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Synthesis of 4-aryl-azetidinones *via* intramolecular alkylation of nucleophilic arenes using acyliminium cations

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The acyliminium cations derived from 4-vinyloxy- or 4-acyloxy-azetidin-2-ones in the presence of Lewis acids can alkylate nucleophilic arenes bound to the β-lactam nitrogen atom through methyloxy, or methylthio tethers. The reactions smoothly proceed to afford the corresponding 3-oxa- or 3-thia-4,5-benzocephams in a good yield. The sulfur atom can be easily removed by Raney nickel reduction to provide the title compounds.

1. Introduction

We have demonstrated that the 4-vinyloxy-azetidinone (**1**) (Chart 1) is an attractive substrate for the synthesis of a variety of bicyclic β-lactams since it allows the N-alkylation of the substrate followed by the oxidation of its vinyloxy group into the acyloxy substituent and subsequent Lewis acid promoted nucleophilic substitution at the C-4 carbon atom to provide oxa-,[1] or carba-cephams.[2,3] It has been shown that the 4-vinyloxy substituent itself in the presence of a Lewis acid can frequently play a role of a leaving group to allow nucleophilic displacement in a similar yield.[4]

The search for a new, efficient synthesis of Ezetimibe (**2**) (Chart 1), a powerful cholesterol absorption inhibitor,[5,6] and related 4-aryl-azetidinones, prompted us to investigate the acid-catalyzed alkylation of arenes by 4-acyloxy-azetidin-2-ones.

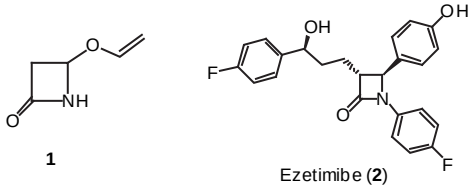
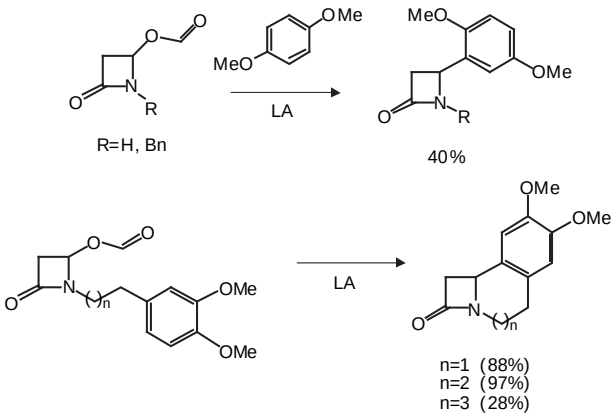


Chart 1.

We have shown that acyliminium cations derived from 4-acyloxy-azetidinones in the presence of Lewis acids can be used to alkylate nucleophilic arenes.[3] The intermolecular reaction can be successfully carried out only with *p*-dimethoxy-benzene, in a moderate yield. Reactions with anisol, or di- and tri-methoxy aryls lead to the opening of the four-membered ring by a second aryl molecule. In the case of the intramolecular process, however, the reaction can be done in a moderate to very good yield if the aryl is bound to the nitrogen atom via a di-, tri-, or tetramethylene tether (Scheme 1).



Scheme 1.

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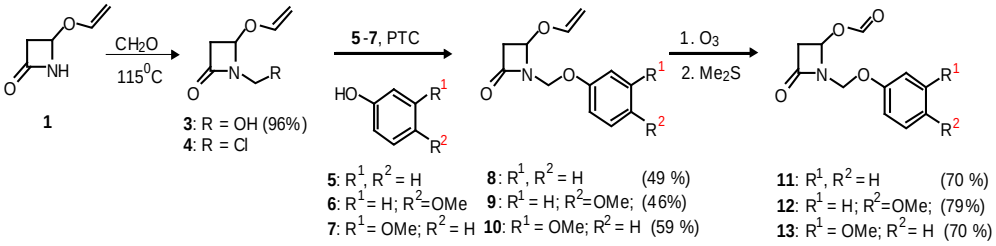
Anticipating the possibility of exploration of additional transformations, such as hydrolysis or the reduction at the later stages of synthesis, we decided to substitute an alkyl-only tether with the *N*-methyloxy or *N*-methylthio unit.

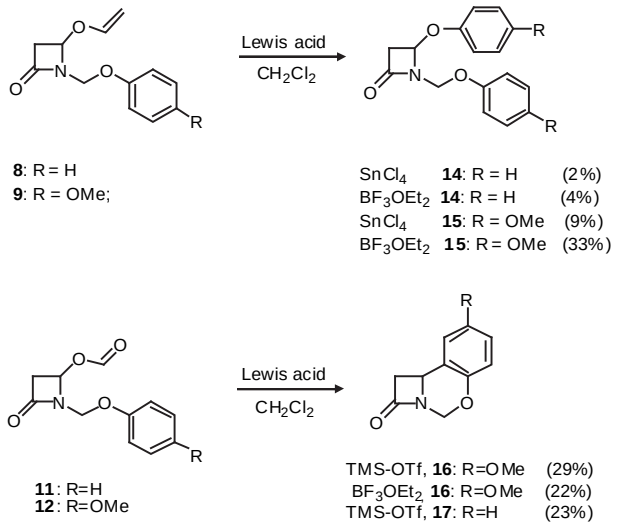
2. Results and discussion

4-Vinyloxy-azetidinone (**1**) treated with formaldehyde yielded the *N*-hydroxymethyl derivative **3** in an excellent yield.[7] Compound **3** was subsequently transformed into *N*-chloromethyl compound **4**, which was used without purification for alkylation of phenols **5**–**7** to provide the corresponding aryl ethers **8**–**10**. Ozonolysis of the double bond in **8**–**10** yielded formates **11**–**13**, respectively (Scheme 2).



Scheme 2.

Vinyl ethers **8**–**10** in the presence of Lewis acids did not furnish the expected 4,5-benzo-3-oxa-cephams providing instead a complicated mixture of products. In the case of **8** and **9**, *N*-substituted 4-aryloxy compounds **14** and **15** were isolated in a very low yield. In the case of formates **11** and **12**, alkylation of the aryl moiety by the acyliminium cation generated from the azetidinone residue afforded the expected products **16** and **17**, respectively, in 20–30% yield (Scheme 3).



Scheme 3.

Attempts to hydrolyze the *N*,*O*-acetal fragment in **16** and **17** were unsuccessful. The use of mineral acids in protic solvents led to opening of the azetidinone ring followed by further decomposition. Hydrolysis under mild conditions, such as treatment with ethyl nitroacetate[8] left the substrate unchanged. The low yield of 3-oxacepham formation and the failure of the acetal hydrolysis prompted us to abandon further efforts of synthesis of 4-aryl-azetidinones via 3-oxa-cephams **16** and **17**.

Formation of 4-aryl-azetidinones via an *N*-methylthio linkage looked more promising. Suitable substrates: **3**, obtained as above and **18**, obtained by treatment of **1** with ethyl glyoxalate, were used to alkylate the methoxy-thio-phenols **19** and **20** (Scheme 4).

