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Synthesis and isomerization of *N*-α-aza-heteroaryl-β-lactams

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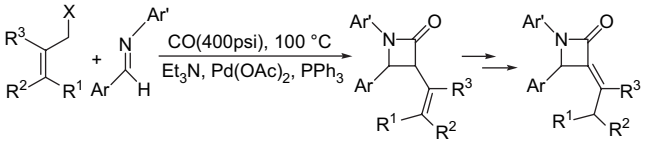
Abstract—The [2+2] carbonylative cycloaddition of *N*-α-aza-heteroaryl substituted imines with allyl bromide led partially to β-lactams, which underwent isomerization to the more stable α,β-unsaturated carbonyl compound. Pyrimidinone derivatives together with doubly unsaturated amides represent the remaining isolated products. The strong electron-withdrawing effect of the two α-aza-heterocycles linked to the nitrogen atom and to the C4 of the 2-azetidinone structure could give a ring expansion, through a 2-azetinone intermediate that affords the pyrimidinone compounds. The substituted amides, instead, should result from a ring-opening reaction of the β-lactam.

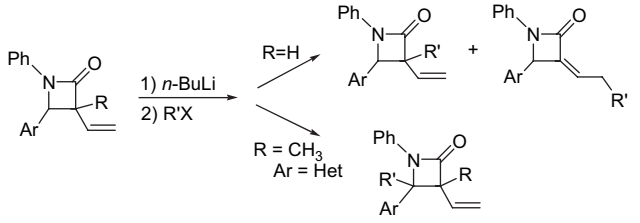
1. Introduction

β-Lactams show a wide range of pharmacological activities and synthetic routes to such compounds continue to be developed.[1–4] The use of 2-azetidinones as starting materials in organic synthesis is based on the impressive variety of transformations that can be derived from this system. For instance, Alcaide and Almendros described the selective bond cleavage and rearrangement of the β-lactam nucleus with applications in the stereocontrolled synthesis.[5] Thus, compounds such as alkaloids,[6,7] carbohydrates[8,9] and different kinds of heterocycles[10–14] have been produced from β-lactams. Recently, we reported the stereoselective synthesis of β-lactams by an improved Pd-catalyzed [2+2] carbonylative cycloaddition of allyl halides with various imines,[15] where the catalytic species involved was Pd(0)[16] (Scheme 1). Moreover, we found that the presence of an α-aza-heterocycle attached to the iminic carbon, for example, where Ar=2-benzothiazole or 2-thiazole or 2-pyridine, led partially to β-lactams having a vinylic moiety conjugated to the carbonyl group.[16] The high electron-withdrawing effect of the α-aza-heterocycle should increase the acidity of the proton linked to C3, favouring isomerization in the presence of Et_3N.



Scheme 1.

The deprotonation and the stereoselective functionalization of the C3 carbon atom of β-lactams have been also reported by us.[17] It has been shown that the deprotonation of the C4 carbon could be achieved only with a structure showing no protons at C3 and having an α-aza-heterocycle linked at C4, which increased the acidity of the directly attached hydrogen (Scheme 2).



Scheme 2.

In order to thoroughly investigate the electron-withdrawing effect of various heterocycles linked at the different positions of the β-lactam nucleus, we thought to perform, under the same conditions, the [2+2] carbonylative cycloaddition of *N*-α-aza-heteroaryl substituted imines with allyl bromide.

Keywords: β-Lactams; Pyrimidinones; Carbonylative cycloaddition; Isomerization.
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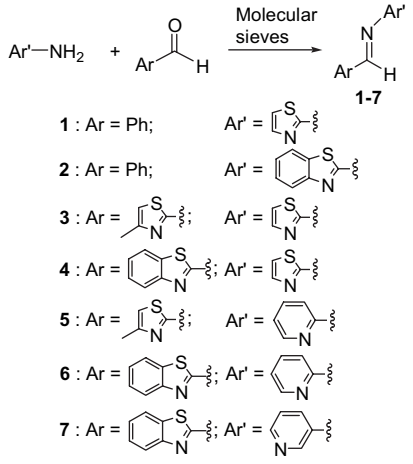
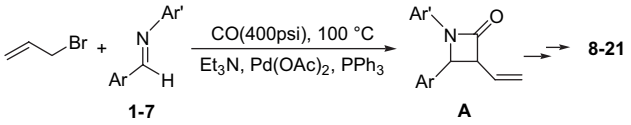
2. Results and discussion

The reacting *N*-α-aza-heteroaryl imines **1–7** were prepared by coupling reactions of the appropriate amines with the corresponding aldehydes according to the Taguchi's methodology (Scheme 3).[18]



Scheme 3.

