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Scientific paper

Synthesis of Novel *cis*-2-Azetidinones from Imines and Chloroacetyl Chloride Using Triethylamine

Handan Can Sakarya[1,*] and Aslı Ketrez[2]

[1] *Department of Chemistry, Faculty of Arts and Science, Eskişehir Osmangazi University, 26480 Eskişehir, Turkey.*

[2] *Department of Chemistry, Graduate School of Natural and Applied Sciences, Eskişehir Osmangazi University, 26480 Eskişehir, Turkey*

** Corresponding author: E-mail: hsakarya@ogu.edu.tr*

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Abstract

A synthesis of a novel series of *cis*-2-azetidinones **2a**–**c** was carried out by the cycloaddition reaction of imine **1a**–**c** and chloroacetyl chloride in dry dichloromethane at 0–5 °C using triethylamine. The cycloaddition of the Schiff bases with chloroacetyl chloride resulted in the corresponding major product *cis*-2-azetidinone stereoisomers **2a**–**c**. The synthesized compounds were characterized by analytical and spectral techniques (infrared, ^{1}H NMR, ^{13}C NMR, and elemental analysis).

Keywords: Benzothiazole, β-lactam, Schiff base, *cis*-2-azetidinone, Staudinger reaction.

1. Introduction

2-Azetidinones, known as β-lactams, are well known heterocyclic compounds. The synthesis of heterocyclic compounds has attracted the attention of chemists for many years because of their important biological activities. In particular, 2-azetidinone ring systems are widely found in the construction of broad-spectrum antibiotics containing penicillin cephalosporin. These antibiotics are used as chemotherapeutic agents for the treatment of microbial diseases and bacterial infections.[1–8] Synthesis and antimicrobial properties of 2-azetidinones have been studied by chemists since the 1990s, to obtain pharmacologically active compounds such as cholesterol absorption and inhibitory activity.[9]

Staudinger ketene-imine reaction is the most common method for the synthesis of 2-azetidinones.[10] In this reaction, ketene is formed thermally or photochemically using acid chlorides and triethylamine.[11–12] Although this reaction is generally known as a [2+2] cycloaddition, the reaction is generally described as a stepwise reaction. The first step of the reaction involves the nucleophilic attack of the imine nitrogen on the sp hybridized carbon of a keten to form the zwitterion intermediate. Then follows the formation of azetidinone ring. The resulting stereochemistry of azetidinone may be *cis*, *trans* or a mixture of both isomers. In the literature, it has been reported that the *cis* product is obtained in higher yield than the *trans* product in this reaction, because of consisting of ketene before the zwitterion intermediate.[13] Also, the group attached to the nitrogen atom in the azetidinone ring determines the stereochemistry of 2-azetidinone. Stereochemistry of 2-azetidinones is important for their biological activity.[3] For example, penicillin and cephalosin antibiotics are *cis* isomer.

In this study, unlike the literature, we designed the synthesis of *cis*-2-azetidinone products by the Staudinger reaction, using electron-donating imine and electron-withdrawing ketene, in apolar solvent environment and adding additives.

2. Experimental

2. 1. General Chemistry Methods

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 Sspectrophotometer at Eskişehir Osmangazi University, Faculty of Art and Sciences, Department of Chemistry. ^{1}H NMR and ^{13}C NMR 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). Chemical shifts are given as δ values in ppm and coupling constants (*J*) are reported in Hertz (Hz) units. Reagents and solvents used for the synthesis were purchased from commercial sources. Solvents were distilled with an appropriate drying agent. Melting points of the synthesized substances were determined by a Gallenkamp device.