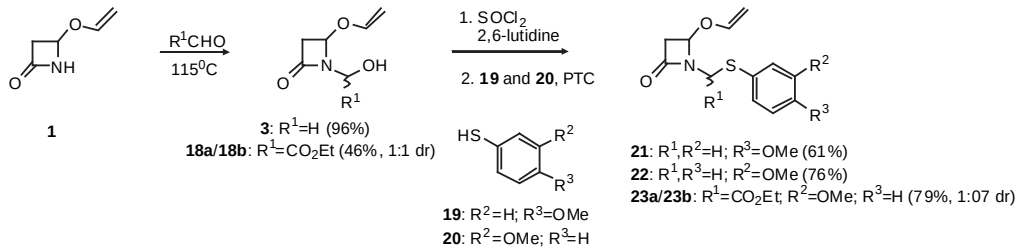
In contrast to the cyclization of aryloxymethyl compounds, only the *p*-methoxy-thiophenyl derivative **21** in the presence of Lewis acid underwent decomposition providing 4-aryloxy-azetidinone **24**. Vinyl ethers **22** and **23** provided expected 3-thia-cephams **25**–**28** in a good yield, as mixtures of two possible regioisomers (Scheme 5). Alkylation *para* to the methoxy group dominated in all cases.

Attempts to open the thiazine ring in **25** by acid hydrolysis, or by treatment with mercury salts were unsuccessful. Both methods lead to the opening of the β-lactam ring leaving the methylene bridge unchanged (**29**), or to degradation of the substrate. We assume that the initially formed mercapto group may subsequently attack the β-lactam carbonyl group to form thiololactone, which undergoes β-elimination to form thiocumarine derivative **30** (Scheme 6).

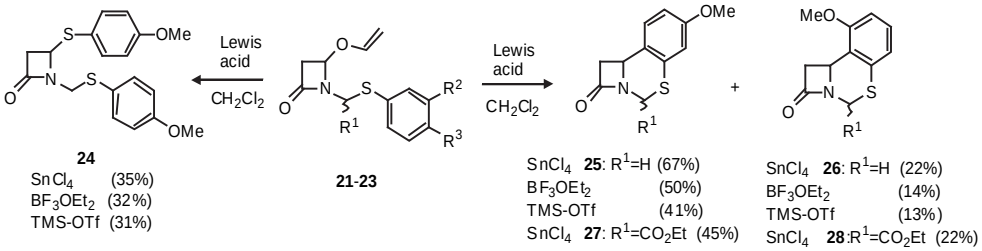
Oxidation of the sulfur atom in **25** with *m*-CPBA gave two diastereomeric sulfoxides **31** and **32** in a ratio 1:1. Compounds **31** and **32** were separated by chromatography. The relative configuration of stereogenic centers was resolved by X-ray crystallography (Fig. 1).[9] All attempts to perform a Pummerer rearrangement on sulfoxide **31** were unsuccessful. As in the case of hydrolysis of **25**, the liberation of the mercapto group leads to the opening of the β-lactam ring to provide dihydro-thiocumarine derivative **33**, which was accompanied by deoxygenated compound **25** (Scheme 7). Desulfurization of thioethers **25** and **27** with Raney nickel gave much better results (Scheme 8). Removal of sulfur proceeded readily in ethanol solution in 15 min to provide the expected compounds **34** and **35**, respectively. 4-Aryl-azetidinone **35** was accompanied by the open chain amide **37**. It was shown that prolongation of the reaction time lead to formation of open chain compounds as the sole products. It was exemplified by hydrogenolysis of **25** to obtain amide **36**.

3. Conclusion

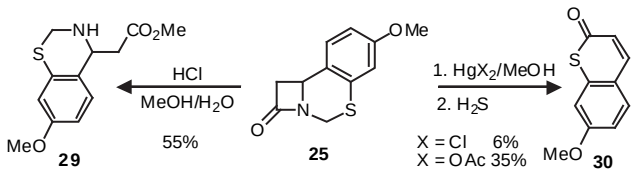
The alkylation of nucleophilic arenes by acyliminium cations, generated from the 4-acyloxy-azetidinones in the presence of Lewis acids, proceeds successfully with a variety of aryls linked to the nitrogen atom by the *N*-methyloxy, or *N*-methylthio tethers. Efforts to achieve the hydrolysis of the *N*,*O*-acetal or *N*,*S*-thioacetal centers as well as attempts to carry out the Pummerer rearrangement of sulfoxides were unsuccessful. On the other hand, the desulfurization with Raney nickel readily proceeds to provide expected 4-aryl-azetidinones.



Scheme 4.



Scheme 5.



Scheme 6.

4. Experimental section

4.1. General

IR spectra were recorded on FT-IR-1600 Perkin–Elmer spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AM 500 and Varian—NMR—vnmrs 600 spectrometers. The high-resolution mass spectra were measured on AMD 606 mass spectrometer. The thin-layer chromatography (TLC) was done using the Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm). The products were purified by the preparative column chromatography on silica gel (Merck Kieselgel 230–400 mesh). The ozonolysis was carried out using Buchi Ozone Generator OZI.

Anhydrous THF was distilled from $LiAlH_4$ and CH_2Cl_2 was distilled from CaH_2. 4-Vinyloxy-azetidinone (**3**) was obtained following known procedure.[1a]

4.2. Synthesis of 1-(hydroxymethyl)-4-(vinyloxy)azetidin-2-one (3)

A mixture of **1** (1 g, 8.8 mmol) and paraformaldehyde (530 mg, 17.6 mmol) was stirred at 115 °C until disappearance of the substrate. Purification of the crude product by flash chromatography on silica gel using acetone/hexane mixture as an eluant afforded **3** as a colorless oil. Yield 1378 mg (96%); R_f (40% acetone/hexane) 0.45; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.45 (dd, J=14.3, 6.7 Hz, 1H), 5.52 (dd, J=3.9, 1.4 Hz, 1H), 4.92 (br dd, J=11.6, 4.4 Hz, 1H), 4.54 (br dd, J=11.6, 8.9 Hz, 1H), 4.45 (dd, J=14.3, 2.5 Hz, 1H), 4.25 (dd, J=6.7, 2.5 Hz, 1H), 3.35–3.29 (m, 1H), 3.20 (dd, J=15.2, 3.9 Hz, 1H), 2.96 (dd, J=15.2, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.7, 148.2, 91.3, 78.3, 63.6, 45.1; IR (CH_2Cl_2): 3392, 2949, 1764, 1643, 1381, 1196, 1039, 944, 841 cm^{-1}; HRMS (ESI) calcd for $C_6H_9NO_3Na$: 166.0475 [M+Na]$^+$, found 166.0481.