According to previous results,[15] the [2+2] carbonylative cycloaddition of the imines **1–7** with allyl bromide under CO pressure, in the presence of Et_3N and $Pd(OAc)_2/Ph_3P$, should afford β-lactams **A** (Scheme 4).

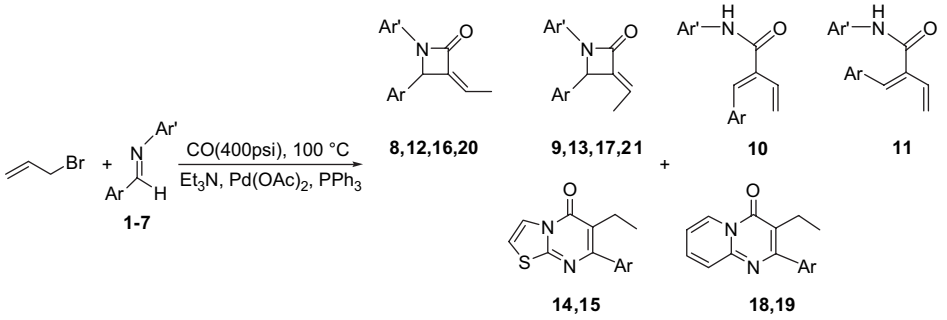


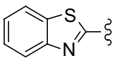
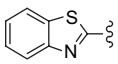
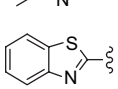
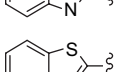
Scheme 4.

Surprisingly, such structures were not obtained but, from the reaction mixtures compounds **8–21** listed in Table 1 were isolated.

The relative configuration of the α,β-unsaturated β-lactams was assigned from their ^1H NMR spectra: the *Z* isomers displayed vinylic protons with an upfield chemical shift, whereas the *E* compounds showed a downfield chemical shift as these protons are in the deshielding region of the neighbouring carbonyl group.[19–21] The structures of compounds **10** and **11** have been assigned by ^1H NMR spectra on the basis of spectroscopic data reported in literature for analogous structures.[22] The structures of compounds **14**

Table 1. [2+2] Carbonylative cycloaddition of imines **1–7** with allyl bromide



Entry	Ar	Ar′	Total yield (%)[a]	Product distributions (%)[b]				
1	Ph		80	**8** (traces)	**9** (54)	—	**10** (24)	**11** (21)
2	Ph		85	**12** (32)	**13** (68)	—	—	—
3			97	—	—	**14** (100)	—	—
4			50	—	—	**15** (100)	—	—
5			98	**16** (traces)	**17** (traces)	**18** (99)	—	—
6			40	—	—	**19** (100)	—	—
7			30	**20** (80)	**21** (20)	—	—	—

[a] Isolated yields.
[b] Diasteromeric ratios evaluated by GC and ^1H NMR spectroscopy.

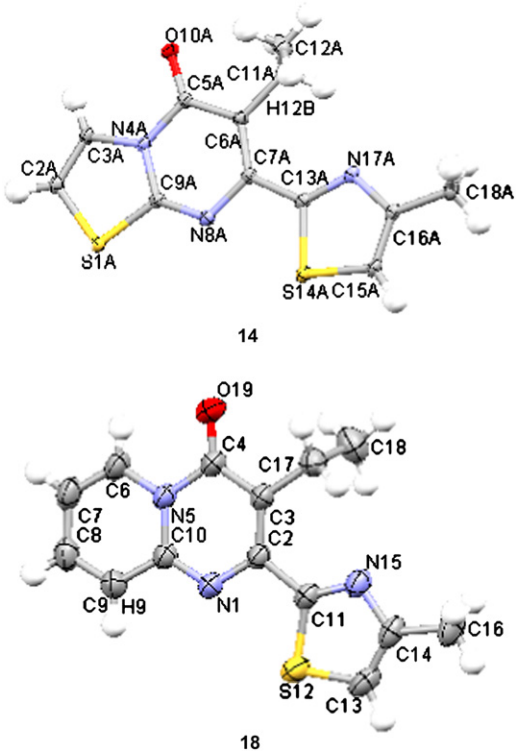
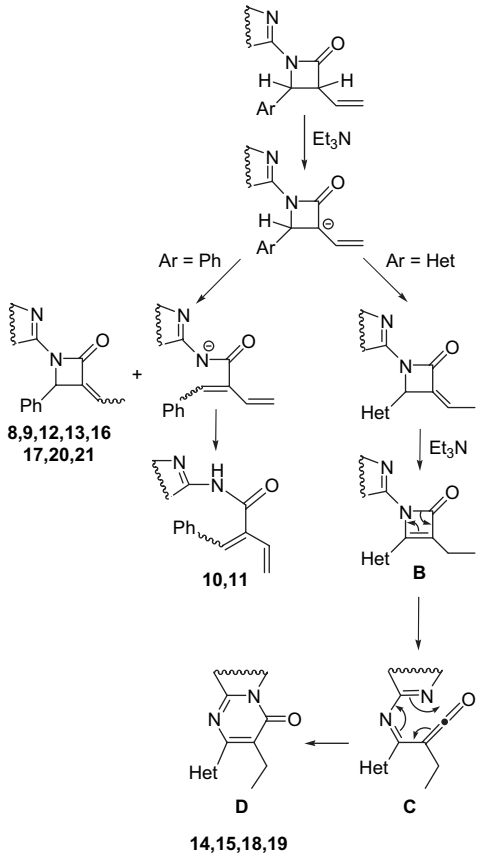