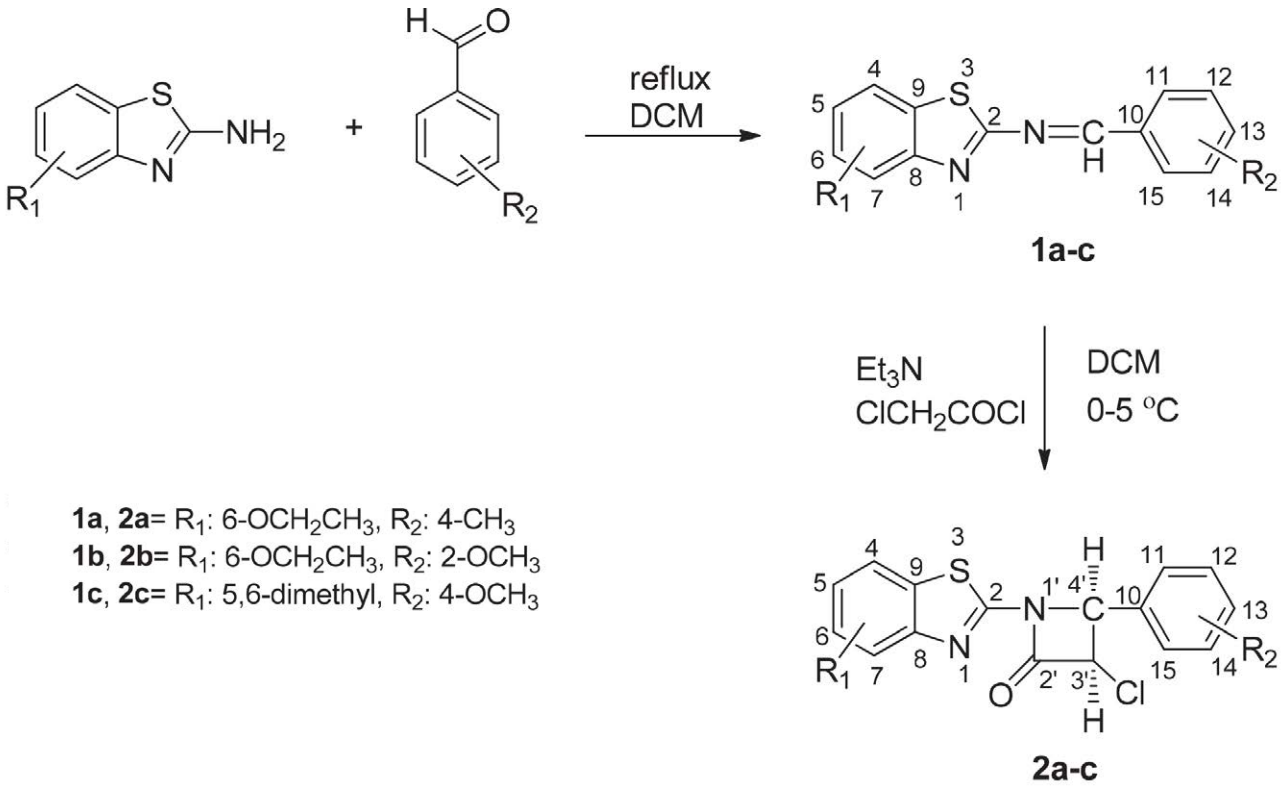
2. 2. General Procedure for the Synthesis of Schiff Bases 1a–c

Schiff bases were synthesized by modifying the procedure suggested by Vicini *et al.*[14] The mixture of 6-ethoxy-2-aminobenzothiazole (0.35 g, 1.8 mmol) and *para*-methyl benzaldehyde (0.107 mL, 0.9 mmol) in dichloromethane (40 mL) was refluxed at 70 °C for 6 h. The liquid fraction was evaporated under reduced pressure. The resultant solid **1a** was recrystallized from ethylacetate:hexane (1:3) solvent system (Scheme 1). Compounds **1b** and **1c** were also synthesized by the same method.

