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An entry to 4-aryl-azetidinones via alkylation of nucleophilic arenes using four-membered acyliminium cations

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ABSTRACT

The acyliminium cations derived from 4-acyloxy-azetidinones in the presence of Lewis acids can be used to alkylate nucleophilic arenes in both the inter- and intramolecular processes. The former reactions were successfully carried out with *p*-dimethoxy-benzene in moderate yield, whereas the latter reactions can be done with a variety of nucleophilic arenes in a good yield.

1. Introduction

Ezetimibe (**1**) (Fig. 1) is a powerful cholesterol absorption inhibitor that reduces the plasma low-density lipoprotein fraction (LDL-C) level and exhibits a long duration of action.[1] The syntheses of ezetimibe (**1**) and related compounds reported to-date involve the ester enolate-imine or ketene-imine azetidin-2-one ring construction methodologies.[1,2]

In 1974 Clauss et al.[3] reported that the 4-acetoxy-azetidin-2-one (**2**) underwent a nucleophilic displacement of acetoxy group with variety of nucleophiles. This observation prompted many laboratories to use 4-acyloxy-azetidinones as substrates for the synthesis of variety of β-lactam antibiotics.[4] The nucleophilic substitution proceeds in both basic and acidic media via an active intermediate, which constitutes an *N*-acyliminium cation.

N-Acyliminium ions are important intermediates in organic synthesis, particularly during syntheses of diverse nitrogen-containing natural products.[5] Such reactive intermediates can act as the electron-deficient carbocations toward weak nucleophiles providing useful methodologies for both the inter- and intramolecular carbon–carbon and carbon–heteroatom bond formation.[6] The *N*-acyliminium species have been generated in acidic media from lactams bearing a leaving group in the α-position to the nitrogen atom. Over the last 40 years, the cationic cyclization involving benzenoid, alkene or alkyne nucleophiles and *N*-acyliminium ions has found a broad application in the synthesis of cyclic systems.[5] The electrophilic aromatic substitution employing the *N*-acyliminium ions generated from β-lactams, however, has not been reported so far.

Recently, we have shown that the 4-vinyloxy-azetidinone (**3**)[7] is an attractive substrate for the synthesis of 5-oxacephams 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 intramolecular nucleophilic substitution at C-4 leading to the ring closure.[8] This work has prompted us to investigate the electrophilic aromatic substitution using *N*-acyliminium ions generated from β-lactams in both the inter- and intramolecular processes. This methodology would provide a new access to 4-aryl-azetidinones related to ezetimibe (**1**).

2. Result and discussion

The 4-formyloxy-azetidinone (**5**) and its *N*-benzyl derivative (**6**), readily available from 4-vinyloxy-azetidinone (**3**)[7] and *N*-benzyl-4-vinyloxy-azetidinone (**4**), were used as alkylating reagents, whereas anisole (**7**), dimethoxy-hydroquinone (**8**), 1,3-dimethoxy-benzene (**9**), and 1,3,5-trimethoxy-benzene (**10**) served as the nucleophilic arenes (Scheme 1). Electrophilic alkylation was performed in the presence of 1 equiv of Lewis acid such as $BF_3{\cdot}OEt_2$, $SnCl_4$, TMS-OTf, $TiCl_4$, $Yb(OTf)_3$, $InCl_3$, $SnCl_2$/TMSCl at 0 °C. The typical ratio of reagent **5** or **6** to arenes **7**–**10** was equal to about 1:5. The lower excess of arenes **7**–**10** appeared to reduce the reaction

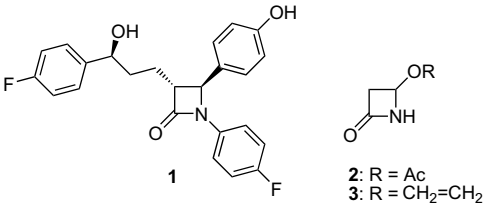

Figure 1.