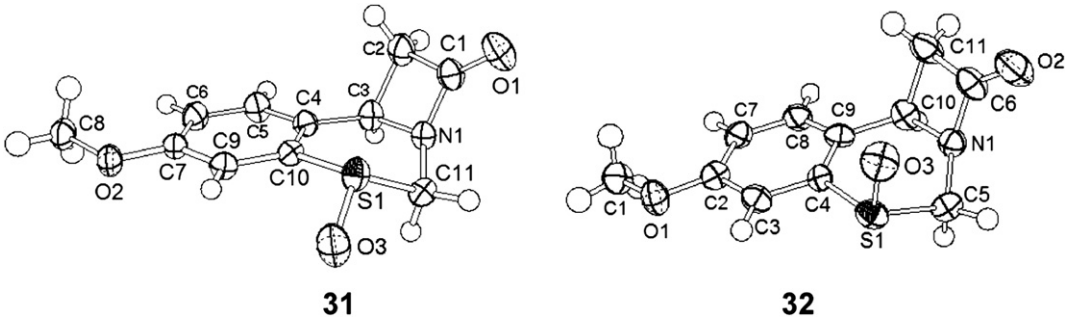
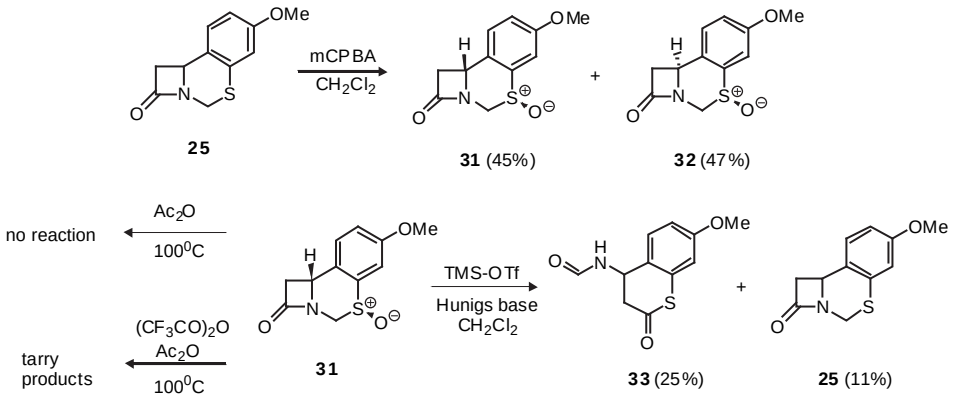


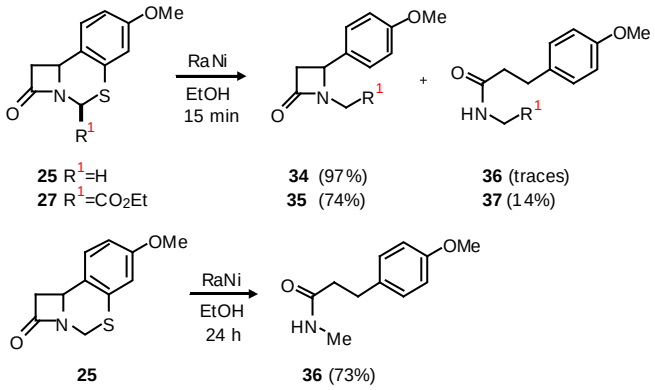
Fig. 1. X-ray structures of racemic sulfoxides **31** and **32** with crystallographic numbering scheme.

4.3. Synthesis of ethyl 2-hydroxy-2-(2-oxo-4-(vinyloxy) azetidin-1-yl)acetate (18)

A mixture of **1** (1 g, 8.8 mmol) and ~50% ethyl glyoxalate solution in toluene (3.6 g of solution, containing 17.6 mmol of substrate) was heated in a sealed tube at 115 °C until disappearance of the substrate. The mixture was then diluted with CH_2Cl_2 (50 mL),



Scheme 7.



Scheme 8.

washed with water (3×150 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel using acetone/hexane mixture as an eluant to afford **18a** and **18b** in 1:1 ratio as colorless oils. Yield 952 mg (46%). Compound **18a**: R_f (40% ethyl acetate/hexane) 0.40; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.44 (dd, J=14.2, 6.7 Hz, 1H), 5.48 (dd, J=3.8, 1.4 Hz, 1H), 5.23 (d, J=8.4 Hz, 1H), 4.44 (dd, J=14.2, 2.4 Hz, 1H), 4.30 (q, J=7.2 Hz, 2H), 4.28 (dd, J=6.7, 2.4 Hz, 1H), 3.90 (d, J=8.4 Hz, 1H), 3.22 (dd, J=15.3, 3.8 Hz, 1H), 3.00 (dd, J=15.3, 1.4 Hz, 1H), 1.35 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.2, 164.2, 147.9, 92.0, 79.2, 71.8, 63.2, 45.3, 14.0; IR (CH_2Cl_2): 3330, 2985, 2940, 1746, 1668, 1538, 1224, 1106, 1020, 859, 604 cm^{-1}; HRMS (ESI) calcd for $C_9H_{13}NO_5Na$: 238.0686 [M+Na]$^+$, found 238.0696. Compound **18b**: R_f (40% acetone/hexane) 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.33 (dd, J=14.1, 6.6 Hz, 1H), 5.51 (dd, J=4.2, 1.5 Hz, 1H), 5.47 (d, J=6.2 Hz, 1H), 4.35 (dd, J=14.1, 2.3 Hz, 1H), 4.30 (q, J=7.2 Hz, 2H), 4.21 (dd, J=6.6, 2.3 Hz, 1H), 4.07 (d, J=6.2 Hz, 1H), 3.21 (dd, J=15.3, 4.1 Hz, 1H), 2.99 (dd, J=15.3, 1.5 Hz, 1H), 1.33 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.4, 164.8, 147.7, 91.6, 77.8, 70.5, 63.4, 45.0, 13.9; IR (CH_2Cl_2): 3332, 2985, 2940, 1745, 1667, 1538, 1225, 1106, 1019, 859, 604 cm^{-1}; HRMS (ESI) calcd for $C_9H_{13}NO_5Na$: 238.0686 [M+Na]$^+$, found 238.0693.

4.4. General procedure for synthesis of *N*-substituted-4-vinyloxy-azetidin-2-ones 8–10, 21, 22, 23a, 23b

$SOCl_2$ (890 mg, 7.5 mmol) was added dropwise under argon to a stirred solution of **3** or **18a**/**18b** (1:1 dr) (5 mmol) and 2,6-lutidine (1070 mg, 10 mmol) in dry THF (70 mL) at −20 °C. The mixture was stirred at −20 °C until disappearance of the substrate (TLC monitoring) and then evaporated. Subsequently the residue was dissolved in benzene (25 m), filtrated, and evaporated. The crude chlorides were dissolved in dry acetonitrile (10 mL) and added to the vigorously stirred mixture of **4**–**6** or **19**–**20** (7.5 mmol), K_2CO_3 (5 g), and TBAB (1610 mg, 5 mmol) in dry acetonitrile (20 mL) in one portion at rt. After 5 min K_2CO_3 excess was filtered off and the mixture was concentrated. Purification of the crude product by column chromatography on silica gel using acetone/hexane or ethyl acetate/hexane mixture as an eluant afforded **8**–**10**, **21**, **22**, **23a**/**23b** (1:1 dr) as colorless oils.