Figure 1. Molecular structure of compound **14** at 90 K, ellipsoids at 50% probability level, H atoms not to scale. Molecular structure of compound **18** at room temperature, ellipsoids at 50% probability level, H atoms not to scale.



Scheme 5.

and **18** have been assigned by X-ray[23] measurements and their molecular structures are reported in Figure 1.

The remaining structures **15** and **19** were assigned comparing the spectroscopic data with those obtained for compounds **14** and **18**.

Scheme 5 shows a possible rearrangement of the β-lactam **A**, obtained by the [2+2] carbonylative cycloaddition reaction, and leading to the compounds listed in Table 1.

Products **8**, **9**, **12**, **13**, **16**, **17**, **20** and **21** should derive from a first deprotonation of **A** at the C3, and a subsequent isomerization of the carbanion to the more stable α,β-unsaturated carbonyl compound. The generation of products **10** and **11** could be explained by a C4–N1 bond breakage in the same intermediate carbanion, which occurs under basic conditions. This latter behaviour is reported in the literature as one of the possible bond cleavages of the β-lactam nucleus.[24] The 2-azetinone **B** should result from a double isomerization: a first deprotonation at the C3 should lead to the α,β-unsaturated β-lactam, while a subsequent deprotonation at the C4 should shift the double bond inside the β-lactamic ring, affording the 2-azetinone. This behaviour could be due to the strong electron-withdrawing effect by both heterocycles directly linked to the ring. The 2-azetinone is often proposed as a short-lived intermediate,[25–28] which evolves to a ketene, for which only in few cases has it been isolated and characterized.[29,30] The high antiaromatic character of this small ring, in fact, does not confer enough thermal stability to the molecule, which rapidly leads to the ketenic form initially, and then finally to the pyrimidinonic product. The proposed relative stability of the three forms is confirmed by free energy quantum chemical calculations of the structures **B**, **C** and **D**, respectively. Calculations were performed at the 6-311G*/B3LYP level (in the gas phase).[31] According to the calculations, the ketenic structure **C** is only 5.3 kcal/mol more stable than **B**, which is strongly antiaromatic, while the stable structure **D** has a free energy 36.1 kcal/mol lower than **C**.

The transformation of **B** to the ketene **C** first, and then to the pyrimidinone **D**, could be related to the presence of two α-aza-heterocycles linked to the nitrogen atom and to the C4 of the 2-azetidinone structure, respectively. A similar rearrangement has been recently described by Alajarin and co-workers on 4-acyloxy-β-lactams resulting in a final cycle broadening, through a 2-azetinone intermediate formation and C2–N1 bond cleavage.[32] Moreover, when C4 does not link a heterocycle (Ar=Ph), the deprotonation at C3, described above, led to a ring-opening reaction of the β-lactamic systems, the cleavage of the C4–N1 bond affording the doubly unsaturated amides **10** and **11**.

3. Conclusion

In summary, we have prepared *N*-α-aza-heteroaryl β-lactams, which underwent isomerization. Novel α,β-unsaturated 2-azetidinones were prepared together with new pyrimidinone derivatives and doubly unsaturated amides. The pyrimidinone compounds seem to be produced from ring expansion

of the rearranged β-lactams through a 2-azetinone intermediate. This behaviour has been observed only for structures showing two heterocyclic moieties linked to the nitrogen atom and to the C4 carbon, respectively. The unsaturated amides are the result of a ring-opening reaction of the β-lactam systems having the heterocycle linked only to the nitrogen atom. The electron-withdrawing effect of the various heterocycles linked at the different positions of the β-lactam nucleus has been thoroughly exploited. A mechanism has been proposed through structures of different relative stabilities, confirmed by free energy quantum chemical calculations. The selective bond cleavage and the rearrangement of the β-lactam nucleus afforded novel structures of potential use in the organic synthesis of biologically and pharmacologically interesting compounds.