2. 3. General Procedure for the Synthesis of *cis*-2-Azetidinones 2a–c

cis-2-Azetidinones were synthesized by modifying the suggested procedure by Mogilaiah *et al.*[15] Chloroacetyl chloride (0.019 mL, 1.5 mmol) was added dropwise within a period of 30 minute to the dichloromethane solution of Et_3N (0.066 mL, 3 mmol), at 0–5 °C cooled, and stirred. Then, the compound **1a** (0.019 g, 0.16 mmol) was added to this well-stirred cold solution. The reaction mixture was then stirred for an additional 9 h at 0–5 °C and left at room temperature for 6 h. The reaction mixture was extracted with, respectively, 10 mL of saturated $NaHCO_3$ solution, 10 mL of 10% HCl and 10 mL of brine. The organic phase was dried with Na_2SO_4. The resultant mixture was concentrated, filtered, and then dried. The product **2a** thus obtained was purified by column chromatography over silica gel using mixture of 20% ethyl acetate, 20% dichloromethane, 60% hexane as the eluent (Scheme 1). Compounds **2b** and **2c** were also synthesized by the same method.

6-Ethoxybenzothiazol-2-yl-(4-methylbenzylidene) amine (1a). This compound was obtained as a yellow solid, yield 0.21 g (79%), m.p. 131–132 °C. FT-IR (KBr) ν_{max} 1595 (–CH=N–), 1554, 1481, 1440 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.40 (t, *J* = 6.93 Hz, 3H, $OCH_2\underline{CH_3}$), 3.03 (s, 3H, $PhCH_3$), 4.10 (q, *J* = 6.90 Hz, 2H, $O\underline{CH_2}CH_3$), 7.10 (dd, *J* = 2.36, 8.86 Hz, 1H, H-5), 7.40 (d, *J* = 7.90 Hz, 2H, H-12 and H-14), 7.64 (d, *J* = 2.29 Hz, 1H, H-7), 7.82 (d, *J* = 8.89 Hz, 1H, H-4), 8.00 (d, *J* = 7.94 Hz, 2H, H-11 and H-15), 9.10 (s, 1H, CH=N) (Fig. S1). ^{13}C NMR (DMSO-d_6) δ 15.11, 21.86, 64.21, 106.19, 116.54, 123.70, 130.28, 130.46, 132.60, 135.88, 144.37, 145.98, 157.00, 166.42, 169.40 (Fig. S2) (Spectra of the compounds are given in supplementary materials). Anal. calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.95; H, 5.53; N, 9.38; S, 10.80.



Scheme 1. Synthesis of Schiff bases **1a–c** and *cis*-2-azetidinones **2a–c**.

6-Ethoxybenzothiazol-2-yl-(2-methoxybenzylidene) amine (1b). This compound was obtained as a yellow solid, yield 0.232 g (82%), m.p. 138–139 °C. FT-IR (KBr) ν_{max} 1597 (–CH=N–), 1564, 1492, 1440 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.40 (s, 3H, $PhCH_3$), 4.00 (t, J = 6.92 Hz, 3H, $\underline{CH_3}CH_2O$), 4.10 (q, J = 6.89 Hz, 2H, $CH_3\underline{CH_2}O$), 7.10 (dd, J = 2.48, 8.86 Hz, 1H, H-5), 7.14 (d, J = 7.52 Hz, 1H, H-12), 7.25 (d, J = 8.48 Hz, 1H, H-4), 7.62 (d, J = 2.45 Hz, 1H, H-7), 7.66 (dt, J = 7.77 Hz, 1H, H-14), 7.84 (d, J = 8.87 Hz, 1H, H-15), 8.10 (dd, J = 2.45, 7.68 Hz, 1H, H-13), 9.50 (s, 1H, CH=N) (Fig. S3). ^{13}C NMR (DMSO-d_6) δ 15.10, 59.52, 64.21, 106.16, 112.90, 116.60, 121.48, 122.88, 123.79, 127.93, 135.91, 145.99, 156.98, 160.95, 169.80 (Fig. S4). Anal. calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.9; S, 10.26. Found: C, 65.50; H, 5.30; N, 8.95; S, 10.30.