*4.4.1. 1-(Phenoxymethyl)-4-(vinyloxy)azetidin-2-one (**8**).* Yield 537 mg (49%); R_f (30% ethyl acetate/hexane) 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33–7.28 (m, 2H), 7.04–6.99 (m, 3H), 6.44 (dd, J=14.3, 6.7 Hz, 1H), 5.43 (dd, J=3.9, 1.3 Hz, 1H), 5.38 (d, J=11.4 Hz, 1H), 4.98 (d, J=11.4 Hz, 1H), 4.45 (dd, J=14.3, 2.5 Hz, 1H), 4.24 (dd, J=6.7, 2.5 Hz, 1H), 3.18 (dd, J=15.3, 3.9 Hz, 1H), 2.96 (br d, J=15.3, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.2, 156.1, 148.3, 129.8, 122.2, 115.3, 91.3, 78.7, 66.7, 45.2; IR (CH_2Cl_2): 3066, 3043, 2948, 1780, 1623, 1496, 1377, 1200, 1013, 757, 693 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{13}NO_3$: 219.0895 [M]$^+$, found 219.0889.

*4.4.2. 1-((4-Methoxyphenoxy)methyl)-4-(vinyloxy)azetidin-2-one (**9**).* Yield 573 mg (46%); R_f (35% ethyl acetate/hexane) 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.97–6.93 (m, 2H), 6.86–6.82 (m, 2H), 6.43 (ddd, J=14.3, 6.7, 0.3 Hz, 1H), 5.30 (dd, J=3.9, 1.4 Hz, 1H), 5.30 (d, J=11.4 Hz, 1H), 4.92 (dd, J=11.4, 0.6 Hz, 1H), 4.45 (dd, J=14.3, 2.5 Hz, 1H), 4.24 (dd, J=6.7, 2.5 Hz, 1H), 3.77 (s, 3H), 3.17 (dd, J=15.3, 3.9 Hz, 1H), 2.95 (ddd, J=15.3, 1.4, 0.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.2, 155.0, 150.0, 148.3, 116.7, 114.9, 91.3, 78.7, 67.6, 55.6, 45.2; IR (CH_2Cl_2): 3116, 3046, 2953, 1780, 1642, 1624, 1509, 1376, 1197, 1037, 829 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}NO_4Na$: 272.0893 [M+Na]$^+$, found 272.0889.

*4.4.3. 1-((3-Methoxyphenoxy)methyl)-4-(vinyloxy)azetidin-2-one (**10**).* Yield 735 mg (59%); R_f (30% ethyl acetate/hexane) 0.55; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.19 (t, J=8.4, 1H), 6.62–6.60 (m, 2H), 6.59 (ddd, J=8.2, 2.2, 0.6 Hz, 1H), 6.44 (dd, J=14.3, 6.8 Hz, 1H), 5.45 (dd, J=4.0, 1.1 Hz, 1H), 5.37 (d, J=11.6 Hz, 1H), 4.98 (d, J=11.6 Hz, 1H), 4.45 (dd, J=14.3, 2.5 Hz, 1H), 4.25 (dd, J=6.8, 2.5 Hz, 1H), 3.79 (s, 3H), 3.19 (dd, J=15.3, 4.0 Hz, 1H), 2.97 (br d, J=15.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.2, 161.0, 157.2, 148.3, 130.2, 108.2, 107.2, 101.3, 91.3, 78.7, 66.6, 55.3, 45.2; IR (CH_2Cl_2): 2944, 1781, 1605, 1494, 1376, 1146, 1042, 1022, 839, 769, 688 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{15}NO_4$: 249.1001 [M]$^+$, found 249.0993.

*4.4.4. 1-((4-Methoxyphenylthio)methyl)-4-(vinyloxy)azetidin-2-one (**21**).* Yield 809 mg (61%); R_f (35% ethyl acetate/hexane) 0.45; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42–7.38 (m, 2H), 6.88–6.84 (m, 2H), 6.33 (dd, J=14.2, 6.7 Hz, 1H), 5.38 (dd, J=3.9, 1.4 Hz, 1H), 4.86 (d, J=14.2 Hz, 1H), 4.42 (dd, J=14.2, 2.3 Hz, 1H), 4.20–4.15 (m, 2H), 3.80

(s, 3H), 3.03 (dd, J=15.0, 3.9 Hz, 1H), 2.84 (dt, J=15.0, 1.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.7, 160.0, 148.2, 134.5, 123.1, 115.0, 91.4, 78.7, 55.3, 45.2, 44.7; IR (CH_2Cl_2): 2940, 1771, 1641, 1622, 1592, 1495, 1382, 1246, 1182, 1079, 1029, 827,685, 523 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}NO_3NaS$: 288.0665 $[M+Na]^+$, found 288.0673.

*4.4.5. 1-((3-Methoxyphenylthio)methyl)-4-(vinyloxy)azetidin-2-one (**22**).* Yield 1007 mg (76%); R_f (30% acetone/hexane) 0.60; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.23 (t, J=8.2, 1H), 7.01–6.97 (m, 2H), 6.80 (ddd, J=8.2, 2.4, 0.8 Hz, 1H), 6.35 (dd, J=14.2, 6.6 Hz, 1H), 5.37 (dd, J=3.8, 1.2 Hz, 1H), 5.04 (d, J=14.5 Hz, 1H), 4.41 (dd, J=14.2, 2.3 Hz, 1H), 4.28 (dd, J=14.5, 1.2 Hz, 1H), 4.20 (dd, J=6.6, 2.3 Hz, 1H), 3.81 (s, 3H), 3.05 (dd, J=15.0, 3.8 Hz, 1H), 2.86 (dt, J=15.0, 1.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.7, 160.0, 148.0, 134.1, 130.0, 122.2, 115.0, 113.4, 91.3, 78.5, 55.3, 44.5, 42.8; IR (CH_2Cl_2): 2939, 1771, 1590, 1482, 1382, 1250, 1194, 1080, 1038, 859, 846, 688 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}NO_3NaS$: 288.0665 $[M+Na]^+$, found 288.0658.

