Synthesis and Characterization of Some 2-Azetidinones and Unexpected Azet-2(1H)-ones

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RECEIVED: June 11, 2018  REVISED: September 24, 2018  ACCEPTED: September 27, 2018

Abstract: 2-Azetidinone (2b–e) and some unexpected azet-2(1H)-one derivatives (3b–f) were synthesized in two steps from the substitution of 2-aminobenzothiazole and different substituted aromatic aldehydes. Firstly, the Schiff bases were prepared via reaction of different 2-aminobenzothiazoles with different aromatic aldehydes. Second step was the formation of corresponding 2-azetidinone and some unexpected azet-2(1H)-one analogues by cyclocondensation of the Schiff bases with chloroacetyl chloride and phenoxy acetyl chloride in the presence of triethylamine. The chemical structures of the newly synthesized compounds were confirmed by FTIR, 1H NMR, 13C NMR, HMQC, elemental analysis and mass spectroscopic analysis.

Keywords: benzothiazole, Schiff base, 2-azetidinone, azet-2-(1H)-one, Staudinger reaction.

INTRODUCTION

In recent years there has been a growing interest of chemists for the synthesis of heterocyclic compounds due to their significant biological characteristics. There are lots of studies on unique structure and strong antibacterial activity of 2-azetidinones. Penicillin, cephalosporin, carbapenem, nocardicin, monobactam, clavulanic acid, sulbactam and tazobactam antibiotics containing 2-azetidinone ring system are extensively used as chemotherapeutical agents for the treatment of bacterial infections and microbial diseases. Studies of synthesis of 2-azetidinone and investigation of its antimicrobial characteristics have been conducted since 1990s. In recent years, various compounds with ß-lactam rings have been synthesized for obtaining the compounds having different pharmacological activities such as cholesterol absorption inhibition activity.

Staudinger’s ketene-imine reaction is the most common method of 2-azetidinones synthesis. Although Staudinger reaction was found a hundred years ago (1907) as the reaction between ketenes and imines, this method has still been used as a useful method for synthesis of 2-azetidinones and their derivatives. This reaction is applied thermally or photochemically for ketene formation by using acid chlorides in triethylamine environment. Although, it is defined as [2+2] cycloaddition, the reaction is usually described as a step by step reaction. The first step of the reaction contains nucleophilic attack of imine nitrogen to sp hybridized carbon of ketene to form zwitterion intermediate product which creates 2-azetidinone ring. The result can be cis, trans or mixture of both isomers in view of stereochemistry of 2-azetidinone. In this study, it has been observed that some unexpected azet-2(1H)-ones have been formed while synthesizing new benzothiazole derivative cis-2-azetidinones through Staudinger ketene-imine reaction (Scheme 1). The mechanism proposed for the reaction is given in Scheme 2.