4. Experimental

4.1. General

THF, triethylamine, palladium(II)acetate, triphenyl-phosphine, allyl bromide, 4-formylmorpholine, 2-pyridinecarboxaldehyde, 2-aminothiazole, 2-aminopyridine, 3-aminopyridine, 4-methyl-thiazole, 2-aminothiophenol, glycolic acid and all other chemicals were of commercial grade (Aldrich) and were used without further purification. Benzaldehyde and allyl bromide of commercial grade (Aldrich), were purified by distillation prior to use. Petroleum ether refers to the 40–60 °C boiling fraction. The ^{1}H and the ^{13}C NMR spectra were recorded on a Bruker Avance 400 apparatus (400.13 MHz and 100.62 MHz, for ^{1}H and ^{13}C, respectively) with $CDCl_3$ as solvent and TMS as internal standard (δ=7.24 for ^{1}H spectra; δ=77.0 for ^{13}C spectra). The IR spectra were recorded with an FT-IR spectrophotometer Digilab Scimitar Series FTS 2000. GC–MS analyses were performed with an Agilent Technologies 6850 series II gas chromatograph (5% phenyl-polymethylsiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with a 5973 Network mass-selective detector operating at 70 eV (EI). The electrospray ionization (HR-ESI-MS) experiments were carried out in a hybrid Q*q*TOF mass spectrometer (PE SCIEX-QSTAR) equipped with an ion spray ionization source. MS (+) spectra were acquired by direct infusion (5 μL/min) of a solution containing the appropriate sample (10 pmol/μL), dissolved in a solution 0.1% acetic acid, methanol/water 50:50 at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50 and 25 V relative to ground, respectively. Elemental analyses were performed on a Carlo Erba C, H, N analyzer. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatographies were performed on silica gel (63–200 μm) using petroleum ether/diethyl ether (Et_2O) mixtures as eluents.

4.2. General procedure for the preparation of *N*-α-aza-heteroaryl imines 1–7

The *N*-α-aza-heteroaryl imines were prepared by coupling reactions of 1 mmol of the appropriate amine with the corresponding aldehyde (1 mmol) in anhydrous Et_2O, in the presence of 7 g of molecular sieves (Aldrich, 4 Å, 1.6 mm pellets) for 24 h, according to Taguchi's method.[18]

4.2.1. Benzylidene-thiazol-2-yl-amine 1. Yield 150 mg (80%), yellow solid, mp 116–117 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 7.23 (d, J=3.5 Hz, 1H), 7.46–7.56 (m, 3H), 7.68 (d, J=3.5 Hz, 1H), 7.97–7.99 (m, 2H), 9.04 (s, 1H). ^{13}C NMR (100.62 MHz): δ 118.3, 128.9, 129.8, 132.6, 135.0, 141.4, 163.3, 173.1, 192.0. GC–MS (70 eV) *m*/*z* (rel int.): 188 (96) M^+, 187 (100), 161 (10), 104 (14), 85 (24), 58 (42). IR ($CHCl_3$): 3060, 3020, 2997, 1607, 1577, 1484, 1451, 1365, 1312, 1194, 1135 cm^{-1}. Anal. Calcd for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88. Found: C, 63.86; H, 4.26; N, 14.86.

4.2.2. Benzothiazol-2-yl-benzylidene-amine 2. Yield 202 mg (85%), yellow solid, mp 82–84 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 7.35 (t, J=8.2 Hz, 1H), 7.46–7.63 (m, 4H), 7.84 (d, J=8.0 Hz, 1H), 7.99 (d, J=7.9 Hz, 1H), 8.03 (d, J=7.0 Hz, 2H), 9.10 (s, 1H). ^{13}C NMR (100.62 MHz): δ 121.7, 123.1, 125.1, 126.4, 129.0, 130.2, 133.2, 135.0, 137.5, 153.1, 166.1, 172.0. GC–MS (70 eV) *m*/*z* (rel int.): 238 (47) M^+, 237 (100), 211 (11), 210 (12), 135 (16), 108 (13). IR ($CHCl_3$): 3060, 3001, 2980, 1605, 1315, 1150 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.75. Found: C, 70.50; H, 4.25; N, 11.80.