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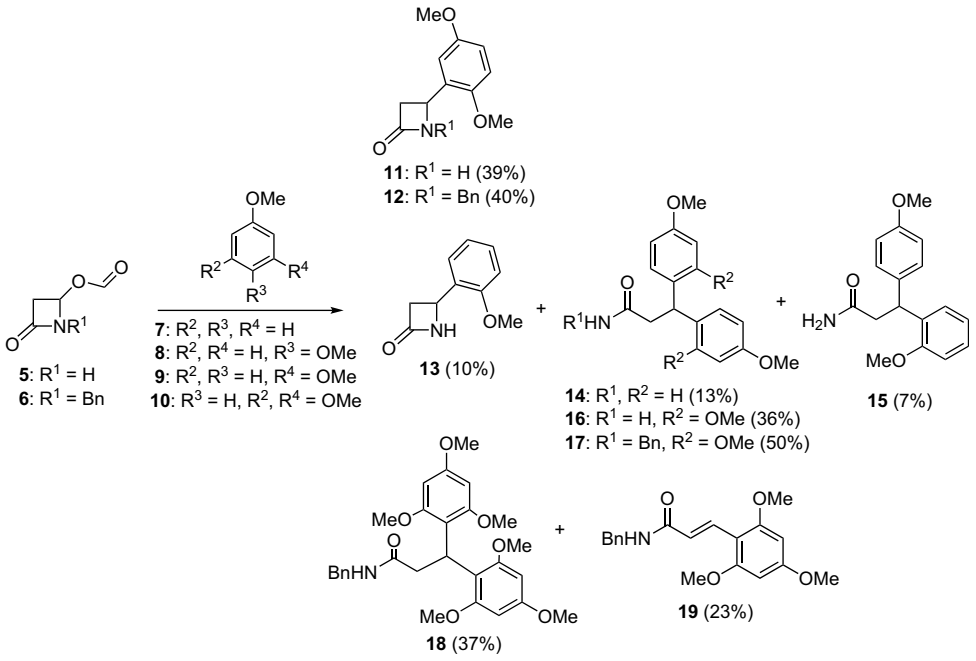
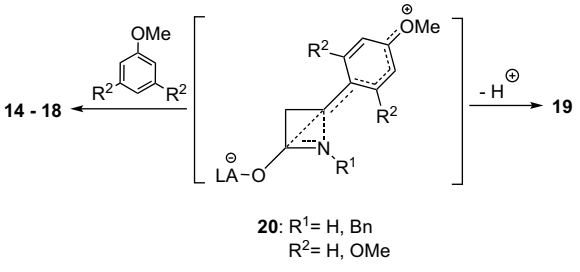
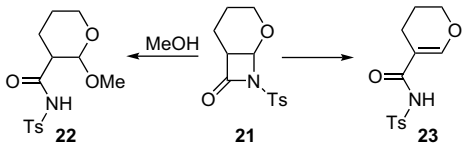


Scheme 1.

yield by causing a slow decomposition of azetidinones **5** and **6**. A successful alkylation was observed only with arene **8** where compounds **11** and **12** were formed in about 40% yield. In the case of arenes **7**, **9**, and **10** the products of double alkylation **14**–**18** were obtained. Reaction of azetidinone **5** with anisole (**7**) gave two regioisomeric products **14** and **15** in a ratio of about 2:1, respectively. In the latter case, the careful examination of the post-reaction mixture allowed also to isolate the desired monosubstituted product **13** in 10% yield. The possible reaction pathway involves the alkylation of arene to form a reactive complex **20**[9] in the first step (Scheme 2). Owing to the stabilization of a partial positive charge at C-4 of the azetidinone ring by the nucleophilic arene and, furthermore, owing to the coordination of the β-lactam carbonyl group by a Lewis acid, the heterolytic cleavage of the C(4)–N bond in the complex **20** is facilitated. Consequently, a second molecule of arene approaches the C-4 carbon atom causing a nucleophilic substitution against the nitrogen atom. The reaction proceeds with opening of the four-membered ring leading to compounds **14**–**18**. The second alkylation process is probably faster than the first one. In the case of arene **8** when alkylation at the *para* position is not possible, the second alkylation step does not take place and consequently, the expected products **11** and **12** are formed in about 40% yield. This is probably also the case of formation of compound **13**; the first alkylation may occur at *para* or *ortho* position, but the second one at *para* only.



Scheme 2.



