ORIGINAL SCIENTIFIC PAPER

CROATICA CHEMICA ACTA

Croat. Chem. Acta 2018, *91*(4), 533–541
Published online: January 4, 2019
DOI: 10.5562/cca3386

HKD 1926

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

Handan Can Sakarya,* Merve Yandımoğlu

Department of Chemistry, Faculty of Art and Sciences, Eskişehir Osmangazi University, Eskişehir, Turkey
* Corresponding author's e-mail address: hsakarya@ogu.edu.tr

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, ^{1}H NMR, ^{13}C NMR, HMQC, elemental analysis and mass spectroscopic analysis.

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

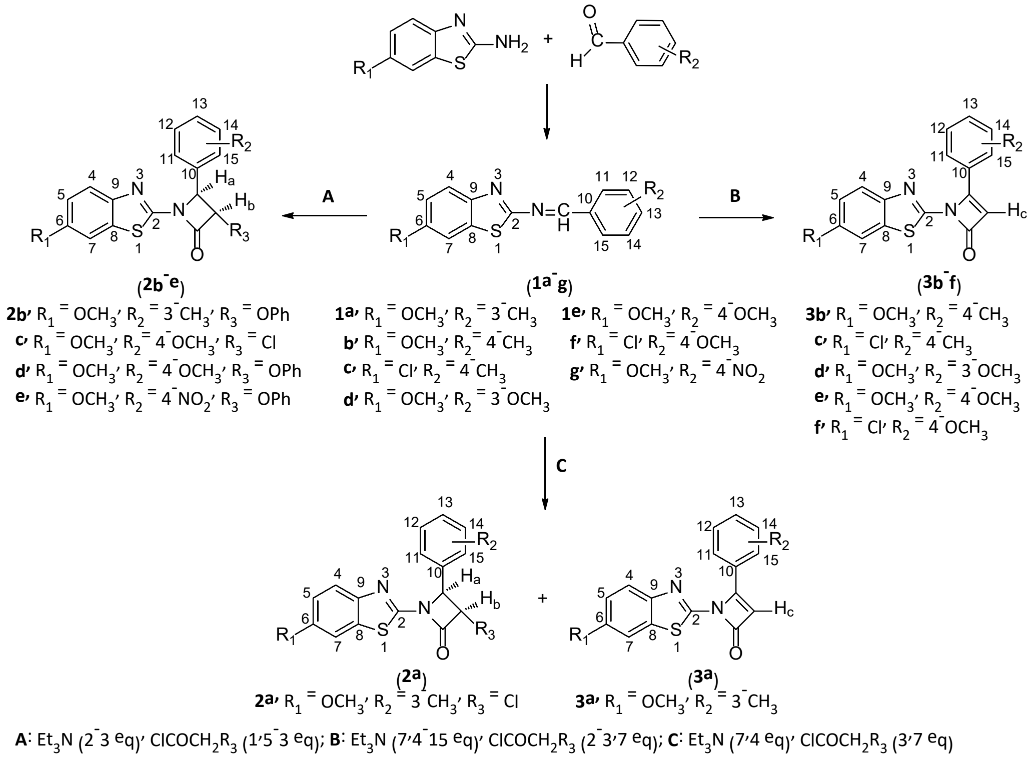
INTRODUCTION

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.[1–8] Studies of synthesis of 2-azetidinone and investigation of its antimicrobial characteristics have been conducted since 1990s. In recent years, various compounds with β-lactam rings have been synthesized for obtaining the compounds having different pharmacological activities such as cholesterol absorption inhibition activity.[9]

Staudinger's ketene-imine reaction is the most common method of 2-azetidinones synthesis.[10] 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.[11] 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.