*4.4.6. Ethyl 2-(4-methoxyphenylthio)-2-(2-oxo-4-(vinyloxy) azetidin-1-yl)acetate (**23a**, **23b**).* Yield 1332 mg (79%) (23a/23b=1:1); R_f (30% acetone/hexane) 0.55; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.71–8.67 (m, 2H), 7.16–7.13 (m, 2H), 7.02 (ddd, J=7.7, 2.4, 0.7 Hz, 1H), 7.00–6.98 (m, 1H), 6.88 (ddd, J=8.4, 2.5, 1.1 Hz, 1H), 6.86 (ddd, J=8.4, 2.4, 0.7 Hz, 1H), 6.49 (dd, J=13.9, 6.6 Hz, 1H), 6.42 (dd, J=14.3, 6.6 Hz, 1H), 5.83 (s, 1H), 5.77 (dd, J=4.2, 1.4 Hz, 1H), 5.63 (s, 1H), 5.47 (dd, J=4.2, 1.7 Hz, 1H); 4.43 (dd, J=14.3, 2.4 Hz, 1H), 4.41 (dd, J=13.9, 2.4 Hz, 1H), 4.25–4.21 (m, 6H), 3.81 (s, 3H), 3.80 (s, 3H), 3.21 (dd, J=15.3, 4.2 Hz, 1H), 2.99 (dd, J=15.3, 4.2 Hz, 1H), 2.93 (dd, J=15.3, 1.4 Hz, 1H), 2.92 (dd, J=15.3, 1.7 Hz, 1H), 1.31–1.28 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 166.9, 165.8, 165.1, 164.9, 160.1, 159.9, 148.6, 148.1, 133.0, 132.1, 130.2, 129.9, 125.5, 124.2, 118.2, 117.1, 115.1, 114.7, 91.7, 91.6, 81.9, 79.3, 62.8, 62.5, 59.1, 58.0, 55.40, 55.37, 45.4, 44.5, 14.0, 13.9; IR (CH_2Cl_2): 3529, 3069, 2982, 2939, 1779, 1742, 1590, 1480, 1364, 1323, 1250, 1195, 1082, 1038, 845, 782, 689 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}NO_5S$: 337.0984 $[M]^+$, found 337.0984.

4.5. Synthesis of *N*-substituted-4-formyloxy-azetidin-2-ones (11)–(13)

A mixture of **8**–**10** (5 mmol) and saturated ethanolic solution of ozonizable dye Sudan red 7B (0.1 mL) in freshly distilled CH_2Cl_2 (50 mL) was cooled to −78 °C and ozone was bubbled through it until the deep red color of the reaction mixture turned to pale yellow. Dimethyl sulfide (1 mL) was then added and the solution was brought to the rt and stirred for 30 min. Evaporation of solvent and purification of crude product by column chromatography on silica gel using ethyl acetate/hexane mixture as an eluant afforded compound **11**–**13** as a colorless oils.

*4.5.1. 1-(Phenoxymethyl)-4-(formyloxy)azetidin-2-one (**11**).* Yield 774 mg (70%); R_f (30% ethyl acetate/hexane) 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.33–7.28 (m, 2H), 7.04–7.00 (m, 3H), 6.21 (dd, J=4.2, 1.2 Hz, 1H), 5.27 (d, J=11.3 Hz, 1H), 5.07 (d, J=11.3, 1H), 3.34 (dd, J=15.6, 4.2 Hz, 1H), 3.04 (dd, J=15.6, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.7, 160.0, 156.0, 129.7, 122.3, 115.6, 75.0, 67.7, 45.2; IR (CH_2Cl_2): 2948, 1784, 1729, 1597, 1495, 1374, 1221, 1201, 1143, 1012, 757, 693 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{11}NO_4$: 221.0688 $[M]^+$, found 221.0691.

*4.5.2. 1-((4-Methoxyphenoxy)methyl)-4-(formyloxy)azetidin-2-one (**12**).* Yield 992 mg (79%); R_f (35% ethyl acetate/hexane) 0.45; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (d, J=0.5 Hz, 1H), 6.98–6.94 (m, 2H), 6.86–6.82 (m, 2H), 6.21–6.18 (ddd, J=4.2, 1.3, 0.5 Hz, 1H), 5.21 (d, J=11.2 Hz, 1H), 5.99 (d, J=11.2, 1H), 3.77 (s, 3H), 3.33 (dd, J=15.6, 4.2 Hz, 1H), 3.03 (dd, J=15.6, 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.6, 160.0, 155.0, 149.9, 117.1, 114.8, 74.9, 68.7, 55.5, 45.1; IR (CH_2Cl_2): 2955, 1784, 1731, 1509, 1376, 1218, 1199, 1145, 1036, 1015, 830 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{13}NO_5$: 251.0794 $[M]^+$, found 251.0791.

*4.5.3. 1-((3-Methoxyphenoxy)methyl)-4-(formyloxy)azetidin-2-one (**13**).* Yield 879 mg (70%); R_f (30% ethyl acetate/hexane) 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.19 (t, J=8.7 Hz, 1H), 6.62–6.56 (m, 3H), 6.21 (dd, J=4.2, 1.2 Hz, 1H), 5.26 (d, J=11.4 Hz, 1H), 5.05 (d, J=11.4, 1H), 3.79 (s, 3H), 3.34 (dd, J=15.6, 4.2 Hz, 1H), 3.04 (dd, J=15.6, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.7, 161.0, 160.1, 157.2, 130.2, 108.3, 107.5, 101.6, 75.0, 67.6, 55.3, 45.2; IR (CH_2Cl_2): 2948, 1784, 1731, 1604, 1494, 1375, 1147, 1016, 837, 770, 689 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{13}NO_5$: 251.0794 $[M]^+$, found 251.0791.

4.6. Reactions of *N*-substituted-azetidin-2-ones 8, 9, 11, 12, 21, 22 and 23a/23b in the presence of Lewis acids

To a solution of compounds **8**, **9**, **11**, **12**, **21**, **22** or **23a**/**23b** (1:1 dr), (0.3 mmol) in anhydrous CH_2Cl_2 (5 mL) Lewis acid (0.3 mmol) was added dropwise at 0 °C under the argon atmosphere. The mixture was stirred at 0 °C until disappearance of the substrate (TLC monitoring). The saturated solution of $NaHCO_3$ (1 mL) was then added and stirring was continued for 10 min. The mixture was then poured into water (20 mL) and extracted with CH_2Cl_2 (20 mL). The extracts were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to afford compounds **14**–**17**, **24**–**28**.

*4.6.1. 4-Phenoxy-1-(phenoxymethyl)azetidin-2-one (**14**).* Yield 2 mg (2%) ($SnCl_4$), 3 mg (4%) (TMS-OTf); colorless needles, mp 63–65 °C; R_f (30% ethyl acetate/hexane) 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35–7.28 (m, 4H), 7.09–7.00 (m, 4H), 6.99–6.94 (m, 2H), 5.74 (dd, J=3.8, 1.1 Hz, 1H), 5.45 (d, J=11.5 Hz, 1H), 4.99 (d, J=11.5 Hz, 1H), 3.31 (dd, J=15.2, 3.8 Hz, 1H) 3.08 (br d, J=15.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.4, 156.2, 156.0, 129.9, 129.8, 122.7, 122.2, 115.7, 115.3, 78.7, 66.6, 46.0; IR (CH_2Cl_2): 2923, 1779, 1597, 1493, 1376, 1220, 1012, 753, 691 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}NO_3Na$: 292.0944 $[M+Na]^+$, found 292.0945.