Scheme 3.

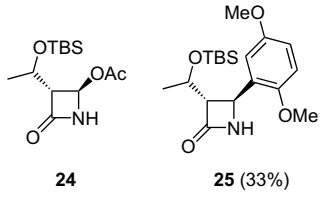
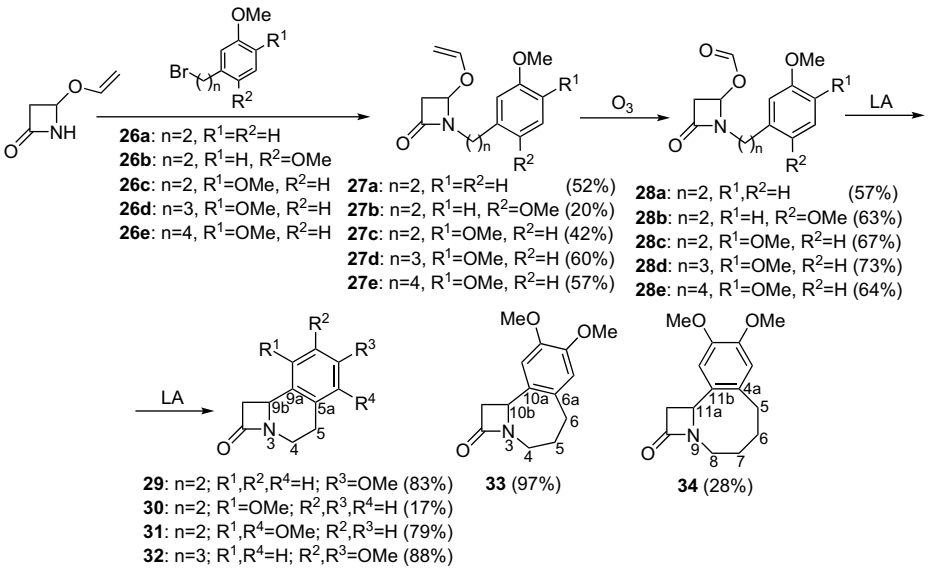


Figure 2.

Analogous processes have been observed by us for adducts of tosyl isocyanate to glycals **21**, which underwent a rapid opening of the four-membered β-lactam ring in the presence of an alcohol to form corresponding glycosides **22**, whereas upon standing they underwent rearrangement to α,β-unsaturated amides **23** (Scheme 3).[10] In that case the activation of the *C–N* bond of the azetidinone ring was achieved by the electron withdrawing substituent at the nitrogen atom.

It should be noted that the commercially available Kaneka azetidinone **24**,[11] in the presence of Lewis acids, undergoes an analogous reaction with the nucleophilic arenes as the azetidinones **5** and **6**. The desired alkylation product **25** was formed in a modest 33% yield, only in reaction of azetidinone **24** with arene **8** (Fig. 2). The reaction of azetidinone **24** with other nucleophilic arenes **7**, **9**, and **10** led to the complex mixtures of products, which were not investigated further.

The intramolecular alkylation of nucleophilic arenes by acyliminium cations is more effective since the second alkylation step is not possible (Scheme 4). Consequently, the chemical reaction yield is much higher. The substrates **27a**–**e** suitable for the intramolecular process were obtained by the N-alkylation of the



Scheme 4.

azetidinone **3** with arenes **26a–e** using the standard phase-transfer procedure. Compounds **27a–e** were subsequently subjected to ozonolysis to corresponding formates **28a–e**. The intramolecular electrophilic alkylation was performed in the presence of 1 equiv of Lewis acid such as $BF_3 \cdot OEt_2$, $SnCl_4$, TMS-OTf, $TiCl_4$, $Yb(OTf)_3$, $InCl_3$, $SnCl_2$/TMSCl at 0 °C. The expected products **29–34** were obtained in a good overall yield. The best results (up to 97%) were noticed for $SnCl_4$. In the case of **28a** two regioisomers **29** and **30**, in a ratio of about 5:1, were obtained. We did not observe formation of side products having dimeric structures.

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 aryl-methyl ethers as an intramolecular process. On the other hand, the intermolecular alkylation has limited applicability, and it can be performed in the case of *p*-dimethoxybenzene only.