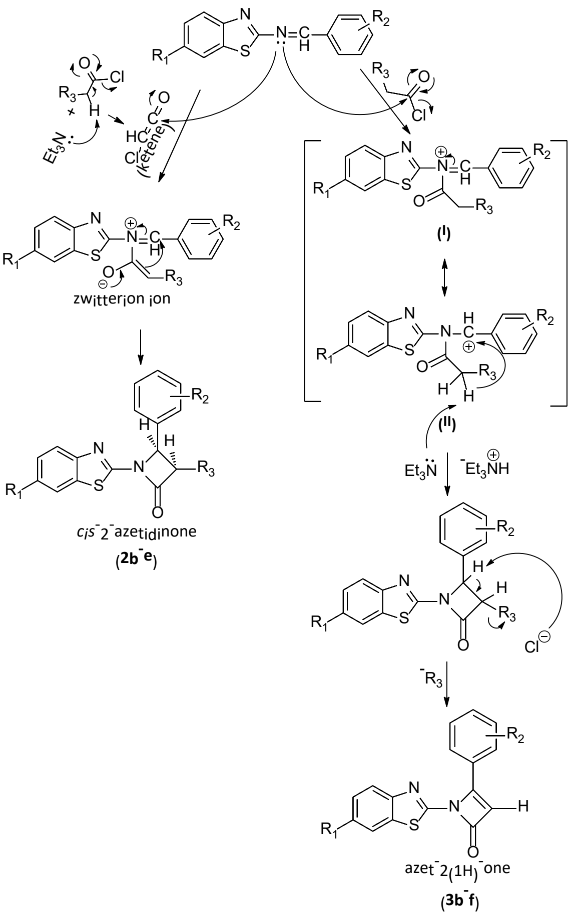
RESULTS AND DISCUSSION

Compound **1a** was synthesized by refluxing *m*-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,

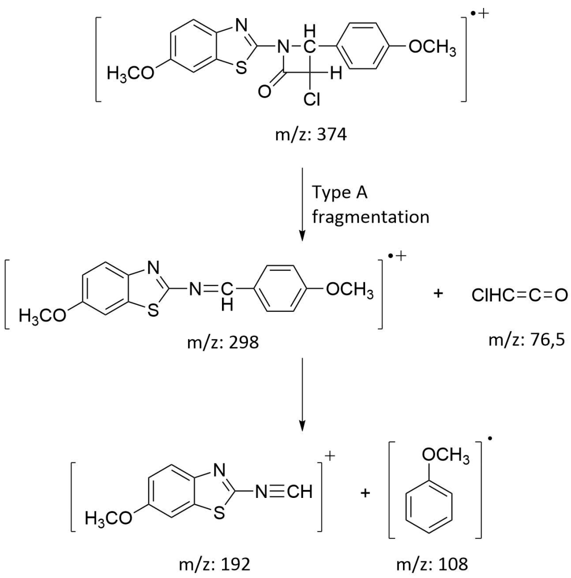


Scheme 1. Synthesis of 2-azetidinones (**2a–e**) and azet-2(1H)-ones (**3a–f**) from Schiff bases (**1a–g**).

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 $Ja,b > 4.0$ Hz coupling constant for H_a and H_b protons for *cis*-stereoisomers with $Ja,b < 3.0$ Hz for *trans*-stereoisomers.[17–19] 3H singlets observed at 3.67 and 3.73 ppm in the ^{1}H NMR spectrum of compound **2d** were marked as OCH_3 protons of benzothiazole and phenyl, respectively. It was observed that the coupling constant of 1H doublet of H_a and H_b protons in *cis*-2-azetidinone ring at 5–6 ppm range is $J \geq 4$ 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_a and H_b protons in 2-azetidi–none ring. The 2H doublets at 7.15 and 7.31 ppm were ascribed to H-12, H-14 and H-11, H-15 protons, respectively. Also, 1H doublets at 7.32 and 8.00 ppm were ascribed to H-4 and H-5 protons, respectively. 6H multiplet at 6.86 ppm was resulted from 5 protons in phenoxy group and H-7 proton. 20 signals were observed in ^{13}C NMR spectrum. While the signals at 55.408 and 56.061 ppm were related with the methoxy carbons, the signals at 62.585 and 75.474 ppm



Scheme 2. Recommended formation mechanism for *cis*-2-azetidinone and azet-2(1H)-ones.



Scheme 3. EI-MS fragmentation of compound **2c**.

were signed as the carbons which are bound to H_a and H_b 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 ^{1}H NMR and ^{13}C 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 H_a and H_b 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.