*4.6.2. 4-(4-Methoxyphenoxy)-1-((4-methoxyphenoxy)methyl) azetidin-2-one (**15**).* Yield 9 mg (9%) ($SnCl_4$), 33 mg (33%) (TMS-OTf); colorless oil; R_f (35% ethyl acetate/hexane) 0.45; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.97–6.93 (m, 2H), 6.92–6.89 (m, 2H), 6.86–6.81 (m, 4H), 5.63 (dd, J=3.9, 1.3 Hz, 1H), 5.35 (d, J=11.4 Hz, 1H), 4.92 (dd, J=11.4, 0.5 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.24 (dd, J=15.2, 3.9 Hz, 1H), 3.05 (ddd, J=15.2, 1.3, 0.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.5, 155.4, 155.0, 150.1, 150.0, 117.4, 116.8, 114.94, 114.86, 79.6, 67.7, 55.68, 55.65, 45.84; IR (CH_2Cl_2): 2934, 1775, 1507, 1373, 1213, 1034, 826 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}NO_5Na$: 352.1155 $[M+Na]^+$, found 352.1169.

*4.6.3. 8-Methoxy-1,9b-dihydroazeto[1,2-c]benzo[e][1,3]oxazin-2 (4H)-one (**16**).* Yield 29% (TMS-OTf), 22% (BF_3OEt_2); colorless needles, mp 79–82 °C; R_f (40% acetone/hexane) 0.55; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.88 (d, J=9.3 Hz, 1H), 6.76 (ddt, J=9.3, 3.1, 0.9 Hz, 1H), 6.59 (dt, J=3.1, 0.9 Hz, 1H), 5.21 (dt, J=3.2, 0.7 Hz, 1H), 4.68 (br d, J=16.6 Hz, 1H), 4.19–4.15 (m, J=11.4, 1H), 3.76 (s, 3H), 3.33 (ddd, J=15.2, 3.2, 2.0 Hz, 1H), 2.99 (br d, J=15.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.6, 154.8, 146.0, 119.2, 118.5, 114.7, 111.5, 75.4, 55.7, 46.1, 39.2; IR (CH_2Cl_2): 3373, 2935, 1771, 1496, 1388, 1202, 1043, 864 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}NO_3Na$: 228.0631 $[M+Na]^+$, found 228.0642.

*4.6.4. 1,9b-Dihydroazeto[1,2-c]benzo[e][1,3]oxazin-2(4H)-one (**17**).* Yield 12 mg (23%) (TMS-OTf); colorless needles, mp

92–93 °C; R_f (30% ethyl acetate/hexane) 0.55; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.22–7.18 (m, 1H), 7.08–7.05 (m, 1H), 7.00 (td, J=7.6, 1.2 Hz, 1H), 6.95 (dd, J=8.2, 0.8 Hz, 1H), 5.27 (d, J=3.2 Hz, 1H), 4.71 (d, J=16.5 Hz, 1H), 4.21 (br d, J=16.5 Hz, 1H), 3.36 (ddd, J=15.0 3.2, 2.1 Hz, 1H), 3.02 (d, J=15.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 128.5, 127.2, 122.4, 118.4, 117.7, 75.3, 46.3, 39.0; IR (KBr): 2955, 2916, 1762, 1490, 1390, 1218, 1045, 766 cm^{-1}; HRMS (EI) calcd for $C_{10}H_9NO_2$: 175.0633 [M]$^+$, found 175.0640.

*4.6.5. 4-(4-Methoxyphenylthio)-1-((4-methoxyphenylthio) methyl) azetidin-2-one (**24**).* Yield 38 mg (35%) ($SnCl_4$), 35 mg (32%) (BF_3OEt_2), 34 mg (31%) (TMS-OTf); colorless needles, mp 47–49 °C; R_f (35% ethyl acetate/hexane) 0.40; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.36 (m, 2H), 7.35–7.32 (m, 2H), 6.87–6.82 (m, 4H), 4.88 (d, J=14.1 Hz, 1H), 4.85 (dd, J=5.1, 2.4 Hz, 1H), 4.22 (dd, J=14.1, 0.8 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.11 (dd, J=15.1, 5.1 Hz, 1H), 2.70 (ddd, J=15.1, 2.4, 0.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.8, 160.6, 159.9, 137.0, 134.5, 123.3, 119.6, 114.94, 114.89, 57.8, 55.33, 55.29, 45.1, 43.9; IR (CH_2Cl_2): 2938, 1762, 1591, 1494, 1373, 1287, 1246, 1173, 1029, 828 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}NO_3NaS_2$: 384.0699 [M+Na]$^+$, found 384.0687.

*4.6.6. 7-Methoxy-1,9b-dihydroazeto[1,2-c]benzo[e][1,3]thiazin-2 (4H)-one (**25**).* Yield 44 mg (67%) ($SnCl_4$), 33 mg (50%) (BF_3OEt_2), 27 mg (41%) (TMS-OTf); colorless needles, mp 96–97 °C; R_f (30% acetone/hexane) 0.45; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.05 (d, J=8.4 Hz, 1H), 6.76–6.71 (m, 2H), 4.83 (d, J=12.4 Hz, 1H), 4.69 (dd, J=5.2, 2.2 Hz, 1H), 4.28 (dd, J=12.4, 0.7 Hz, 1H), 3.78 (s, 3H), 3.50 (ddd, J=15.1, 5.2, 0.7 Hz, 1H), 2.80 (dd, J=15.1, 2.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.2, 158.6, 132.0, 128.4, 124.1, 113.2, 112.9, 55.4, 47.8, 44.3, 39.1; IR (CH_2Cl_2): 2937, 1761, 1602, 1494, 1237, 1058, 871, 811, 701 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}NO_2NaS$: 244.0403 [M+Na]$^+$, found 244.0396.

*4.6.7. 9-Methoxy-1,9b-dihydroazeto[1,2-c]benzo[e][1,3]thiazin-2 (4H)-one (**26**).* Yield 15 mg (22%) ($SnCl_4$), 9 mg (14%) (BF_3OEt_2), 8 mg (12%) (TMS-OTf); colorless needles, mp 162–164 °C; R_f (30% acetone/hexane) 0.45; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.14 (td, J=8.1, 0.5 Hz, 1H), 6.77 (dd, J=8.1, 0.8 Hz, 1H), 6.65 (dd, J=8.1, 0.7 Hz, 1H), 4.86 (d, J=12.6 Hz, 1H), 4.70 (dd, J=5.2, 2.4 Hz, 1H), 4.31 (dd, J=12.6, 0.5 Hz, 1H), 3.83 (s, 3H), 3.53 (dd, J=15.4, 5.2 Hz, 1H), 2.74 (dd, J=15.4, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.0, 157.4, 131.8, 128.1, 120.5, 119.7, 107.0, 55.4, 45.0, 44.9, 38.3; IR (CH_2Cl_2): 2937, 1761, 1572, 1459, 1259, 1046, 776 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}NO_2NaS$: 244.0403 [M+Na]$^+$, found 244.0394.