4. Experimental section

4.1. General

IR spectra were recorded on FT-IR-1600 Perkin–Elmer spectrometer. The ^1H NMR and ^{13}C NMR spectra were measured on a Bruker AM 500 spectrometer. 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. Compounds **3** and **5** were obtained following known procedures.[7]

Bromides **26a–e** were obtained from commercially available corresponding alcohols or acids according to standard procedures[12,13] and their properties were consistent with the published values.[14]

4.2. Synthesis of *N*-benzyl-4-(vinyloxy)azetidin-2-one (4)

To a vigorously stirred mixture of the benzyl bromide (2.26 g, 13.3 mmol) and TBAB (2.85 g, 8.8 mmol) in 50% NaOH (100 mL)/toluene (100 mL) was added a solution of 4-vinyloxyazetidin-2-one (**3**) (1 g, 8.8 mmol) in toluene (20 mL) dropwise at room temperature within 15 min. The mixture was then poured into water (200 mL) and extracted with toluene (100 mL). The extract was dried over $MgSO_4$ and concentrated. Purification of the crude product by column chromatography on silica gel using acetone/hexane mixture as an eluant afforded **4** as a colorless oil. Yield 88%; R_f (25% acetone/hexane) 0.47; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.25 (m, 5H), 6.29 (dd, J=14.2, 6.7 Hz, 1H), 5.14 (dd, J=3.7, 1.2 Hz, 1H), 4.68 (d, J=15.2 Hz, 1H), 4.29 (dd, J=14.2, 2.3 Hz, 1H), 4.14 (dd J=6.7, 2.3 Hz, 1H), 4.13 (d, J=15.2 Hz, 1H), 3.15 (dd, J=14.9, 3.7 Hz, 1H), 2.93 (dd, J=14.9, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.2, 147.9, 135.2, 128.8, 128.3, 127.9, 91.2, 79.5, 44.9, 44.5; IR (CH_2Cl_2): 3032, 1770, 1641, 1621, 1394, 1195, 1075, 719 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{13}NO_2Na$: 226.0839 $[M+Na]^+$, found 226.0848.

4.3. Synthesis of *N*-benzyl-4-(formyloxy)azetidin-2-one (6)

A mixture of **4** (1 g, 4.9 mmol) and saturated ethanolic solution of ozonizable dye Sudan red 7B (0.1 mL) in anhydrous 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 (0.5 mL) was added and the solution was brought to the room temperature and stirred for 30 min. Evaporation of solvent and purification of crude product by column chromatography on silica gel using acetone/hexane mixture as an eluant afforded compound **6** as a colorless oil. Yield 66%; R_f (25% acetone/hexane) 0.41; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.37–7.28 (m, 5H), 6.01 (d, J=3.9 Hz, 1H), 4.56 (d, J=15.2 Hz, 1H), 4.23 (d, J=15.2 Hz, 1H), 3.30 (dd, J=15.1, 3.9 Hz, 1H), 3.01 (d, J=15.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.9, 160.1, 135.4, 128.8, 128.3, 127.9, 75.6, 45.2, 45.0; IR (CH_2Cl_2): 3032, 2938, 1771, 1725, 1391, 1352, 1151, 1091, 1010, 709 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}NO_3Na$: 228.0631 $[M+Na]^+$, found 228.0629.

4.4. Alkylation of nucleophilic arenes 7–10 by 4-formyloxy-azetidin-2-one (5) and 1-benzyl-4-formyloxy-azetidin-2-one (6). General procedure

To a mixture of azetidinone **5** or **6** (0.3 mmol) and arenes **7**–**10** (1.5 mmol) in anhydrous CH_2Cl_2 (5 mL) the solution of $SnCl_4$ in anhydrous CH_2Cl_2 (1 M, 0.3 mL, 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). Subsequently a saturated water solution of $NaHCO_3$ (1 mL) was added, and stirring was continued for 10 min. The mixture was then poured into the water (20 mL) and extracted with CH_2Cl_2 (20 mL). The organic 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 **11**–**19**.