RESULTS AND DISCUSSION

Compound 1a was synthesized by refluxing 1-methylbenzaldehyde (1 eq) and 2-amino-6-methoxybenzothiazole (1 eq) in toluene for 2 days. The other Schiff bases were synthesized by the same method (1b–g) (Scheme 1). Compound 1e was obtained with a high yield as 85 % along with the synthesized other Schiff bases (1a–g) most probably because of the electron-donating groups increasing the efficiency of forming of the Schiff base. In the second step,
2-azetidinone compounds were synthesized according to the method described in the experimental section. This method was applied to all the Schiff bases (1a–g) and different products were obtained (Scheme 1). Various studies have reported that different ratios of cis and trans isomers of β-lactams are formed depending on the addition of reactant order.[12-14] Cis-β-lactam was found to be the exclusive or major product when acid chloride was added dropwise at room temperature to the solution of imines and a tertiary base.[15] In Staudinger reaction, when the ketene occurs before the cyclocondensation, the β-lactam product becomes predominantly in cis form. On the other hand, when the imine reacts directly with the acyl chloride, the subsequent intramolecular $S_N2$ displacement determines the final trans selectivity.[16] In this study, to synthesize the cis-2-azetidinone product, ketene formation was carried out by adding acyl chloride derivative in the presence of triethylamine before forming of zwitterion. The reaction was initiated by the nucleophilic attack of an imine to a ketene, giving rise to a zwitterionic intermediate. A conrotatory electrocyclic ring-closure of the zwitterionic intermediate produces cis-2-azetidinone compounds (Scheme 2). When the concentrations of triethylamine and acyl chloride derivative were used within 2–3 eq and 1.5–3 eq respectively and dichloromethane was used as solvent, cis-2-azetidinone compounds were formed in a good yield. Compound 2c was obtained from the reaction of 6-methoxy-N-(4-methoxybenzylidene)benzo[d]thiazol-2-amine (1 eq) (1e) and chloroacetyl chloride (1.5 eq) in the presence of triethylamine (2 eq) at 0–5 °C in dry dichloromethane. The other 2-azetidinones were synthesized by the same method (2b–e) (Scheme 1). The synthesized compounds were characterized by spectral data and elemental analysis. Stereochemistry of these compounds were determined by comparing $J_{Ha, Hb}$ and $J_{H1, H15}$ protons, respectively. It was observed that the coupling constant of 1H doublet of $H_1$ and $H_15$ protons in cis-2-azetidinone ring at 5–6 ppm range is $J \approx 4$ Hz as mentioned in the literature and 1H doublet at 5.07 ($J = 15$ Hz) and 5.37 ($J = 15.5$ Hz) ppm were marked as related with the $H_1$ and $H_15$ protons in 2-azetidinone ring. The 2H doublets at 7.15 and 7.31 ppm were ascribed to H-2 and H-3 proton respectively.

**Scheme 1.** Synthesis of 2-azetidinones (2a–e) and azet-2(1H)-ones (3a–f) from Schiff bases (1a–g).
were signed as the carbons which are bound to H₆ and H₇ protons, respectively. In 2-azetidinone ring, C=O carbon signal in 2-azetidinone ring was observed at 166.610 ppm and the other signals were ascribed to aromatic carbons. The sharp signal observed at 1728.16 cm⁻¹ in IR spectrum was attributed to the carbonyl group in 2-azetidinone ring.

The similar signals in the spectrum of compound 2d were observed in ¹H NMR and ¹³C NMR spectra of compound 2c. In the mass spectrum of compound 2c, molecular ion peak was observed at m/z: 374.5. 2-Azetidinone ring has two types of fragmentation at EI-MS. These are the type A fragmentation leads to formation of ketene and imine ions or the type B fragmentation leads to formation of olefin and isocyanate ions.[20] The 2-azetidinone ring in compound 2c showed type A fragmentation, resulting in peaks at m/z: 298 and m/z: 192, respectively (Scheme 3).

Two contours at 4-6 ppm range in HMQC spectrum of the compound 2c can be related to H₆ and H₇ protons (Scheme 4). These spectroscopic data confirmed that this compound is 3-chloro-1-(6-methoxybenzo[d]thiazol-2-yl)-4-(4-methoxyphenyl)azetidin-2-one.