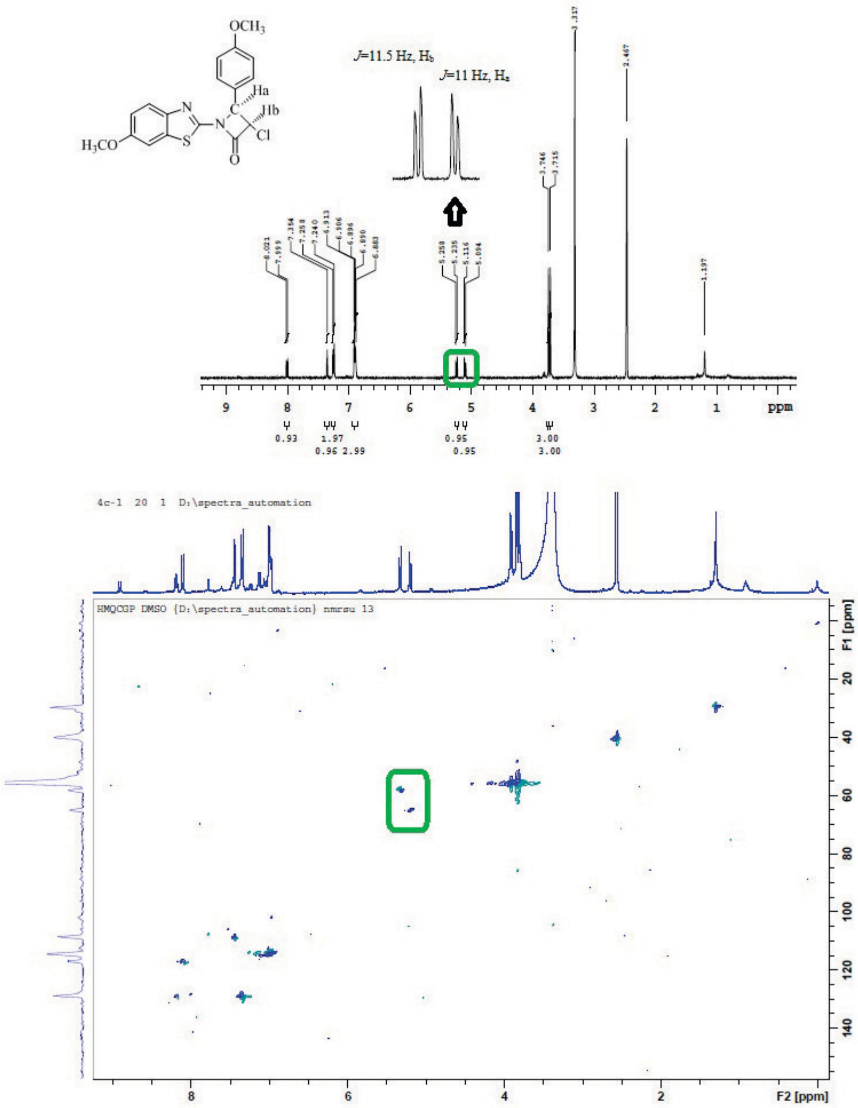
Reactions were carried out at different temperatures by using different equivalents, different substitute Schiff bases and different acyl chloride derivatives. *Cis*-2-azetidinones were obtained in good yield by using phenoxyacetyl chloride (1.5–3 eq) and triethylamine (2–3 eq) concentration. However, 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 S_N2 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 arised 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).

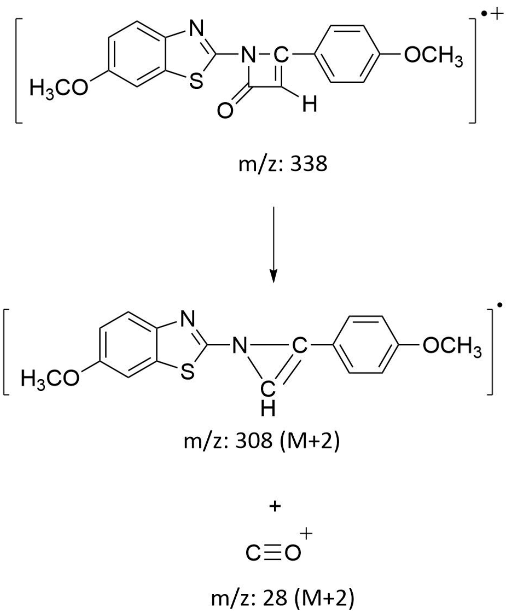
Schiff base (1 eq), triethylamine (7.4–15 eq) and chloroacetyl chloride (2.3–7 eq) were refluxed in dry dichloromethane at 0–5 °C for 8 hours to give the unexpected azet-2(1H)-ones (**3a–f**) (Scheme 1) and characterized by ^{1}H NMR, ^{13}C NMR and mass spectrum.

Compound **3e** was synthesized with 75% yield by using Schiff base **1e** (1 eq), triethylamine (9 eq) and chloroacetyl chloride (5 eq). In ^{1}H NMR spectrum of the compound **3e**, at 3.80 ve 3.81 ppm, 3H singlets were observed for Bt-OCH_3 and Ph-OCH_3, respectively. 2H dublets at 7.03 and 8.10 ppm are related to H-11, H-15 and H-12, H-14 protons, 1H dublets 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 H_a and H_b in the 2-azetidinone ring were not observed, while the 1H singlet at 6.88 ppm was observed for the H_c 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



Scheme 4. ^{1}H NMR and HMQC spectra of compound **2c**.



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

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 spectroscopic data, it was determined that the compound **3e** is 1-(6-methoxybenzo[d]thiazol-2-yl)-4-(4-methoxyphenyl)azet-2(1H)-one.