5,6-Dimethylbenzothiazol-2-yl-(4-methoxybenzylidene)amine (1c). This compound was obtained as a yellow solid, yield 0.217 (81%), m.p. 142–143 °C. ^1H NMR (DMSO-d_6) δ 2.37 (s, 6H, Bzt. CH_3), 2.43 (s, 3H, $PhOCH_3$), 7.41 (d, J = 7.98 Hz, 2H, H-12 and H-14), 7.73 (s, 1H, H-4), 7.82 (s, 1H, H-7), 7.99 (d, J = 8.02 Hz, 2H, H-11 and H-15), 9.10 (s, 1H, CH=N). ^{13}C NMR (DMSO-d_6) δ 30.15, 30.70, 40.70, 122.46, 123.46, 130.29, 130.54, 131.78, 132.54, 134.95, 135.99, 139.31, 144.49, 150.48, 166.91, 170.84.

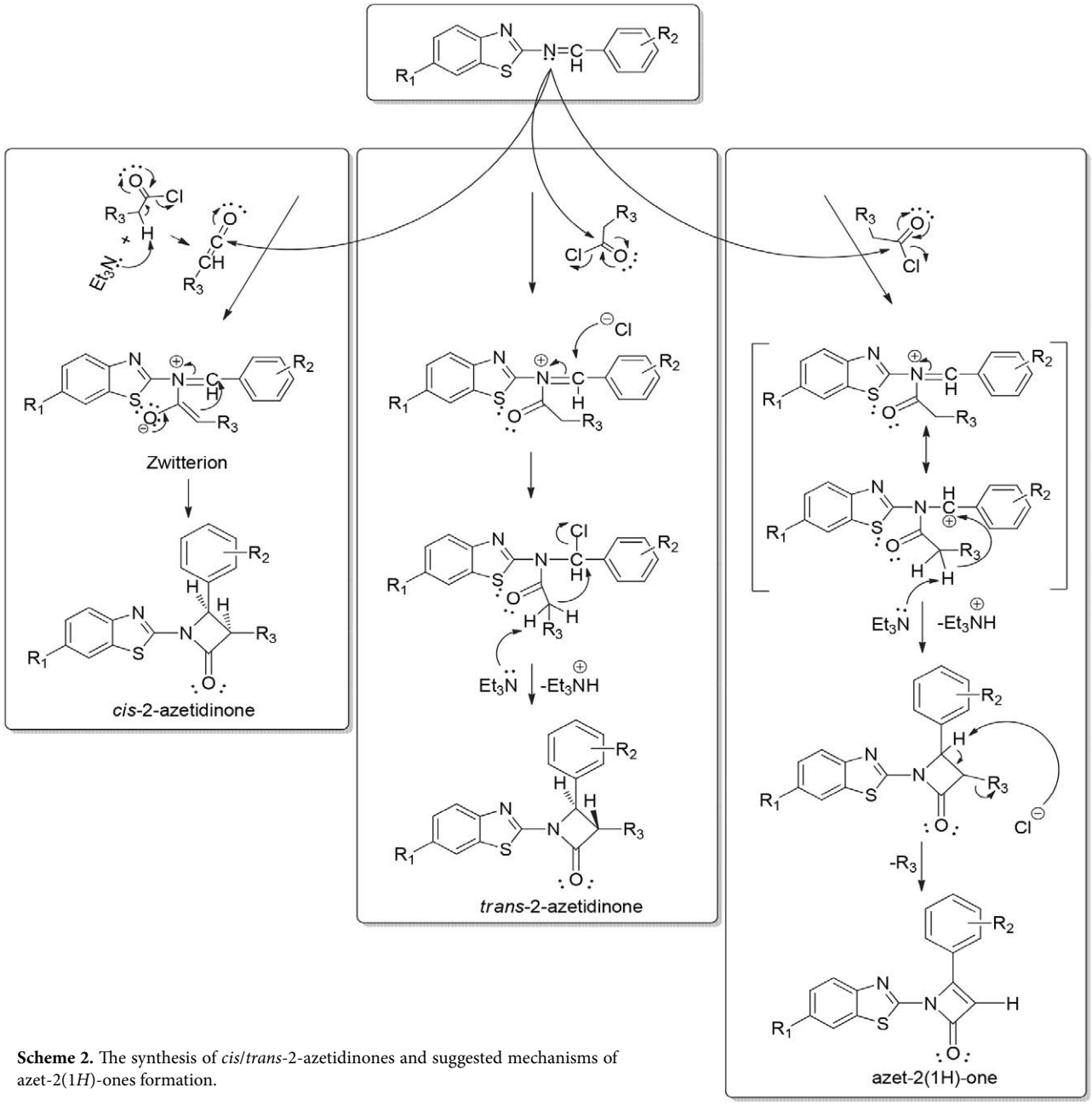
3-Chloro-1-(6-ethoxybenzothiazol-2-yl)-4-*para*-tolylazetidin-2-one (2a). This compound was obtained as a white solid, yield 0.016 g (65%), m.p. 220–221 °C. FT-IR (KBr) ν_{max} 2976, 2925 (C–H), 1666 (C=O), 1595 and 1517 cm^{-1} (Aryl C-H). ^1H NMR (DMSO-d_6) δ 1.35 (t, J = 5.10 Hz, 3H, $\underline{CH_3}CH_2O$), 2.30 (s, 3H, $PhCH_3$), 4.07 (q, J = 6.95 Hz, 2H, $CH_3\underline{CH_2}O$), 5.17 (d, J = 8.82 Hz, 1H, H-3'), 5.29 (d, J_{cis} = 8.8 Hz, 1H, H-4'), 6.93 (dd, J = 2.41, 9.12 Hz, 1H, H-5), 7.20 (d, J =7.96 Hz, 2H, H-12 and H-14), 7.27 (d, J = 8.09 Hz, 2H, H-11 and H-15), 7.39 (d, J = 2.4 Hz, 1H, H-7), 8.04 (d, J = 8.89 Hz, 1H, H-4) (Fig. S5). ^{13}C NMR (DMSO-d_6) δ 15.06, 22.22, 29.45, 64.35, 65.48, 109.3, 113.33, 124.48, 127.88, 128.96, 129.64, 132.30, 137.91, 163.09 (Fig. S6). Anal. calcd for $C_{19}H_{17}ClN_2O_2S$: C, 61.20; H, 4.60; N, 7.51; S, 8.60. Found: C, 61.03; H, 4.62; N, 7.53; S, 8.67.