Reactions were carried out at different temperatures by using different equivalents, different substitute Schiff bases and different acyl chloride derivatives. Cis-2-azetidinones were obtained in good yield by using phenoxacetyl chloride (1.5–3 eq) and triethylamine (2–3 eq) concentration. However, some unexpected azet-2(1H)-ones were synthesized instead of cis-2-azetidinone product by using triethylamine (7.4–15 eq) and chloroacetyl chloride (2–3,7 eq) concentration without changing the other reaction conditions such as temperature and solvent type (Scheme 1). Actually, direct acylation of the imine with the appropriate acid chloride yields N-acyliminium chloride (I) which may be at equilibrium with chloro amide (II) (Scheme 2). The reaction with N-acyliminium chloride or chloro amide bases gives β-lactam.[21–23] When the imine reacted directly with the acyl chloride, the subsequent intramolecular S₆2 displacement determined the final trans selectivity.[16] The nonpolar solvents can not stabilize the zwitterionic intermediates which are facilitating the direct ring closure to form cis products, while the polar solvents can stabilize the zwitterionic intermediates and increase their half-life which increases the isomerization of the imine moiety to form trans products.[24] However, as mentioned in the literature, we could not obtain trans products using triethylamine (5-15 eq) and chloroacetyl chloride (2-3,7 eq) concentration without changing the other reaction conditions such as temperature and solvent type but unexpected azet-2(1H)-ones were synthesized instead of the trans product. We conclude that the formation of azet-2(1H)-ones arises from an increase in triethylamine concentration the mechanism of which was suggested.
Formation mechanism of azet-2(1H)-ones is shown in Scheme 2. In addition to 2-azetidinone 2a and azet-2(1H)-one 3a was also obtained at the rate of 1:1 when the reaction was carried out by using of 7.4 eq of triethylamine and 3.7 eq of chloroacetyl chloride. 3a compound was purified by column chromatography using ethylacetate: dichloromethane:hexane solvent system in a ratio of 0.1 : 2 : 1.2, but 2a compound was not purified (Scheme 1).

Schiff base (1 eq), triethylamine (7.4–15 eq) and chloroacetyl chloride (2.3–7 eq) were refluxed in dry dichloromethane at 0–5 °C for 8 hours to give the unexpected azet-2(1H)-ones (3a–f) (Scheme 1) and characterized by 1H NMR, 13C NMR and mass spectrum.

Compound 3e was synthesized with 75% yield by using Schiff base 1e (1 eq), triethylamine (9 eq) and chloroacetyl chloride (5 eq). In 1H NMR spectrum of the compound 3e, at 3.80 ve 3.81 ppm, 3H singlets were observed for Bt-CH3 and Ph-CH3, respectively. 2H doublets at 7.03 and 8.10 ppm are related to H-11, H-15 and H-12, H-14 protons, 1H doublets at 7.14 and 8.81 ppm are belong to H-4 and H-5 protons and 1H singlet at 7.70 ppm is related to H-7 proton. At about 4–6 ppm, the signals for the protons of H6 and H7 in the 2-azetidinone ring were not observed, while the 1H singlet at 6.88 ppm was observed for the H6 proton in the azet-2(1H)-one.

In IR spectrum, stretching vibrations of C=O group in azet-2(1H)-one ring and 2-azetidinone ring were observed at 1676.08 cm⁻¹ and 1728 cm⁻¹, respectively. As expected, presence of conjugation in azet-2(1H)-one ring decreased the intensity of stretching signal of C=O group. The different fragmentations were observed in the mass spectrum of compound 2c when compared with EI-MS.
Schiff bases were synthesized by modifying the procedure provided in the reference. The reactions were carried out under reflux, and the products were purified by column chromatography. The purity of the synthesized compounds was confirmed by TLC and spectral analyses.

**EXPERIMENTAL**

The chemicals and reagents used for the synthesis were obtained from commercial sources. Solvents were distilled with an appropriate drying agent. Melting points of the synthesized substances were determined by a Gallenkamp apparatus. The elemental (C, H, N, S) analysis were carried out with an appropriate drying agent. The melting points of the synthesized compounds were determined by a Gallenkamp apparatus. The elemental (C, H, N, S) analysis were carried out with an appropriate drying agent. The melting points of the synthesized compounds were determined by a Gallenkamp apparatus. The elemental (C, H, N, S) analysis were carried out with an appropriate drying agent. The melting points of the synthesized compounds were determined by a Gallenkamp apparatus.

**General Procedure for the Synthesis of Schiff Bases 1a–g**

Schiff bases were synthesized by modifying the procedure suggested by Vicini et al.**p-Methyl benzaldehyde (0.65 mL, 5.55 mmol) in toluene (40 mL) was added into 1 % H2SO4 solution (0.1 mL) and 2-amino-6-methoxybenzothiazole (1.0 g, 5.55 mmol) and refluxed for 2 days. The obtained product was extracted with dichloromethane. Liquid fraction was evaporated under reduced pressure. The residue was recrystallized from (1:3) ethylacetatehexane solvent system (1a). Other Schiff bases (1b–g) were synthesized by the same method.