4.2.3. (4-Methyl-thiazol-2-yl-methylene)-thiazol-2-yl-amine 3. Yield 203 mg (97%), yellow solid, mp 80–82 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 2.56 (s, 3H), 7.18 (s, 1H), 7.31 (d, J=3.4 Hz, 1H), 7.73 (d, J=3.4 Hz, 1H), 9.16 (s, 1H). ^{13}C NMR (100.62 MHz): δ 17.1, 119.2, 119.6, 142.0, 155.2, 155.8, 166.7, 171.2. GC–MS (70 eV) *m*/*z* (rel int.): 209 (100) M^+, 182 (52), 125 (73), 111 (55), 99 (20), 72 (60). IR ($CHCl_3$): 3019, 2977, 2825, 1522, 1423 cm^{-1}. Anal. Calcd for $C_8H_7N_3S_2$: C, 45.91; H, 3.37; N, 20.08. Found: C, 45.98; H, 3.36; N, 20.15.

4.2.4. Benzothiazol-2-yl-methylene-thiazol-2-yl-amine 4. Yield 196 mg (80%), yellow solid, mp 172–174 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 7.39 (d, J=3.4 Hz, 1H), 7.51–7.58 (m, 2H), 7.78 (d, J=3.4 Hz, 1H), 7.97 (d, J=7.5 Hz, 1H), 8.16 (d, J=7.6 Hz, 1H), 9.34 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 120.6, 122.2, 124.7, 126.8, 127.8, 135.9, 142.3, 154.2, 155.9, 165.8, 170.7. GC–MS (70 eV) *m*/*z* (rel int.): 245 (100) M^+, 218 (41), 161 (24), 135 (19), 108 (19). IR ($CHCl_3$): 3067, 2999, 2928, 2857, 1698, 1586, 1477, 1262 cm^{-1}. Anal. Calcd for $C_{11}H_7N_3S_2$: C, 53.85; H, 2.88; N, 17.13. Found: C, 53.76; H, 2.85; N, 17.10.

4.2.5. (4-Methyl-thiazol-2-yl-methylene)-pyridin-2-yl-amine 5. Yield 199 mg (98%), yellow solid, mp 66–67 °C (petroleum ether). ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 7.11 (s, 1H), 7.21 (dd, J=5.0, 7.0 Hz, 1H), 7.37 (d, J=7.9 Hz, 1H), 7.76 (t, J=7.9 Hz, 1H), 8.51 (d, J=5 Hz, 1H), 9.3 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 17.1, 118.0, 120.3, 122.7, 138.2, 149.0, 155.3, 155.5, 159.5, 165.9. GC–MS (70 eV) *m*/*z* (rel int.): 203 (77) M^+, 175 (8), 158 (19), 125 (24), 79 (100), 78 (71). IR ($CHCl_3$): 3057, 2992, 2927, 1689, 1589, 1510, 1428, 1241 cm^{-1}. Anal. Calcd for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N, 20.67. Found: C, 59.15; H, 4.48; N, 20.62.

4.2.6. Benzothiazol-2-yl-methylene-pyridin-2-yl-amine 6. Yield 232 mg (97%), yellow solid, mp 140–141 °C (petroleum ether). ^{1}H NMR ($CDCl_3$): δ 7.24–7.27 (m, 1H), 7.42–7.60 (m, 3H), 7.80 (td, J=1.8, 7.7 Hz, 1H), 7.95 (d, J=7.8 Hz, 1H), 8.15 (d, J=7.9 Hz, 1H), 8.55 (d, J=3.5 Hz, 1H), 9.50 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 120.9, 122.1, 123.3, 124.5, 126.5, 127.0, 135.6, 138.2, 149.1, 154.1, 156.3, 159.0, 167.0. GC–MS (70 eV) *m/z* (rel int.): 239 (88) M^+, 238 (25), 211 (22), 186 (4), 135 (20), 79 (100), 78 (50). IR ($CHCl_3$): 3063, 2998, 2860, 1698, 1615, 1587, 1485, 1460, 1436, 1320, 1237 cm^{-1}. Anal. Calcd for $C_{13}H_9N_3S$: C, 65.25; H, 3.79; N, 17.56. Found: C, 65.30; H, 3.80; N, 17.58.