3-Chloro-1-(6-ethoxybenzothiazol-2-yl)-4-(2-methoxyphenyl)azetidin-2-one (2b). This compound was obtained as a white solid, yield 0.0731 g (84%), m.p. 228–229 °C. FT-IR (KBr) ν_{max} 1658 (C=O), 1593, 1552, 1514, 2925, 2854 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.35 (t, J = 6.85 Hz, 3H, $\underline{CH_3}CH_2O$), 2.90 (s, 3H, OCH_3), 4.50 (q, J = 6.95 Hz, 2H, $CH_3\underline{CH_2}O$), 5.43 (d, J_{cis} = 5.24 Hz, 1H, H-3'), 5.10 (d, J_{cis}= 5.3 Hz, 1H, H-4'), 6.92 (dd, J = 2.7, 9.02 Hz, 1H, H-12), 6.97 (t, J = 7.43 Hz, 1H, H-11), 7.09 (d, J = 8.12 Hz, 1H, H-4), 7.19 (dd, J = 1.58, 7.53 Hz, 1H, H-5), 7.36 (dd, J = 2.35, 8.06 Hz, 1H, H-10), 7.39 (d, ^4J = 0.95 Hz, 1H, H-7), 8.05 (d, J = 9.02 Hz, 1H, H-13) (Fig. S7). ^{13}C NMR (DMSO-d_6, ppm): δ 15.10, 56.52, 64.21, 106.16, 112.90, 116.60, 121.48, 122.88, 123.79, 127.93, 135.91, 145.99, 156.98, 160.95, 160.98, 169.80 (Fig. S8). Anal. calcd for $C_{19}H_{17}ClN_2O_3S$: C, 58.68; H, 4.41; N, 7.20; S, 8.25. Found: C, 58.70; H, 4.35; N, 7.17; S, 8.31.