**6-METHOXY-N-(3-METHYLBENZYLIDENE)BENZO[d]THIAZOL-2-AMINE (1a)**

(64 %); yellow solid, mp 131–133 °C; FTIR (KBr) νmax/cm⁻¹: 3100, 2927.93, 1604.83 (N=CH), 1521.07, 1466.48, 1264.30, 1223.35, 1057.01; 1H NMR (500 MHz, DMSO-d6) δ/ppm: 2.42 (s, 3H, -CH3), 3.86 (s, 3H, -OCH3), 7.13 (dd, 1H, J = 8.9 Hz, 4J = 2.5 Hz, H-5), 7.48 (d, 2H, J = 8.4 Hz and H-15), 7.68 (s, 1H, 1J = 2.5 Hz, H-7), 7.85 (d, 1H, J = 8.8 Hz, H-13), 7.88 (t, 1H, J = 4.1 Hz, H-14), 7.92 (s, 1H, H-7), 9.11 (s, 1H, -N=CH2); 13C NMR (125 MHz, DMSO-d6) δ/ppm: 21.30, 56.22, 107.71, 116.28, 123.79, 128.00, 129.53, 130.46, 134.51, 146.05, 157.82, 166.75, 169.30; Anal. Calcd for C16H12N2OS: C, 67.88; H, 5.07; N, 9.85; S, 11.79 %.

**6-METHOXY-N-(4-METHYLBENZYLIDENE)BENZO[d]THIAZOL-2-AMINE (1b)**

(71 %); yellow solid, mp 118–119 °C; FTIR (KBr) νmax/cm⁻¹: 2956.77, 2900.83, 2829.47, 1595.07 (N=CH); 1H NMR (500 MHz, DMSO-d6) δ/ppm: 2.42 (s, 3H, -CH3), 3.86 (s, 3H, -OCH3), 7.11 (dd, 1H, J = 9.0 Hz, 4J = 2.5 Hz, H-5), 7.40 (d, 2H, J = 8.0 Hz, H-12 and H-14), 7.66 (s, 1H, 1J = 1.8 Hz, H-7), 7.82 (d, 1H, J = 8.5 Hz, H-4), 7.97 (d, 2H, J = 8.0 Hz, H-11 and H-15), 9.10 (s, 1H, -N=CH2); Anal. Calcd for C17H14N2OS: C, 68.06; H, 5.00; N, 9.92; S, 11.36 %.

**6-CHLORO-N-(4-METHYLBENZYLIDENE)BENZO[d]THIAZOL-2-AMINE (1c)**

(66 %); light yellow solid, mp 151–154 °C; FTIR (KBr) νmax/cm⁻¹: 3435.10, 3049.35, 2977.98, 1595.07 (N=CH), 1564.21, 1539.14, 1153.39, 815.86; 1H NMR (500 MHz, DMSO-d6) δ/ppm: 2.39 (s, 3H, -CH3), 3.79 (d, 2H, J = 9.0 Hz, H-12 and H-14), 7.51 (d, 1H, J = 8.3 Hz, H-4), 7.89 (d, 1H, J = 8.1 Hz, H-5), 7.96 (d, 2H, J = 8.5 Hz, H-11 and H-15), 8.21 (s, 1H, H-7), 9.11 (s, 1H, -N=CH2); 13C NMR (125 MHz, DMSO-d6) δ/ppm: 21.87, 42.95, 124.134, 127.525, 129.861, 130.317, 130.772, 132.304, 135.984, 144.920, 150.542, 168.241, 172.801; Anal. Calcd for C18H16ClN2OS: C, 62.82; H, 3.87; N, 9.77; S, 11.18 %.