4.2.7. Benzothiazol-2-yl-methylene-pyridin-3-yl-amine 7. Yield 225 mg (94%), yellow solid, mp 165–167 °C (petroleum ether). ^{1}H NMR ($CDCl_3$): δ 7.37 (dd, J=4.7, 8.0 Hz, 1H), 7.47–7.56 (m, 2H), 7.63 (d, J=8.0 Hz, 1H), 7.95 (d, J=8.0 Hz, 1H), 8.13 (d, J=8.0 Hz, 1H), 8.56 (d, J=4.7 Hz, 1H), 8.63 (d, J=2.2 Hz, 1H), 8.82 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 122.1, 123.8, 124.4, 126.7, 127.1, 127.7, 135.5, 143.2, 145.4, 148.7, 153.7, 155.2, 166.4. GC–MS (70 eV) *m/z* (rel int.): 239 (41) M^+, 238 (100), 212 (27), 186 (7), 135 (12), 78 (22). IR ($CHCl_3$): 3065, 2994, 2860, 1699, 1622, 1498, 1475, 1420, 1319, 1240 cm^{-1}. Anal. Calcd for $C_{13}H_9N_3S$: C, 65.25; H, 3.79; N, 17.56. Found: C, 65.18; H, 3.76; N, 17.50.

4.3. General procedure for the preparation of compounds 8–21

A mixture of 1.0 mmol of **1–7**, 1.5 mmol of allyl bromide, 0.08 mmol of PPh_3, 0.02 mmol of $Pd(OAc)_2$ and 2 mmol of Et_3N were dissolved in 10 mL of solvent (THF) and placed in a 45 mL autoclave. The autoclave was purged, pressurized (400 psi of CO), and then heated to 100 °C for 18–65 h. The reaction was then cooled to room temperature, worked up by addition of water (15 mL) and extracted with Et_2O (3×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O=7/3) to afford the pure products (**8–21**); yields: 30–98%.

4.3.1. (*Z*)-3-Ethylidene-4-phenyl-1-thiazol-2-yl-azetidin-2-one 8. Traces measured by GC–MS (70 eV) *m/z* (rel int.): 256 (100) M^+, 241 (14), 227 (24), 179 (95), 129 (36), 115 (25).

4.3.2. (*E*)-3-Ethylidene-4-phenyl-1-thiazol-2-yl-azetidin-2-one 9. Yield 110 mg (43%), white solid, mp 158–159 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.83 (d, J=7.4 Hz, 3H), 5.78 (s, 1H), 6.08 (d, J=5.3 Hz, 1H), 7.13 (d, J=5.3 Hz, 1H), 7.27–7.35 (m, 7H). ^{13}C NMR (100.62 MHz): δ 14.7, 61.1, 105.6, 120.6, 126.6, 126.7, 127.9, 128.8, 140.8, 142.1, 155.9, 160.0. GC–MS (70 eV) *m/z* (rel int.): 256 (100) M^+, 241 (15), 227 (26), 179 (93), 129 (34), 115 (31). IR ($CHCl_3$): 3019, 1670, 1540, 1205 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93; S, 12.51. Found: C, 65.65; H, 4.76; N, 10.89.

4.3.3. (*E*)-*N*-Thiazol-2-yl-2-benzylidene-but-3-enamide 10. Yield 49 mg (19%), yellow solid, mp 96–98 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 5.61 (d, J=11.3 Hz, 1H), 5.74 (d, J=17.9 Hz, 1H), 6.83 (ddd, J=1.2, 11.3, 17.9 Hz, 1H), 6.95 (d, J=3.6 Hz, 1H), 7.34–7.45 (m, 8H). ^{13}C NMR (100.62 MHz): δ 113.7, 122.1, 128.5, 129.1, 130.1, 130.5, 132.8, 134.7, 136.7, 137.3, 159.2, 165.9. GC–MS (70 eV) *m/z* (rel int.): 256 (44) M^+, 157 (68), 129 (85), 128 (100). IR ($CHCl_3$): 3399, 3020, 2967, 1676, 1530, 1212 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.53; H, 4.70; N, 10.96.

4.3.4. (*Z*)-*N*-Thiazol-2-yl-2-benzylidene-but-3-enamide 11. Yield 43 mg (17%), yellow solid, mp 104–108 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 5.27 (d, J=10.7 Hz, 1H), 5.29 (d, J=17.4 Hz, 1H), 6.54 (ddd, J=0.8, 10.7, 17.4 Hz, 1H), 6.70 (s, 1H), 6.96 (d, J=3.6 Hz, 1H), 7.15–7.22 (m, 6H), 7.28 (d, J=3.6 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 113.3, 117.5, 128.3, 128.5, 129.0, 133.0, 134.4, 135.3, 135.9, 136.8, 159.3, 166.4. GC–MS (70 eV) *m/z* (rel int.): 256 (38) M^+, 157 (65), 129 (85), 128 (100). IR ($CHCl_3$): 3399, 3020, 2967, 1676, 1530, 1212 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.69; H, 4.74; N, 10.87.