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 device. The elemental (C, H, N, S) analysis were carried out using an Elementar VARIO EL III element analysis device. IR spectra were taken by a Perkin Elmer Precisely Spectrum 100 FT-IR Spectrophotometer at Eskişehir Osmangazi University, Faculty of Art and Sciences, Department of Chemistry. ^{1}H NMR, ^{13}C NMR and HMQC spectra were recorded in $CDCl_3$ and DMSO-d_6 using a Bruker DPX FT NMR 500 MHz Spectrometer of Anadolu University, Center of Plants, Drugs and Scientific Studies (AÜBİBAM). Mass spectrum was determined with an Agilent 6460 Triple Quad LC/MS at Anadolu University, Center of Plants, Drugs and Scientific Studies (AÜBİBAM).

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

Schiff bases were synthesized by modifying the procedure suggested by Vicini *et al.*[25] *p*-Methyl benzaldehyde (0.65 mL, 5.55 mmol) in toluene (40 mL) was added into 1 % H_2SO_4 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) ethylacetate:hexane 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) υ_{max} / cm^{-1}: 3100, 2927.93, 1604.83 (-N=CH-), 1521.07, 1466.48, 1264.30, 1223.35, 1057.01 ; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm*:* 2.42 (s, 3H, -CH_3), 3.86 (s, 3H, -OCH_3), 7.13 (dd, 1H, *J*= 8.9 Hz, $^{1,4}J$= 2.5 Hz, H-5), 7.48 (d, 2H, H-4 and H-15), 7.68 (s, 1H, $^{1,4}J$= 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=CH-); ^{13}C NMR (125 MHz, DMSO-d_6) δ / ppm: 21.30, 56.22, 105.61, 116.28, 123.79, 128.00, 129.53, 130.46, 134.51, 135.10, 139.01, 146.05, 157.82, 166.75, 169.30; *Anal.* Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92; S, 11.36 %. Found: 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) υ_{max} / cm^{-1}: 2956.77, 2900.83, 2829.47, 1595.07 (-N=CH-), 1554.57, 1469.70, 1218.97, 823.57 ; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm :2.42 (s, 3H, -CH_3), 3.85 (s, 3H, -OCH_3), 7.11 (dd, 1H, *J*=9.0 Hz, $^{1,4}J$=2.5 Hz, H-5), 7.40 (d, 2H, *J*=8.0 Hz, H-12 and H-14), 7.66 (s, 1H, $^{1,4}J$=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=CH-); *Anal.* Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92; S, 11.36 %. Found: C, 68.09; H, 4.92; N, 9.87; S, 11.65 %.

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

(66 %); light yellow solid, mp 151–154 °C; FTIR (KBr) υ_{max} / cm^{-1}: 3435.10, 3049.35, 2977.98, 1595.07 (-N=CH-), 1564.21, 1539.14, 1153.39, 815.86 ; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 2.39 (s, 3H, -CH_3), 7.39 (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=CH-); ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm : 21.876, 122.495, 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 $C_{15}H_{11}ClN_2S$: C, 62.82; H, 3.87; N, 9.77; S, 11.18 %. Found: C, 61.44; H, 3.89; N, 9.81; S, 11.60 %.

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

(72 %); yellow solid, mp 140–142 °C; FTIR (KBr) υ_{max} /cm^{-1}: 3090, 2962.55, 1604.72 (-N=CH-), 1575.79, 1485.13,

1226.68, 1055.02, 800.43 ; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 3.85 (s, 3H, Bt-OCH_3), 3.86 (s, 3H, Ph-OCH_3), 7.13 (dd, 1H, *J*= 8.8 Hz, $^{1,4}J$= 2.5 Hz, H-13), 7.23 (dd, 1H, *J*= 8.2 Hz, $^{1,4}J$= 2.5 Hz, H-5), 7.50 (t, 1H, *J*= 7.8 Hz, H-14), 7.65 (d, 2H, *J*= 8.1 Hz, H-4 and H-11), 7.68 (s, 1H, $^{1,4}J$= 2.1 Hz, H-7), 7.84 (d, 1H, *J*=8.8 Hz, H-15), 9.12 (s, 1H, -N=CH-); ^{13}C NMR (125 MHz, DMSO-d_6) δ / ppm : 55.82, 56.21, 113.91, 116.33, 120.25, 123.42, 123.82, 130.72, 130.83, 135.98, 136.50, 146.02, 157.86, 160.14, 166.59, 169.11; *Anal.* Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.75 %. Found: C, 63.74; H, 4.79; N, 9.43; S, 10.56 %.