**6-METHOXY-N-(3-METHOXYBENZYLIDENE)BENZO[d]THIAZOL-2-AMINE (1d)**

(72 %); yellow solid, mp 140–142 °C; FTIR (KBr) νmax/cm⁻¹: 3090, 2962.55, 1604.72 (N=CH); 1575.79, 1485.13

**Scheme 5. EI-MS fragmentation of compound 3e.**

The spectrum of compound 3e. Basic peak of compound 3e was observed at m/z: 338. By separating m/z: 28 group from the basic state, m/z: 308 peak was observed (Scheme 5). As a result of these spectral data, it was determined that the compound 3e is 1-((6-methoxybenzo[d]thiazol-2-yl)-4-(4-methoxyphenyl)azet-2(1H)-one.
Azetidinones were synthesized by modifying the suggested procedure by Mogilia et al. (2017) Chloroacetyl chloride (60 µL, 0.75 mmol) was added dropwise to the dichloromethane solution of Et$_2$N (140 µL, 1 mmol) at 0–5 °C. 6-Methoxy-N-(4-ethoxybenzylidene)benzod[d]thiazol-2-amine (1c) (0.15 g, 0.5 mmol) was stirred in an ice bath for 8 hours. The reaction was terminated by a TLC control (1:3, ethylacetate:hexane). The mixture was allowed to stand at room temperature overnight. The reaction mixture was extracted with saturated NaHCO$_3$ solution (10 mL), 10% HCl solution (10 mL) and 5% NaCl solution (10 mL) respectively. The organic phase was dried with Na$_2$SO$_4$. The solution was filtered, and liquid fraction was evaporated under reduced pressure. The residue was purified by column chromatography to give compound 2c. Other 2-azetidinones (2b–e) were also synthesized by the same method above.

6-METHOXY-4-(METHOXYBENZYLIDENE)BENZOD[d]THIAZOL-2-AMINE (1e) (56 %); light yellow solid, mp 137–139 °C; $^1$H NMR (500 MHz, DMSO-d$_6$) δ / ppm: 2.88 (s, 3H, -OCH$_3$), 4.55 (d, 2H, J= 11.5 Hz, H-5), 7.12 (d, 1H, J= 8.3 Hz, H-7), 7.85 (d, 1H, J= 8.9 Hz, H-4), 7.90 (d, 1H, J= 8.5 Hz, H-6), 8.07 (d, 2H, J= 9.0 Hz, H-12 and H-14), 8.23 (d, 1H, J= 2 Hz, H-7), 9.11 (s, 1H, -N=CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ / ppm: 55.59, 55.66, 105.08, 114.68, 115.54, 122.98, 127.38, 132.06, 135.18, 145.55, 157.11, 161.26, 165.28, 169.18; Anal. Calcd for C$_{16}$H$_{14}$N$_2$O$_2$: C, 64.41; H, 4.73; N, 9.39; S, 10.75 %. Found: C, 64.07; H, 4.91; N, 9.32; S, 11.21 %.

3-CHLORO-1-(6-METHOXYBENZYLIDENE)BENZOD[d]THIAZOL-2-YL)-4-(METHOXYPHENYL)AZETIDIN-2-ONE (2c) (90 %); light yellow solid, mp 247–249 °C; FTIR (KBr) $\nu_{max}$ / cm$^{-1}$: 3130.35, 2906.62, 1732.01 (2 -OH); 1670.50, 1591.14, 1530.62, 1380.36 (3 -CH$_2$); 1249.83, 1176.54, 829.36 (%); white solid, mp 139 °C; $^1$H NMR (500 MHz, DMSO-d$_6$) δ / ppm: 3.71 (s, 3H, -OCH$_3$), 4.55 (d, 2H, J= 11.5 Hz, H-5), 7.12 (d, 1H, J= 8.3 Hz, H-7), 7.85 (d, 1H, J= 8.9 Hz, H-4), 7.90 (d, 1H, J= 8.5 Hz, H-6), 8.07 (d, 2H, J= 9.0 Hz, H-12 and H-14), 8.23 (d, 1H, J= 2 Hz, H-7), 9.11 (s, 1H, -N=CH$_2$); Anal. Calcd for C$_{16}$H$_{14}$N$_2$O$_2$: C, 64.41; H, 4.73; N, 9.39; S, 10.75 %. Found: C, 59.18; H, 3.69; N, 9.28; S, 10.71 %.