3-Chloro-1-(5,6-dimethylbenzothiazol-2-yl)-4-(4-methoxyphenyl)azetidin-2-one (2c). This compound was obtained as a white solid, yield 0.103 g (82%), m.p. 274–275 °C. FT-IR (KBr) ν_{max} 1651 (C=O), 2854 and 2923 cm^{-1} (C–H). ^1H NMR (DMSO-d_6) δ 2.40 (s, 6H, CH_3), 3.81 (s, 3H, $PhOCH_3$), 4.13 (d, J_{cis} = 5.34 Hz, 1H, H-3'), 4.15 (d, J_{cis} = 5.51 Hz, 1H, H-4'), 7.20 (d, J = 8.06 Hz, 2H, H-15 and H-11), 7.7 (d, J = 8.01 Hz, 2H, H-12 and H-14), 8.20 (s, 1H, H-4), 8.87 (s, 1H, H-7) (Fig. S9). Anal. calcd for $C_{19}H_{17}ClN_2O_2S$: C, 61.20; H, 4.60; N, 7.51; S, 8.60. Found: C, 61.03; H, 4.85; N, 7.53; S, 8.67.

3. Results and Discussion

Azetidinones were prepared via the Staudinger reaction. The Staudinger reaction involves the nucleophilic attack of an imine on a ketene, leading to a zwitterion intermediate, which then undergoes stepwise ring closure to yield the β-lactam ring.[16] Stereoselectivity depends directly on the competition between ring closure and isomerization of the imine moiety in the zwitterion intermediate. In the Staudinger reaction, ketene formation prior to the cyclocondensation results in the formation of the β-lactam product as the major *cis* form. However, the direct reaction of imine with acid chloride gives the exclusive or major product of *trans*-β-lactam[17,18] (Scheme 2). The competition between the isomers depends on many factors, such as the electronic effect of the ketene substituents and the steric hindrance of the N substituent of imines. Another factor influencing the Staudinger reaction is solvents, possibly affecting the stability and half-life of the zwitterion intermediate, causing changes in stereoselectivity.[18] In our previous study, the Staudinger reactions were carried out at different temperatures using different equivalents, differently substituted Schiff bases, and different acid chloride derivatives. *cis*-2-Azetidinones were obtained in good yields using the concentration of acid chloride derivates (1.5–3 eq) and triethylamine (2–3 eq). However, some unexpected azet-2(1*H*)-ones were synthesized by changing the order of addition of the reactants and concentrations of triethylamine (7.4–15 eq) and chloroacetyl chloride (2–3.7 eq) without changing other reaction conditions such as temperature and solvent type.[19] We proposed that the formation of azet-2(1*H*)-ones depends on the concentration of triethylamine, and the suggested mechanism of azet-2(1*H*)-ones formation is given in Scheme 2. In the first step, the novel Schiff bases **1a–c** are synthesized by the reaction of benzaldehyde and the substituted benzothiazole in dichloromethane solution (DCM). The reaction time was 6 hours. These novel Schiff bases **1a–c** were iso-



Scheme 2. The synthesis of *cis*/*trans*-2-azetidinones and suggested mechanisms of azet-2(1*H*)-ones formation.