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

(85 %); yellow solid, mp 149–150 °C; FTIR (KBr) υ_{max} / cm^{-1}: 2968.34, 2895.05, 1597 (-N=CH-), 1558.43, 1510.21, 1257.54, 829.36 ; ^{1}H NMR (500 MHz, $CHCl_3$-d_1) δ / ppm : 3.90 (s, 6H, Bt-OCH_3, Ph-OCH_3), 6.99 (d, 2H, *J*= 9.0 Hz, H-12 and H-14), 7.05 (dd, 1H, *J*= 8.7 Hz, $^{1,4}J$= 2.1 Hz, H-5), 7.28 (d, 1H, $^{1,4}J$= 2.0 Hz, H-7), 7.82 (d, 1H, *J*= 9.0 Hz, H-4), 7.96 (d, 2H, *J*= 8.5 Hz, H-11 and H-15), 8.91 (s, 1H, -N=CH-); ^{13}C NMR (125 MHz, $CHCl_3$-d_1) δ / ppm : 55.59, 55.66, 105.08, 114.68, 115.54, 122.98, 127.38, 132.06, 135.18, 145.55, 157.11, 163.47, 165.28, 169.18; *Anal.* Calcd for $C_{16}H_{14}N_2O_2S$: 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 %.

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

(60 %); light yellow solid, mp 166–170 °C; FTIR (KBr) υ_{max} / cm^{-1}:3064.78, 2837.19, 1595.07 (-N=CH-), 1149.53, 765.71; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 3.89 (s, 3H, -OCH_3), 7.16 (d, 2H, *J*= 8.5 Hz, H-11 and H-15), 7.54 (dd, 1H, *J*= 8.7 Hz, $^{1,4}J$= 2.2 Hz, H-5), 7.90 (d, 1H, *J*= 8.5 Hz, H-4), 8.07 (d, 2H, *J*= 9.0 Hz, H-12 and H-14), 8.23 (d, 1H, $^{1,4}J$= 2 Hz, H-7), 9.11 (s, 1H, -N=CH-); *Anal.* Calcd for $C_{15}H_{11}ClN_2OS$: C, 59.50; H, 3.66; N, 9.25; S, 10.59 %. Found: C, 59.18; H, 3.69; N, 9.28; S, 10.71 %.

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

(75 %); orange solid, mp 258–260 °C; FTIR (KBr) υ_{max} / cm^{-1}: 3060.92, 2833.33, 1741.66, 1595.07 (-N=CH-), 1510.21, 1338.55; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 3.86 (s, 3H, -OCH_3), 7.15 (dd, 1H, $^{1,4}J$= 2.6 Hz, *J*= 8.93 Hz, H-4), 7.71 (d, 1H, $^{1,4}J$= 2.6 Hz, H-7), 7.89 (d, 1H, *J*= 8.9 Hz, H-5), 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-); *Anal.* Calcd for $C_{15}H_{11}N_3O_3S$: 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 Mogilaiah *et al.*[26] Chloroacetyl chloride (60 µL, 0.75 mmol) was added dropwise to the dichloromethane solution of Et_3N (140 µL, 1 mmol) at 0–5 °C. 6-Methoxy-*N*-(4-ethoxybenzylidene)benzo[d]thiazol-2-amine (**1e**) (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_2SO_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-METHOXYBENZO[D]THIAZOL-2-YL)-3-PHENOXY-4-(M-TOLYL)AZETIDIN-2-ONE (2b)

(56 %); white solid, mp 137–139 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm: 2.28 (s, 3H, -CH_3), 3.77 (s, 3H, -OCH_3), 5.13 (d, 1H, *J*= 12.15 Hz, H_a), 5.41 (d, 1H, *J* = 12.20 Hz, H_b), 6.90 (m, 6H, -OPh, H-5), 7.25 (m, 4H, H-11, H-13, H-14 and H-15), 7.35 (d, 1H, H-7), 8.20 (d, 1H, *J* = 7.9 Hz H-4); *Anal.* Calcd for $C_{24}H_{20}N_2O_3S$: C, 69.21; H, 4.84; N, 6.73; S, 7.70 %. Found: C, 68.58; H, 4.89; N, 6.52; S, 7.93 %.

3-CHLORO-1-(6-METHOXYBENZO[D]THIAZOL-2-YL)-4-(4-METHOXYPHENYL)AZETIDIN-2-ONE (2c)

(90 %); light yellow solid, mp 247–249 °C; FTIR (KBr) υ_{max} / cm^{-1}: 3130.35, 2906.62, 1732.01 (2-azetidinone C=O), 1639.43, 1249.83, 1176.54, 829.36 ; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 3.71 (s, 3H, Bt-OCH_3), 3.74 (s, 3H, Ph-OCH_3), 5.10 (d, 1H, *J* = 11.0 Hz, H_a), 5.25 (d, 1H, *J*=11.5 Hz, H_b), 6.90 (m, 3H, H-11, H-15 and H-4), 7.25 (d, 2H, *J* = 9.0 Hz, H-12 and H-14), 7.35 (s, 1H, H-7), 8.01 (d, 1H, *J* = 8.8 Hz, H-5); ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm : 55.537, 56.114, 57.972, 65.081, 108.862, 112.762, 114.377, 117.268, 124.490, 128.996, 129.080, 130.438, 154.965, 157.825, 159.441, 163.128; EI-MS *m* / *z* 374.5 [M+]; *Anal.* Calcd for $C_{18}H_{15}ClN_2O_3S$: C, 57.68; H, 4.03; N, 7.47; S, 8.55 %. Found: C, 57.04; H, 4.09; N, 7.62; S, 9.01 %.