4.3.5. (*Z*)-1-Benzothiazol-2-yl-3-ethylidene-4-phenyl-azetidin-2-one 12. Yield 83 mg (27%), yellow solid, mp 155–156 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 2.19 (d, J=7.2 Hz, 3H), 5.41 (s, 1H), 6.21 (q, J=7.2 Hz, 1H), 7.23–7.70 (m, 8H), 8.32 (d, J=7.9 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 16.6, 66.3, 117.8, 121.7, 121.8, 125.6, 126.3, 126.9, 127.0, 127.7, 128.3, 128.4, 128.7, 140.1, 154.0, 161.9. GC–MS (70 eV) *m/z* (rel int.): 306 M^+ (100), 291 (15), 277 (25), 229 (72). IR ($CHCl_3$): 3060, 2990, 1650, 1500, 1450, 1340, 1180 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.60; N, 9.14. Found: C, 70.62; H, 4.59; N, 9.19.

4.3.6. (*E*)-1-Benzothiazol-2-yl-3-ethylidene-4-phenyl-azetidin-2-one 13. Yield 177 mg (58%), yellow solid, mp 142–144 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.87 (d, J=7.1 Hz, 3H), 5.82 (s, 1H), 7.18 (q, J=7.1 Hz, 1H), 7.29–7.59 (m, 8H), 8.33 (d, J=7.9 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 14.6, 60.3, 117.9, 121.5, 123.4, 125.5, 126.3, 126.6, 127.7, 128.8, 129.1, 135.9, 140.4, 141.2, 154.8, 161.7. GC–MS (70 eV) *m/z* (rel int.): 306 M^+ (100), 291 (15), 277 (23), 229 (70). IR ($CHCl_3$): 3060, 2990, 1650, 1500, 1450, 1340, 1180 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.60; N, 9.14. Found: C, 70.45; H, 4.58; N, 9.11.

4.3.7. 3-Ethyl-2-(4-methyl-thiazol-2-yl)-thiazolo[3,2-α]-pyrimidin-4-one 14. Yield 269 mg (97%), yellow solid, mp 169–171 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.23 (t, J=7.3 Hz, 3H), 2.54 (s, 3H), 3.32 (q, J=7.3 Hz, 2H), 6.96 (d, J=4.5 Hz, 1H), 7.08 (s, 1H), 7.95 (d, J=4.5 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 12.8, 17.5, 18.8, 111.3, 117.6, 118.8, 121.8, 148.8, 155.0, 158.4, 160.0, 166.5. GC–MS (70 eV) *m/z* (rel int.): 277 M^+ (100), 262 (18), 248 (41), 234 (59). IR ($CHCl_3$): 3123, 3007, 2970, 2931, 2873, 1661, 1561, 1520, 1341, 1194, 1062, 980, 918 cm^{-1}. Anal. Calcd for $C_{12}H_{11}N_3OS_2$: C, 51.96; H, 4.00; N, 15.15. Found: C, 51.99; H, 3.98; N, 15.20.

4.3.8. 2-Benzothiazol-2-yl-3-ethyl-thiazolo[3,2-α]pyrimidin-4-one 15. Yield 156 mg (50%), yellow solid, mp 236–238 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.30 (t, J=7.3 Hz, 3H), 3.43 (q, J=7.3 Hz, 2H), 7.01 (d, J=4.8 Hz, 1H), 7.45 (t, J=7.5 Hz, 1H), 7.53 (t, J=7.5 Hz, 1H), 7.96–8.00 (m, 2H), 8.13 (d, J=8.9 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 13.0, 19.0, 111.9, 120.9, 121.6, 121.9, 124.4, 126.0, 126.2, 136.4, 148.8, 154.7, 158.5, 159.9, 167.6. GC–MS (70 eV) *m/z* (rel int.): 313 M^+ (100), 298 (37), 284 (51), 270 (56), 186 (15). IR ($CHCl_3$): 3030, 3000, 2928, 2855, 1664, 1560, 1496, 1458 cm^{-1}. Anal. Calcd for $C_{15}H_{11}N_3OS_2$: C, 57.49; H, 3.54; N, 13.41. Found: C, 57.40; H, 3.52; N, 13.37.

4.3.9. 3-Ethylidene-4-(4-methyl-thiazol-2-yl)-1-pyridin-2-yl-azetidin-2-one 16 and 17. Traces measured by GC–MS (70 eV) *m/z* (rel int.): 271 M^+ (47), 256 (24), 242 (88), 228 (100), 78 (51).