6-METHOXY-4-(4-NITROBENZYLIDENE)BENZOD[d]THIAZOL-2-YL)-4-(METHOXYPHENYL)AZETIDIN-2-ONE (2e) (75 %); orange solid, mp 258–260 °C; FTIR (KBr) $\nu_{max}$ / cm$^{-1}$: 3060.92, 2833.33, 1741.66, 1595.07 (-N=CH$_2$), 1510.21, 1338.55; $^1$H NMR (500 MHz, DMSO-d$_6$) δ / ppm: 3.86 (s, 3H, -OCH$_3$), 7.15 (dd, 1H, J= 1.4 Hz, H-7), 7.71 (d, 1H, J= 2.6 Hz, H-5), 7.89 (d, 1H, J= 8.9 Hz, H-4), 8.33 (d, 2H, J= 8.6 Hz, H-12 and H-14), 8.41 (d, 2H, J= 8.4 Hz, H-11 and H-15), 9.30 (s, 1H, -N=CH$_2$); Anal. Calcd for C$_{22}$H$_{13}$N$_2$O$_2$: C, 57.50; H, 3.54; N, 13.41; S, 10.23 %. Found: C, 56.69; H, 3.57; N, 13.33; S, 10.58 %.

General Procedure for the Synthesis of 2-Azetidinones 2b–e

2-Azetidinones were synthesized by modifying the suggested procedure by Mogilia et al. (2017) Chloroacetyl chloride
129.315, 129.619, 132.365, 154.752, 157.506, 158.743, 158.993, 166.610; Anal. Calcd for C_{14}H_{20}N_{2}O_{2}S; C, 66.65; H, 4.66; N, 6.48; S, 7.41 %; Found: C, 65.85; H, 4.68; N, 6.52; S, 7.58 %.

1-(6-METHOXYBENZO[D]THIAZOL-2-YL)-4-(4-NITROPHENYL)-3-PHENOXAZETIDIN-2-ONE (2e) (41 %); light yellow solid, mp 296–298 °C; ¹H NMR (500 MHz, DMSO-d$_6$) $\delta$ / ppm: 3.86 (3H, -OCH$_3$), 5.42 (d, 1H, $J = 12.7$ Hz, H$_3$), 5.49 (d, 1H, $J = 12.7$ Hz, H$_2$), 6.85-7.23 (m, 5H, -OPh), 7.76 (d, 1H, $J = 2.9$ Hz, H-7), 8.22 (d, 1H, $J = 8.7$ Hz, H-4), 8.34 (d, 2H, $J = 8.9$ Hz, H-12 and H-14), 8.43 (d, 2H, $J = 8.9$ Hz, H-11 and H-15), 8.87 (d, 1H, $J = 9.2$ Hz, H-5); Anal. Calcd for C$_{25}$H$_{21}$N$_2$O$_3$S; C, 66.59; H, 4.42; N, 8.57; S, 10.09 %; Found: C, 64.62; H, 3.41; N, 8.60; S, 9.98 %.

General Procedure for the Synthesis of Azet-2(1H)-ones 3b–f
Chloroacetyl chloride (120 μL, 1.5 mmol) was added to the dichloromethane solution of 6-methoxy-N-(4-methoxybenzyldene)benz[d]thiazol-2-amine (1e) (0.15 g, 0.5 mmol) at 0–5 °C and after a while added EtN (700 μL, 5 mmol) and stirred in an ice bath for 8 hours. The reaction was terminated by a TLC control (1:3; ethylacetate:hexane). The mixture was allowed to stand at room temperature overnight. The reaction mixture was extracted with saturated NaHCO$_3$ solution (10 mL), 10 % HCl solution (10 mL) and 5 % NaCl solution (10 mL) respectively. The organic phase was dried over satd. Na$_2$SO$_4$ and then washed with ethylacetate to give compound 3e. Other azet-2(1H)-ones (3b–f) were also synthesized by the same method above.