*4.6.8. Ethyl 7-methoxy-2-oxo-1,2,4,9b-tetrahydroazeto[1,2-c]benzo [e][1,3]thiazine-4-carboxylate (**27**).* Yield 40 mg (45%) ($SnCl_4$); colorless wax; R_f (35% ethyl acetate/hexane) 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.08 (d, J=8.6 Hz, 1H), 6.75 (dd, J=8.6, 2.6 Hz, 1H), 6.65 (d, J=2.6 Hz, 1H), 5.59 (s, 1H), 5.00 (dd, J=5.3, 2.3 Hz, 1H), 4.26–4.18 (m, 2H), 3.77 (s, 3H), 3.58 (dd, J=15.1, 5.3 Hz, 1H), 2.74 (dd, J=15.4, 2.3 Hz, 1H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.3, 166.9, 158.6, 129.5, 128.2, 122.9, 113.3, 111.8, 62.3, 55.4, 49.2, 47.3, 45.6, 14.0; IR (CH_2Cl_2): 2924, 1770, 1741, 1604, 1497, 1311, 1261, 1240, 1026, 841, 813 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{15}NO_4S$: 293.0722 [M]$^+$, found 293.0720.

*4.6.9. Ethyl 9-methoxy-2-oxo-1,2,4,9b-tetrahydroazeto[1,2-c]benzo [e][1,3]thiazine-4-carboxylate (**28**).* Yield 19 mg (22%) ($SnCl_4$); colorless wax; R_f (35% ethyl acetate/hexane) 0.55; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.15 (td, J=8.1, 0.4 Hz, 1H), 6.71 (dd, J=8.1, 0.6 Hz, 1H), 6.67 (d, J=8.1 Hz, 1H), 5.59 (s, 1H), 5.00 (dd, J=5.3, 2.5 Hz, 1H), 4.26–4.14 (m, 2H), 3.84 (s, 3H), 3.58 (dd, J=15.5, 5.3 Hz, 1H), 2.80 (dd, J=15.5, 2.5 Hz, 1H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.5, 167.2, 157.1, 129.3, 128.3, 119.4, 118.9, 107.4, 62.2, 55.5, 48.7, 45.2, 44.9, 14.0; IR (CH_2Cl_2): 2925, 1770, 1742, 1574, 1460, 1309, 1262, 1046, 775 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{15}NO_4S$: 293.0722 [M]$^+$, found 293.0708.

4.7. Synthesis of methyl 2-(7-methoxy-3,4-dihydro-2*H*-benzo [*e*][1,3]thiazin-4-yl)acetate (29)

A solution of **25** (66 mg, 0.3 mmol) in 5 mL of 1 N methanolic hydrochloric acid (prepared by dilution of 1 mL of 38% aqueous hydrochloric acid to 12 mL with absolute methanol) was stirred at rt for 24 h. The mixture was then poured into water (40 mL) and extracted with CH_2Cl_2 (20 mL). The extracts were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel using acetone/hexane mixture as an eluant to afford compounds **29**. Yield 42 mg (55%); colorless needles, mp 78–81 °C; R_f (30% acetone/hexane) 0.55; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.99 (d, J=8.5 Hz, 1H), 6.64 (d, J=2.6 Hz, 1H), 6.60 (dd, J=8.5, 2.6 Hz, 1H), 4.51 (d, J=12.4 Hz, 1H), 4.45 (dd, J=9.1, 5.3 Hz, 1H), 4.34 (d, J=12.4 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 2.88–2.77 (m, 2H), 2.25 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.7, 158.3, 133.8, 127.9, 125.0, 112.5, 111.5, 55.3, 52.5, 51.8, 45.0, 40.2; IR (CH_2Cl_2): 3331, 2950, 1735, 1600, 1493, 1437, 1232, 1058, 1035, 755 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{15}NO_3S$: 253.0773 [M]$^+$, found 253.0777.

4.8. Synthesis of 7-methoxy-2*H*-thiochromen-2-one (30)

4.8.1. Method A. A solution of **25** (66 mg, 0.3 mmol) and $HgCl_2$ (163 mg, 0.6 mmol) in absolute methanol (5 mL) was stirred at reflux for 24 h. Subsequently the mixture was cooled to 0 °C and H_2S was bubbled through it for 20 min. HgS was then filtered off, washed twice with absolute methanol (20 mL), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using acetone/hexane mixture as an eluant to give **30**. Yield 4 mg (7%); colorless needles, mp 98–100 °C; R_f (30% acetone/hexane) 0.80; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.64 (d, J=10.6 Hz, 1H), 7.53–7.70 (m, 1H), 6.96–6.94 (m, 2H), 6.41 (d, J=10.6 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 185.2, 160.9, 143.7, 140.2, 133.0, 121.2, 119.7, 114.7, 109.1, 55.7; IR (CH_2Cl_2): 2921, 2851, 1639, 1604, 1535, 1342, 1219, 1025, 839 cm^{-1}; HRMS (EI) calcd for $C_{10}H_8O_2S$: 192.0245 [M]$^+$, found 192.0250.

4.8.2. Method B. A solution of **25** (66 mg, 0.3 mmol) and $Hg(OAc)_2$ (190 mg, 0.6 mmol) in absolute methanol (5 mL) was stirred at rt for 4 h. Afterward the mixture was cooled to 0 °C and H_2S was bubbled through it for 20 min. HgS was then filtered off, washed twice with absolute methanol (20 mL), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using acetone/hexane mixture as an eluant to give **30** (20 mg, 35% yield).

4.9. Synthesis of sulfoxides (31), (32)

To a solution of **25** (1106 mg, 5 mmol) in freshly distilled CH_2Cl_2 (50 mL) a *m*-CPBA (860 mg, 5 mmol) was added in small portions at 0 °C. The mixture was warmed to rt and stirred until disappearance of the substrate (TLC monitoring). The saturated solution of Na_2SO_3 (5 mL) was then added, and stirring was continued for 10 min. The mixture was then poured into the water (150 mL) and extracted once with CH_2Cl_2 (25 mL). The extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel to afford compounds **31** and **32**.

4.9.1. (5S, 9bS*)-7-Methoxy-1,9b-dihydro-2H-azeto[1,2-c][1,3] benzothiazin-2-one-5-oxide (**31**).* Yield 533 mg (45%); colorless

needles, mp 177–178 °C; R_f (50% acetone/hexane) 0.40; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45 (d, J=2.7 Hz, 1H), 7.20 (d, J=8.6 Hz, 1H), 7.05 (dd, J=8.6, 2.7 Hz, 1H), 5.39 (d, J=12.0 Hz, 1H), 4.83 (dd, J=5.5, 2.8 Hz, 1H), 3.91 (d, J=12.0 Hz, 1H), 3.88 (s, 3H), 3.58 (dd, J=15.4, 5.5 Hz, 1H), 2.87 (dd, J=15.4, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.7, 160.2, 142.4, 128.3, 124.9, 118.5, 110.5, 56.6, 55.8, 48.9, 46.8; IR (CH_2Cl_2): 3492, 2935, 1757, 1604, 1496, 1351, 1236, 1064, 1040, 816, 531 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{11}NO_3S$: 237.0460 [M]$^+$, found 237.0466.