4.3.10. 3-Ethyl-2-(4-methyl-thiazol-2-yl)-pyrido[1,2-α]-pyrimidin-4-one 18. Yield 265 mg (98%), yellow solid, mp 149–150 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.27 (t, J=7.3 Hz, 3H), 2.54 (d, J=0.8 Hz, 3H), 3.41 (q, J=7.3 Hz, 2H), 7.01–7.05 (m, 1H), 7.08 (q, J=0.8 Hz, 1H), 7.57–7.60 (m, 2H), 8.95–8.97 (m, 1H). ^{13}C NMR (100.62 MHz): δ 12.8, 17.5, 19.5, 114.7, 117.6, 118.1, 126.1, 126.9, 134.6, 148.0, 149.7, 154.8, 159.3, 167.3. GC–MS (70 eV) *m/z* (rel int.): 271 M^+ (89), 256 (29), 242 (76), 228 (100), 78 (81). IR ($CHCl_3$): 3009, 2971, 2930, 2873, 1666, 1637, 1538, 1489, 1243 cm^{-1}. Anal. Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.48. Found: C, 61.85; H, 4.80; N, 15.53.

4.3.11. 2-Benzothiazol-2-yl-3-ethyl-pyrido[1,2-α]pyrimidin-4-one 19. Yield 123 mg (40%), yellow solid, mp 217–218 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.34 (t, J=7.3 Hz, 3H), 3.52 (q, J=7.3 Hz, 2H), 7.01–7.11 (m, 1H), 7.44 (t, J=7.3 Hz, 1H), 7.52 (t, J=7.0 Hz, 1H), 7.66 (d, J=3.5 Hz, 2H), 7.98 (d, J=8.0 Hz, 1H), 8.14 (d, J=8.0 Hz, 1H), 9.01 (d, J=7.3 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 13.1, 19.7, 115.2, 120.0, 121.5, 124.4, 125.9, 126.1, 126.4, 127.1, 134.9, 136.5, 148.1, 149.8, 154.8, 159.4, 168.6. GC–MS (70 eV) *m/z* (rel int.): 307 M^+ (100), 292 (78), 278 (83), 264 (86), 78 (60). IR (KBr): 3100, 3060, 2973, 2924, 2874, 1662, 1632, 1536, 1483, 1210, 922, 771, 753, 729, 701 cm^{-1}. Anal. Calcd for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.35; H, 4.25; N, 13.70.

4.3.12. (*Z*)-4-Benzothiazol-2-yl-3-ethylidene-1-pyridin-3-yl-azetidin-2-one 20. Yield 24% (evaluated by GC analysis of the crude product), brown oil. ^{1}H NMR (400.13 MHz): δ 2.16 (d, J=7.2 Hz, 3H), 5.87 (s, 1H), 6.03 (q, J=7.2 Hz, 1H), 7.10–7.24 (m, 1H), 7.43 (t, J=7.2 Hz, 1H), 7.52 (t, J=8.0 Hz, 1H), 7.83–7.87 (m, 2H), 8.06 (d, J=8.2 Hz, 1H), 8.31–8.34 (m, 1H), 8.68 (d, J=2.0 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 29.7, 60.4, 122.0, 123.5, 123.80, 123.83, 126.0, 126.5, 131.1, 134.2, 135.1, 138.27, 139.3, 145.4, 153.0, 161.0, 168.2. GC–MS (70 eV) *m/z* (rel int.): 307 M^+ (100), 278 (48), 186 (67), 78 (18). IR ($CHCl_3$): 3064, 2992, 2927, 2855, 1757, 1486, 1435, 1366 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{17}H_{13}N_3OS$: 307.0781, $[M+H]^+$; found: 307.0790.

4.3.13. (*E*)-4-Benzothiazol-2-yl-3-ethylidene-1-pyridin-3-yl-azetidin-2-one 21. Compound characterized only by ^{1}H NMR as it was isolated in low quantity containing an inseparable mixture of the two *Z* and *E* isomers (**20**+**21**). Yield 6% (evaluated by GC analysis of the crude product). ^{1}H NMR (400.13 MHz): δ 1.91 (d, J=7.0 Hz, 3H), 7.55 (q, J=7.0 Hz, 1H), 7.10–7.24 (m, 1H), 7.43 (t, J=7.2 Hz, 1H), 7.52 (t, J=8.0 Hz, 1H), 7.83–787 (m, 2H), 8.06 (d, J=8.2 Hz, 1H), 8.31–8.34 (m, 1H), 8.68 (d, J=2.0 Hz, 1H). GC–MS (70 eV) *m/z* (rel int.): 307 M^+ (100), 278 (53), 186 (72), 78 (14).

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