp (°C)	Yield (%)
			4a	181	60
	2		4b	194	64
	2		4c	154	72
	2		4d	167	56
	2		4e	183	67
	2		4e	189	74
	2		4f	180	65
	2		4g	194	64

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