1-(6-METHOXYBENZO[D]THIAZOL-2-YL)-4-(4-METHOXYPHENYL)-3-PHENOXYAZETIDIN-2-ONE (2d)

(74 %); off-white solid, mp 157–161 °C; FTIR (KBr) υ_{max} / cm^{-1}: 3066.71, 2933.62, 1728.16 (2-azetidinone C=O), 1652.94, 1487.06, 1247.90, 827.43 ; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 3.67 (s, 3H, Bt-OCH_3), 3.73 (s,3H, Ph-OCH_3), 5.07 (d, 1H, *J* = 15.0 Hz, H_a), 5.37 (d, 1H, *J* = 15.5 Hz, H_b), 6.86 (m, 6H, -OPh ve H-7), 7.15 (d, 2H, *J*=8,2 Hz H-11 and H-15), 7.31 (d, 2H, *J* = 8,0 Hz H-12 and H-14), 7.32 (d, 1H, *J* = 8,3 Hz, H4), 8.00 (d, 1H, *J* = 8,5 Hz, H-5); ^{13}C NMR (125 MHz, DMSO-d_6) δ / ppm : 55.408, 56.061, 62.585, 75.474, 108.710, 112.511, 113.937, 115.880, 116.889, 121.713, 124.968, 129.300,

129.315, 129.619, 132.365, 154.752, 157.506, 158.743, 158.993, 166.610; *Anal.* Calcd for $C_{24}H_{20}N_2O_4S$: 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-PHENOXYAZETIDIN-2-ONE (2e)

(41 %); light yellow solid, mp 296–298 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 3.86 (s, 3H, -OCH_3), 5.42 (d, 1H, *J*= 12.7 Hz, H_a), 5.49 (d, 1H, *J*= 12.7 Hz, H_b), 6.85-7.23 (m, 5H, -OPh), 7.76 (d, 1H, $^{1,4}J$ = 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 $C_{23}H_{17}N_3O_5S$: C, 61.74; H, 3.83; N, 9.39; S, 7.17 %. Found: C, 61.22; H, 3.75; N, 9.13; S, 7.49 %.

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-methoxybenzylidene)benzo[d]thiazol-2-amine (**1e**) (0.15 g, 0.5 mmol) at 0–5 °C and after a while added Et_3N (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 NaHCO3 solution (10 mL), 10 % HCl solution (10 mL) and 5 % NaCl solution (10 mL) respectively. The organic phase was dried with Na_2SO_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) υ_{max} /cm^{-1}: 3020.42, 2947.12, 1678.01 (azet-2(1H)-one C=O), 1606.65, 1529.50, 815.86 ; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 2.37 (s, 3H, -CH_3), 3.86 (s, 3H, -OCH_3), 6.96 (s, 1H, H_c), 7.18 (dd, 1H, *J* = 7.7 Hz, $^{1,4}J$= 2.5 Hz, H-5), 7.33 (d, 2H, *J* = 8.5 Hz, H-11 and H-15), 7.73 (s, 1H, $^{1,4}J$ = 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); ^{13}C NMR (125 MHz, $CHCl_3$-d_1) δ / ppm : 21.44, 55.84, 103.10, 106.22, 113.70, 120.97, 125.88, 127.18, 129.58, 129.92, 133.18, 141.17, 158.55, 159.76, 161.52; *Anal.* Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; 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) υ_{max} /cm^{-1}: 3114.92, 3084.06, 1674.15 (azet-2(1H)-one C=O), 1523.71, 1494.78, 825.50 ; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm: 2.34 (s, 3H, -CH_3), 6.96 (s, 1H, H_c), 7.29 (d, 2H, *J* = 9.2 Hz, H-12 and H-14), 7.62 (dd, 1H, *J* = 8.1 Hz, $^{1,4}J$ = 3 Hz, H-5), 8.02 (d, 2H, *J* = 8.4 Hz, H-11 and H-15), 8.22 (s, 1H, $^{1,4}J$= 3 Hz, H7), 8.88 (d, 1H, *J* = 8.7 Hz, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ / ppm : 68.191, 102.892, 120.409, 123.132, 126.698, 127.456, 127.578, 129.952, 131.470, 132.782, 135.179, 141.484, 159.039, 161.201, 162.301; *Anal.* Calcd for $C_{17}H_{11}ClN_2OS$: C, 62.48; H, 3.39; N, 8.57; S, 9.81 %. Found: C, 62.54; H, 3.41; N, 8.60; S, 9.98 %.