lated with yields ranging from 79–82% (Scheme 1). Among the Schiff bases prepared **1a**–**c**, the compound **1b** was isolated with the highest efficiency (82%), which is explained as follows: Electron-donating groups attached to the 2-aminobenzothiazole ring increase the reactivity of the amino group for nucleophiles and accelerate the formation of Schiff bases. The structures of Schiff bases were confirmed by ^{1}H NMR, ^{13}C NMR and FT-IR spectra. In the FT-IR spectrum for compound **1b**, the signal observed at 1597 cm^{-1} was assigned as the imine (–CH=N–) group. In the ^{1}H NMR spectrum of the same compound, one singlet of the methyl proton was observed at 1.40 ppm and another singlet of the protons of an imine at 9.50 ppm. (The numbering of protons is given in Scheme 1). Additionally, the signal observed as a result of the long-range interaction at 7.62 ppm (^{4}J = 2.45 Hz) was marked as belonging to the H-7 proton. Likewise, at 7.66 ppm, the triplet of the doublet was assigned as belonging to the H-14 proton, while at 7.10 ppm (^{3}J = 8.86 Hz, ^{4}J = 2.48 Hz) and 8.10 ppm (^{3}J = 7.68 Hz, ^{4}J = 2.45 Hz) the doublet of the doublet was marked as belonging to the H-5 and H-13 protons, respectively. In the compound **1b**, the other three doublets at 7.14, 7.25, and 7.84 ppm were assigned the protons H-12, H-4, and H-15, respectively. The triplet and a quartet observed at 4.0 and 4.10 ppm belong to the methyl and methylene groups in the ethoxy group, respectively. In the ^{13}C

NMR spectrum of compound **1b**, 17 signals belonging to the carbons of the compound were observed and from these signals, the signal at 169.80 ppm was observed for the C=N carbon in the benzothiazole ring. The signal at 160.98 ppm was marked as belonging to the imine carbon.

Azetidinone was obtained from electron donating novel Schiff bases **1a**–**c** by Staudinger reaction in the second step as depicted in the Scheme1. In this reaction, ketene electrophiles and imine molecules can act as a nucleophile. The order of addition of chloroacetyl chloride and imine affects stereoselectivity, so ketene formation was carried out by adding chloroacetyl chloride in the presence of triethylamine before the formation of zwitterion intermediate. Thus, ketene and the resulting zwiterion intermediate were subjected to stepwise ring closure to give the β-lactam ring and producted mostly *cis*-2-azetidinones **2a**–**c**. Especially depending on the concentrations of triethylamine and chloroacetyl chloride, for example triethylamine 2–3 eq, chloroacetyl chloride 1.5–3 eq and dichloromethane as the solvent, *cis*-2-azetidinone compounds were formed in good yield**.** Based on the reference 18, the *cis*- and *trans*-2-azetidinone formation mechanism of the novel synthesized compounds is shown in Scheme 2. By mixing the imine, substituted with electron-donating substituent, and the ketene, having electron-withdrawing substituents, in a nonpolar solvent and with the addition of triethylamine at 0–5 °C in an ice bath for 9 h, almost only the single isomer *cis*-2-azetidinone was obtained with 65–84% yield. However, it is declared in the literature that imines having electron-withdrawing substituents and ketens having electron-donating substituents cause *cis*-β-lactam formation.[16] On the contrary, when the concentration of acid chloride and triethylamine is adjusted, *cis*-β-lactam stereoisomer can be obtained by the Staudinger reaction from the reaction of the imine having electron-donating substituents and from ketene, having electron-withdrawing substituents (Scheme 1).