4.9.2. (5R, 9bS*)-7-Methoxy-1,9b-dihydro-2H-azeto[1,2-c][1,3] benzothiazin-2-one-5-oxide (**32**).* Yield 557 mg (47%); colorless needles, mp 191–193 °C; R_f (50% acetone/hexane) 0.30; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 (d, J=8.6 Hz, 1H), 7.21 (d, J=2.7 Hz, 1H), 7.15 (dd, J=8.6, 2.7 Hz, 1H), 5.20 (d, J=13.6 Hz, 1H), 4.86 (dd, J=5.4, 3.0 Hz, 1H), 4.11 (d, J=13.6 Hz, 1H), 3.86 (s, 3H), 3.69 (dd, J=15.2, 5.4 Hz, 1H), 3.33 (dd, J=15.2, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.6, 159.1, 137.9, 129.6, 124.6, 120.2, 116.0, 58.7, 55.8, 48.3, 48.0; IR (CH_2Cl_2): 3484, 2986, 1759, 1605, 1497, 1351, 1241, 1016, 853, 668 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{11}NO_3S$: 237.0460 [M]$^+$, found 237.0453.

4.10. Synthesis of *N*-(7-methoxy-2-oxothiochroman-4-yl) formamide (33)

To a solution of **31** (71 mg, 0.3 mmol) and Hunigs base (39 mg, 0.3 mmol) in anhydrous CH_2Cl_2 (5 mL) a TMS-OTf (66 mg, 0.3 mmol) was added dropwise at 0 °C under the argon atmosphere. The mixture was stirred at 0 °C until disappearance of the substrate (TLC monitoring). The reaction was then quenched with saturated solution of $NaHCO_3$ (1 mL), poured into water (20 mL) and extracted with CH_2Cl_2 (10 mL). The extracts were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to afford **33** (18 mg, 25% yield) and **25** (7 mg, 11% yield).

*4.10.1. N-(7-Methoxy-2-oxothiochroman-4-yl)formamide (**33**).* Yield 18 mg (25%); colorless needles, mp 150–152 °C; R_f (40% acetone/hexane) 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.2 (s, 1H), 7.34 (d, J=8.2 Hz, 1H), 6.81–6.76 (m, 2H), 6.06 (br s, 1H), 5.50–5.45 (m, 1H), 3.81 (s, 3H), 3.22 (dd, J=16.0, 4.9 Hz, 1H), 2.92 (dd, J=16.0, 3.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.8, 160.4, 160.0, 132.2, 130.4, 123.9, 113.2, 112.7, 55.6, 47.4, 45.3; IR (CH_2Cl_2): 3264, 3009, 2966, 1684, 1602, 1496, 1237, 1058, 1033, 819 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{11}NO_3S$: 237.0460 [M]$^+$, found 237.0465.

4.11. Reduction of (25) and (27) with Raney nickel

4.11.1. Method A. To the vigorously stirred suspension of excess of Raney nickel (500 mg) in absolute EtOH (25 mL) a **25** or **27** (0.3 mmol) was added in one portion at rt. After 30 min the reaction mixture was filtered through Celite washing thoroughly with EtOH (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using acetone/hexane mixture as an eluant to give **34**, **35**, and **37**.

4.11.2. Method B. To the vigorously stirred suspension of excess of Raney nickel (500 mg) in absolute EtOH (25 mL) a **25** (66 mg, 0.3 mmol) was added in one portion at rt. After 24 h the reaction mixture was filtered through Celite washing thoroughly with EtOH (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using acetone/hexane mixture as an eluant to give **36** as colorless wax.

*4.11.3. 4-(4-Methoxyphenyl)-1-methylazetidin-2-one (**34**).* Yield 55 mg (96%); colorless needles, mp 65–67 °C; R_f (30% acetone/hexane) 0.40; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.24–7.20 (m, 2H), 6.94–6.90 (m, 2H), 4.43 (dd, J=5.1, 2.1 Hz, 1H), 3.82 (s, 3H), 3.45 (ddd, J=14.6, 5.1, 0.6 Hz, 1H), 2.80 (ddd, J=14.6, 2.1, 0.9 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.6, 159.8, 129.9, 127.5, 114.4, 55.3, 55.2, 47.3, 26.9; IR (CH_2Cl_2): 2959, 1731, 1384, 1031, 832 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{13}NO_2$: 191.0950 [M]$^+$, found 191.0946.

*4.11.4. Ethyl 2-(2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)acetate (**35**).* Yield 144 mg (74%); colorless needles, mp 46–48 °C; R_f (30% acetone/hexane) 0.30; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27–7.22 (m, 2H), 6.93–6.81 (m, 2H), 4.82 (dd, J=5.3, 2.2 Hz, 1H), 4.30 (d, J=18.0 Hz, 1H), 4.22–4.10 (m, 2H), 3.81 (s, 3H), 3.45 (dd, J=14.8, 5.3 Hz, 1H), 3.41 (d, J=18.0 Hz, 1H), 2.89 (dd, J=14.8, 2.2 Hz, 1H), 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.2, 167.7, 159.9, 129.3, 127.8, 114.4, 61.4, 55.3, 54.4, 47.4, 41.5, 14.1; IR (CH_2Cl_2): 2981, 2960, 2937, 1764, 1743, 1515, 1249, 1204, 1177, 1029, 838 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{17}NO_4$: 263.1158 [M]$^+$, found 263.1152.

*4.11.5. 3-(4-Methoxyphenyl)-N-methylpropanamide (**36**).* Yield 42 mg (73%); colorless wax; R_f (30% acetone/hexane) 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.13–7.09 (m, 2H), 6.84–6.80 (m, 2H), 5.37 (br s, 1H), 3.78 (s, 3H), 2.91 (t, J=7.7 Hz, 2H), 2.77 (d, J=3.5 Hz, 3H), 2.44 (t, J=7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.8, 158.1, 132.9, 129.3, 114.0, 55.3, 38.7, 31.0, 26.3; IR (CH_2Cl_2): 3297, 2955, 2925, 2853, 1639, 1569, 1456, 1038, 815, 695, 527 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{15}NO_2$: 193.1103 [M]$^+$, found 193.1100.

*4.11.6. Ethyl 2-(3-(4-methoxyphenyl) propanamido)acetate (**37**).* Yield 11 mg (14%); colorless needles, mp 48–51 °C; R_f (30% acetone/hexane) 0.40; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.14–7.10 (m, 2H), 6.84–6.81 (m, 2H), 5.89 (br s, 1H), 4.21 (q, J=7.1 Hz, 2H), 4.01 (d, J=5.0 Hz, 2H), 3.30 (s, 3H), 2.92 (t, J=7.8 Hz, 2H), 2.52 (t, J=7.8 Hz, 2H), 1.28 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 170.0, 158.1, 132.7, 129.2, 114.0, 61.5, 55.2, 41.4, 38.3, 30.6, 14.1; IR (CH_2Cl_2): 3312, 2933, 1749, 1656, 1513, 1247, 1200, 1034, 826, 764, 750 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{19}NO_4$: 265.1314 [M]$^+$, found 265.1309.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.09.024

References and notes

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9. The crystallographic data for compounds **31** and **32** have been deposited with the Cambridge Crystallographic Data Center as a supplementary publication number CCDC 782149 and CCDC 782150.