1-(6-METHOXYBENZO[D]THIAZOL-2-YL)-4-(3-METHOXYPHENYL)AZET-2(1H)-ONE (3d)

(71 %); off-white solid, mp 211–214 °C; FTIR (KBr) υ_{max} / cm^{-1}: 3072.49, 2935.55, 1672.22 (azet-2(1H)-one C=O), 1585.43, 1512.14, 1257.54, 783.07; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 3.80 (s, 3H, Bt-OCH_3), 3.81 (s, 3H, Ph-OCH_3), 6.99 (s, 1H, H_c), 7.05 (dd, 1H, *J* = 8.1 Hz, $^{1,4}J$=2.4 Hz, H-13), 7.13 (dd, 1H, *J* = 9.2 Hz, $^{1.4}J$ = 2.6 Hz, H-5), 7.39 (t, 1H, *J* = 7.9 Hz, H-14), 7.61 (s, 1H, $^{1,4}J$ = 1.7 Hz, H-11), 7.69 (s, 1H, $^{1,4}J$ = 2.5 Hz, H-7 and d, 1H, H-15), 8.80 (d, 1H, *J* = 8.9 Hz, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ / ppm : 55.742, 56.235, 103.612, 107.565, 112.397, 114.446, 117.200, 119.870, 120.227, 126.182, 129.801, 130.370, 137.281, 158.417, 158.439, 160.055, 160.981, 161.997; EI-MS *m* / *z* 338 [M+]; *Anal.* Calcd for $C_{18}H_{14}N_2O_3S$: C, 63.89; H, 4.17; N, 8.28; S, 9.48 %. Found: C, 63.23; H, 4.19; N, 8.05; S, 9.83 %.

1-(6-METHOXYBENZO[D]THIAZOL-2-YL)-4-(4-METHOXYPHENYL)AZET-2(1H)-ONE (3e)

(75 %); light yellow solid, mp 263–265 °C; FTIR (KBr) υ_{max} / cm^{-1}: 3076.35, 2931.69, 1676.08 (azet-2(1H)-one C=O), 1602.79, 1531.42, 1244.04, 829.36 ; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 3.80 (s, 3H, Bt-OCH_3), 3.81 (s, 3H, Ph-OCH_3), 6.88 (s, 1H, H_c), 7.03 (d, 2H, *J* = 8.5 Hz, H-11 and H-15), 7.14 (d, 1H, *J* = 7.9 Hz, H-4), 7.70 (s, 1H, H-7), 8.10 (d, 2H, *J* = 8.1 Hz, H-12 and H-14), 8.81 (d, 1H, *J* = 8.0 Hz, H-5); EI-MS *m* / *z* 338.6 [M+]; *Anal.* Calcd for $C_{18}H_{14}N_2O_3S$: C, 63.89; H, 4.17; N, 8.28; S, 9.48 %. Found: C, 63.21; H, 4.20; N, 8.45; S, 9.35 %.

1-(6-CHLOROBENZO[D]THIAZOL-2-YL)-4-(4-METHOXYPHENYL)AZET-2(1H)-ONE (3f)

(58 %); white solid, mp 205–207 °C; FTIR (KBr) υ_{max} /cm^{-1}: 3074.42, 2923.98, 1674.15 (azet-2(1H)-one C=O), 1604.72, 1251.76; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 3.83 (s, 3H, -OCH_3), 6.97 (s, 1H, H_c), 7.07 (d, 2H, *J* = 8.5 Hz, H-11 and H-15), 7.67 (dd, 1H, *J* = 9 Hz, $^{1,4}J$ = 2.5 Hz, H-5), 8.15 (d, 2H, *J* = 8.5 Hz, H-12 and H-14), 8.26 (s, 1H, $^{1,4}J$ = 2.5 Hz, H-7), 8.92 (d, 1H, *J* = 9 Hz, H-4); *Anal.* Calcd for $C_{17}H_{11}ClN_2O_2S$: 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)benzo-[d]thiazol-2-amine (1a) (0.05 g, 0.18 mmol) and Et_3N (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 N_2 (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 $NaHCO_3$ 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 ^{1}H 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) υ_{max} /cm^{-1}: 3050.00, 2912.41, 2835.26, 1726.23 (2-azetidinone C=O), 1666.44 (azet-2(1H)-one C=O), 1643.29, 1597.00, 1512.14, 1255.61, 1176.54, 1024.16; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 2.32 (s, 3H, -CH_3), 3.79 (s, 3H, -OCH_3), 5.15 (d, 1H, J = 9.4 Hz, H_a), 5.34 (d, 1H, J = 9.4 Hz, H_b), 6.94 (dd, 1H, J = 9.04 Hz, $^{1,4}J$ = 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, ^4J = 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) υ_{max} / cm^{-1}: 3050.00, 2912.41, 2835.26, 1666.44 (azet-2(1H)-one C=O), 1643.29, 1597.00, 1512.14, 1255.61, 1176.54, 1024.16; ^{1}H NMR (500 MHz, DMSO-d_6) δ / ppm : 2.42 (s, 3H, -CH_3), 3.88 (s, 3H, -OCH_3), 6.99 (s, 1H, H_c), 7.19 (dd, 1H, J = 9.2 Hz, $^{1,4}J$ = 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, $^{1,4}J$ = 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); ^{13}C NMR (125 MHz, $CHCl_3$-d_1) δ / 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, 136.08, 138.75, 158.73, 159.97, 161.48; *Anal.* Calcd for $C_{18}H_{14}N_2O_2S$: 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 Et_3N at 2–3 eq range and chloroacetyl chloride at 1.5–3 eq range for 1 eq Schiff base in dichloromethane solution at 0–5 °C, synthesis of azet-2(1H)-ones was implemented instead of *cis*-2-azetidinone by using Et_3N 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 Et_3N 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.