1-(6-METHOXYBENZO[D]THIAZOL-2-YL)-4-(P-TOLYL)AZET-2(1H)-ONE (3b) (80 %); white solid, mp 249–251 °C; FTIR (KBr) $\nu_{max}$ / cm$^{-1}$: 3020.42, 2947.12, 1678.01 (azet-2(1H)-one C=O), 1606.65, 1529.50, 815.86; ¹H NMR (500 MHz, DMSO-d$_6$) $\delta$ / ppm: 2.37 (3H, -CH$_3$), 3.86 (3H, -OCH$_3$), 6.96 (1H, H$_7$), 7.18 (dd, 1H, $J = 7.7$ Hz, 1.4Hz, 2.5 Hz, H-5), 7.33 (2H, $J = 8.5$ Hz, H-11 and H-15), 7.73 (1H, $J = 1.4$Hz, 2.5 Hz, H-7), 8.06 (d, 2H, $J = 8.0$ Hz, H-12 and H-14), 8.85 (d, 1H, $J = 9.0$ Hz, H-4); ¹C NMR (125 MHz, CHCl$_3$-d$_2$) $\delta$ / ppm: 21.44, 55.84, 103.10, 106.22, 113.70, 120.97, 125.88, 129.58, 129.92, 133.18, 141.17, 158.55, 159.76, 161.52; Anal. Calcd for C$_{14}$H$_{12}$N$_2$O$_3$S; C, 67.06; H, 4.48; N, 8.69; S, 9.95 %. Found: C, 66.59; H, 4.42; N, 8.57; S, 10.09 %.

1-(6-CHLOROBENZO[D]THIAZOL-2-YL)-4-(P-TOLYL)AZET-2(1H)-ONE (3c) (83 %); white solid, mp 244–246 °C; FTIR (KBr) $\nu_{max}$ / cm$^{-1}$: 3114.92, 3084.06, 1674.15 (azet-2(1H)-one C=O), 1523.71, 1494.78, 825.50; ¹H NMR (500 MHz, DMSO-d$_6$) $\delta$ / ppm: 2.34 (3H, -CH$_3$), 6.96 (1H, H$_7$), 7.29 (d, 2H, $J = 9.2$ Hz, H-12 and H-14), 7.62 (dd, 1H, $J = 8.1$ Hz, 1.4Hz, 2.6 Hz, H-5), 8.02 (d, 2H, $J = 8.4$ Hz, H-11 and H-15), 8.22 (s, 1H, $J = 3.8$ Hz, H-7), 8.88 (d, 1H, $J = 8.7$ Hz, H-4); ¹C NMR (125 MHz, DMSO-d$_6$) $\delta$ / ppm: 68.19, 102.89, 120.49, 123.12, 126.608, 127.456, 127.578, 129.952, 131.470, 132.782, 135.179, 141.484, 159.039, 161.201, 162.301; Anal. Calcd for C$_{14}$H$_{23}$ClN$_2$O$_3$S; C, 59.56; H, 3.23; N, 8.17; S, 9.35 %. Found: C, 58.87; H, 3.28; N, 8.25; S, 9.31 %.
General Procedure for the Synthesis of Mixture 2-Azetidinone 2a and Azet-2(1H)-one 3a

A solution of 6-methoxy-N-[3-methylbenzylidene]benzoyl[d]thiazol-2-amine (1a) (0.05 g, 0.18 mmol) and Et3N (183 µL, 1.31 mmol) in dichloromethane (35 mL) was added into chloroacetyl chloride (52 µL, 0.66 mmol) at 0–5 °C in the atmosphere of N2 (g), stirred in an ice bath for 8 hours and then left at room temperature overnight. The reaction was terminated by TLC control (1:3, ethylacetate:hexane). The obtained product was extracted sequentially with saturated NaHCO3 solution (10 mL), 10 % HCl solution (10 mL) and 5 % NaCl solution (10 mL). It was determined that the product obtained was a mixture of 2-azetidinone and azet-2(1H)-one in the 1:1 ratio of 1H NMR spectral data. 3a compound was purified by column chromatography using (0.1 : 2 : 1.2) ethylacetate : dichloromethane : hexane solvent system, but 2a compound was not separated as pure.