The structure of *cis*-2-azetidinones is confirmed by ^{1}H NMR, ^{13}C NMR and FT-IR spectra. In the FT-IR spectrum of compound **2b**, the imine signal was not observed at 1597 cm^{-1}, while the strong peak observed at 1658 cm^{-1} confirmed the presence of a carbonyl group in the *cis*-2-azetidinone ring. The peaks at 2976 and 2887 cm^{-1} were marked as belonging to the aliphatic CH_3 and CH_2 groups of the imine compound, and the CH signal in the *cis*-2-azetidinone ring was also observed as a strong signal in the same region. In the ^{1}H NMR spectrum of compound **2b**, three doublet doublets at 6.92, 7.19 and 7.36 ppm due to long distance coupling have been marked as belonging to H-12, H-5 and H-10 protons, respectively. (The numbering of protons is given in Scheme 1.) Signals for protons H-11, H-4, and H-13, respectively, have been observed as a triplet at 6.97 ppm and two doublets at 7.09 and 8.05 ppm. Additionally, at 6.97, 7.09 and 8.05 ppm observed a triplet and two doublets, belong to the H-11, H-4, and H-13 protons, respectively, The value of the spin-spin coupling constant of the protons H-3' and H-4' in the 2-azetidinone cyclobutane ring determined whether the product is *cis* or *trans*. The stereoisomer of these compounds is determined by the spin-spin coupling constant of the protons in the azetidinone ring, where $J > 4.0$ Hz for the *cis* isomers, $J \leq 3.0$ Hz for the *trans* isomers,and the stereoisomer of the synthesized compounds was determined by comparing these values.[19–23] For compound **2b**, while the two doublets observed at 5.43 and 5.10 ppm were marked as belonging to the H-3' and H-4' protons in the azetidinone ring, the coupling constant values of these protons were calculated as 5.24 and 5.30 Hz. For compound **2a**, the spin-spin coupling constant of the doublets were observed at 8.82 and 8.86 Hz, respectively (Figure S5). For compound **2b**, the coupling constant of protons in the 2-azetidinone ring was found to be 5.24 and 5.30 Hz. Similarly, for compound **2c**, the coupling constant of protons in the 2-azetidinone ring was found to be 5.34 and 5.51 Hz. Based on these data, the stereoisomer of the synthesized azetidinone was determined to be *cis*-2-azetidinone.

4. Conclusions

Electron-donating substituents on the phenyl and benzothiazole rings of the Schiff bases increase the nucleophilicity of the imine nitrogen, while the electron withdrawing substituents of the chloroacetyl chloride increase the acidity of α-hydrogen, and elimination with triethylamine accelerates the formation of ketene. Ketene and imine give the intermediate zwitterion, and the presence of nitrogen and sulfur in the benzothiazole ring ionizes the imine moiety, accelerating ring closure, and *cis*-2-azetidinone is formed. As a result, contrary to what is said in the literature, when conditions such as apolar solvent, the amount of triethylamine, the electronic effect of the imine, the cold environment and the addition order of the reagents are adjusted, the keten with electron-withdrawing substituent and the imine with electron-donating substituent could produce *cis*-2-azetidinone. These *cis*-2-azetidinone derivatives have been synthesized from the reaction of the ketene source (chloroacetyl chloride) and novel Schiff bases in the presence of triethylamine via Staudinger reaction, in good yields (65–84%). The concentration of chloroacetyl chloride and triethylamine has been found to affect the reaction mechanism of 2-azetidinone formation. We concluded that *cis*-2-azetidinones were formed in good yields using 1 eq. of a Schiff base, 3 eq. of Et_3N and 1.5 eq. of chloroacetyl chloride in dichloromethane solution at 0–5 °C.

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Povzetek

S pomočjo cikloadicijske reakcije iminov **1a**–**c** in kloroacetil klorida v suhem diklorometanu pri 0–5 °C z dodatkom trietilamina smo uspešno pripravili serijo novih *cis*-2-azetidinonov **2a**–**c**. S cikloadicijo Schiffovih baz na kloroacetil klorid so kot ustrezni glavni stereoizomeri nastali produkti *cis*-2-azetidinoni **2a**–**c**. Pripravljene spojine smo karakterizirali z analitskim in spektroskopskimi tehnikami (infrardeča spektroskopija, ^{1}H NMR, ^{13}C NMR ter elementna analiza).