REFERENCES

[1] C. M. L. Delpiccolo, M. A. Fraga, E. G Mata, *J. Comb. Chem*. **2003**, *5*, 208.
[2] T. D. Gootz, *Clin. Microbiol. Rev.* **1990**, *3*, 13.
[3] G. S. Singh, *Mini Rev. Med. Chem.* **2004**, *4*, 69.
[4] G. S. Singh, *Mini Rev. Med. Chem.* **2004,** *4*, 93.
[5] C. D. Risi, G. P. Pollini, A. C. Veronese, V. Bertolasib, *Tetrahedron Lett.* **1999,** *40*, 6995.
[6] I. Ojima, *The Organic Chemistry of β-Lactams,Vol.6* (Ed. G. I. Georg, New York: VCH, **1993,** pp. 197–255).
[7] R. F. Abdulla, K. H. Fuhr, *J. Med. Chem*. **1975**, *18*, 625.
[8] W. Durckheimer, J. Blumbach, R. Lattrell, K. H. Scheunemann, *Angew. Chem. Int. Ed.* **1985,** *24*, 180.
[9] D. A. Burnett, M. A. Caplen, J. H. R. Davis, R. E. Burrier, J. W. Clader, *J. Med. Chem*. **1994**, *37*, 1733.
[10] [H. Staudinger, *Justus Liebigs Ann. Chem*. **1907**, *356*, 51.
[11] Y. Liang, L. Jiao, S. Zhang, J. Xu, *J. Org. Chem*. **2005**, *70*, 334.
[12] A. K. Bose, Y. H. Chiang, M. S. Manhas, *Tetrahedron Lett*. **1972**, *13*, 4091.
[13] Y. Oshiro, M. Komatsu, M. Uesaka, T. Agawa, *Heterocycles* **1984**, *22*, 549.
[14] T. W. Doyle, B. Belleau, B.-Y. Luh, C. F. Ferrari, M. P. Cunningham, *Can. J. Chem.* **1977**, *55*, 468.
[15] B. K. Banik, I. Banik, F. F. Becker, *Bioorg. Med. Chem.* **2005**, *13*, 3611.
[16] D. A. Nelson, *J. Org. Chem.* **1972**, *37*, 1447.
[17] K. D. Barrow, T. M. Spotswood, *Tetrahedron Lett.* **1965**, *6*, 3325.
[18] J. Decazes, J. L. Luche, H. B. Kagan, *Tetrahedron Lett.* **1970**, *11*, 3665.
[19] D. A. Nelson, *Tetrahedron Lett*. **1971**, *12*, 2543.

[20] B. Alcaide, B. Miranda, J. Perez-Castells, M. A. Sierra, *J. Org. Chem*. **1993**, *58*, 297.

[21] F. Duran, L. Ghosez, *Tetrahedron Lett.* **1970**, 11, 245.

[22] H. Bohme, S. Ebel, K. Hartke, *Chem. Ber.* **1965**, *98*, 1463.

[23] A. K. Bose, G. Spiegelman, M. S. Manhas, *Tetrahedron Lett.* **1971**, 12, 3167.

[24] A. Arrieta, B. Lecea, F. P. Cossio, *J. Org. Chem.* **1998**, *63*, 5869.

[25] P. Vicini, A. Geronikaki, M. Incerti, B. Busonera, G. Poni, C. A. Cabras, P. L. Colla, *Bioorg. Med. Chem.* **2003**, *11*, 4785.

[26] K. Mogilaiah, R. B. Rao, K. N. Reddy, *Indian J. Chem.* **1999**, *38B*, 818.