3-CHLORO-1-(6-METHOXYBENZO[D]THIAZOL-2-YL)-4-(M-TOLYL)AZETIDIN-2-ONE (2a) (41 %); FTIR (KBr) \( \nu_{\text{max}} \) cm\(^{-1}\): 3050.00, 2912.41, 2835.26, 1726.23 (2-azetidinone C=O), 1666.44 (azetidinone C=O), 1643.29, 1597.00, 1512.14, 1255.61, 1176.54, 1024.16; 1H NMR (500 MHz, DMSO-d6) \( \delta \) / ppm : 2.32 (3H, -CH3), 3.79 (3H, -OCH3), 5.15 (1H, J = 9.4 Hz, H2), 5.34 (d, 1H, J = 9.4 Hz, H5), 6.94 (dd, 1H, J = 9.04 Hz, 1.4J = 2.7 Hz, H-5), 7.14 (s, 1H, H-11), 7.15 (d, 1H, J = 6.6 Hz, H-15), 7.22 (d, 1H, J = 7.7 Hz, H-13), 7.28 (t, 1H, J = 7.5 Hz, H-14), 7.39 (s, 1H, J = 2.2 Hz, H-7), 8.06 (d, 1H, J = 9.04 Hz, H-4).

1-(6-METHOXYBENZO[D]THIAZOL-2-YL)-4-(M-TOLYL)AZET-2(1H)-ONE (3a) (41 %); off-white solid, mp 232–234 °C; FTIR (KBr) \( \nu_{\text{max}} \) cm\(^{-1}\): 3050.00, 2912.41, 2835.26, 1666.44 (azetidinone C=O), 1643.29, 1597.00, 1512.14, 1255.61, 1176.54, 1024.16; 1H NMR (500 MHz, DMSO-d6) \( \delta \) / ppm : 2.42 (3H, -CH3), 3.88 (3H, -OCH3), 6.99 (s, 1H, -CH), 7.19 (dd, 1H, J = 9.2 Hz, 1.4J = 2.6 Hz, H-5), 7.36 (d, 1H, J = 7.4 Hz, H-15), 7.42 (t, 1H, J = 7.6 Hz, H-14), 7.75 (s, 1H, 1.4J = 2.6 Hz, H-7), 7.95 (d, 1H, J = 8.04 Hz, H-13), 8.0 (s, 1H, H-11), 8.86 (d, 1H, J = 9.2 Hz, H-4); 13C NMR (125 MHz, CHCl3-d1) \( \delta \) / ppm : 21.58, 29.61, 55.99, 103.97, 106.47, 113.96, 121.27, 124.48, 126.09, 128.05, 128.94, 129.83, 131.61, 130.08, 138.75, 158.73, 159.97, 161.48; Anal. Calcd for C10H12N2O2S: C, 67.06; H, 4.38; N, 8.69; S, 9.95 %. Found: C, 66.10; H, 4.42; N, 8.45; S, 9.91 %.

CONCLUSION

It has been found that when synthesis of cis-2-azetidinones was implemented in a good yield by using Et3N at 2–3 eq range and chloroacetyl chloride at 1.5–3 eq range for 1 eq Schff base in dichloromethane solution at 0–5 °C, synthesis of azet-2(1H)-ones was implemented instead of cis-2-azetidinone by using Et3N at 7.4–15 eq range and chloroacetyl chloride at 2–3.7 eq range. Furthermore, both cis-2-azetidinones and azet-2(1H)-ones were synthesized by using 7.4 eq Et3N and 3.7 eq chloroacetyl chloride without changing reaction conditions of temperature and solvent type. The recommended reaction mechanism is given in Scheme 2.

Acknowledgment. The authors would like to thank the Eskişehir Osmangazi University Scientific Research Projects Council for financial support (Project No. 2014/19A208).

Supplementary Information. Supporting information to the paper is attached to the electronic version of the article at: http://doi.org/10.5562/cca3386.

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