4.4.1. 4-(2,5-Dimethoxyphenyl)-azetidin-2-one (**11**)

Yield 39%; colorless needles, mp 135–136 °C; R_f (35% acetone/hexane) 0.22; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.91 (d, J=1.5 Hz, 1H), 6.8 (d, J=2.3 Hz, 2H), 6.26 (br s, 1H), 4.94 (dd, J=5.4, 2.6 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.41 (ddd, J=14.8, 5.4, 2.6 Hz), 2.84 (dd, J=14.8, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.3, 153.7, 151.1, 129.4, 113.0, 112.2, 111.3, 55.81, 55.78, 46.1, 45.9; IR (CH_2Cl_2): 3233, 1739, 1500, 1217 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{13}NO_3$: 207.0895 [M]$^+$, found 207.0886.

4.4.2. N-Benzyl-4-(2,5-dimethoxyphenyl)azetidin-2-one (**12**)

Yield 40%; colorless oil; R_f (50% acetone/hexane) 0.36; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31–7.23 (m, 3H), 7.19–7.16 (m, 2H), 6.80–6.78 (m, 3H), 4.78 (dd, J=5.4, 2.5 Hz, 1H), 4.74 (d, J=15.1 Hz, 1H), 3.92 (d, J=15.1 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.31 (dd, J=14.6, 5.4 Hz, 1H), 2.85 (dd, J=14.6, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.9, 153.9, 151.7, 136.0, 128.6, 128.5, 127.5, 127.3, 113.6, 112.7, 111.9, 55.9, 55.7, 48.9, 45.6, 45.3; IR (CH_2Cl_2): 2953, 1751, 1501, 1218, 1045 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{19}NO_3$: 297.1365 [M]$^+$, found 207.1370.

4.4.3. 4-(2-Methoxyphenyl)azetidin-2-one (**13**)

Yield 10%; colorless needles, mp 146–149 °C; R_f (50% acetone/hexane) 0.86; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34–7.27 (m, 2H), 7.29 (dt, J=7.5, 0.9 Hz, 1H), 6.88 (d, J=8.2 Hz, 1H), 6.14 (br s, 1H), 4.96 (dd, J=5.3, 2.6 Hz, 1H), 3.84 (s, 3H), 3.41 (ddd, J=14.8, 5.4, 2.6 Hz, 1H), 2.87 (ddd, J=14.8, 2.7, 0.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.3, 157.0, 129.0, 128.2, 125.7, 120.6, 110.3, 96.1, 55.3, 46.0, 45.9; IR (CH_2Cl_2): 3193, 1747, 1712, 1494, 1250, 1027, 749 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{11}NO_2$: 177.0790 [M]$^+$, found 177.0787.

4.4.4. 3,3-Bis-(4′-methoxyphenyl)-propionamide (**14**)

Yield 13%; colorless oil; R_f (50% acetone/hexane) 0.55; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.26 (br s, 1H), 7.13 (d, J=8.7 Hz, 4H), 6.81 (d, J=8.7 Hz, 4H), 6.66 (br s, 1H), 4.35 (t, J=8.0 Hz, 1H), 3.69 (s, 6H), 2.73 ppm (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 172.2, 157.4, 136.8, 128.3, 113.6, 54.9, 44.9, 41.4; IR (CH_2Cl_2): 3346, 3191, 1666, 1509, 1246, 1177, 1027, 825 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{19}NO_3$: 285.1365 [M]$^+$, found 285.1360.

4.4.5. 3-(2′-Methoxyphenyl)-3-(4′-methoxyphenyl)-propionamide (**15**)

Yield 7%; colorless needles, mp 97–100 °C; R_f (50% acetone/hexane) 0.51; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.22–7.12 (m, 4H), 6.93–6.79 (m, 4H), 5.53–5.30 (m, 2H), 4.83 (t, J=8.0 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.97 (m, 1H), 2.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.1, 158.1, 156.7, 135.2, 132.2, 128.9, 127.8, 127.7, 120.7, 113.8, 111.0, 55.5, 55.2, 41.6, 39.9; IR (CH_2Cl_2): 3333, 3192, 1663, 1511, 1246, 1179, 1030, 755 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{19}NO_3$: 285.1365 [M]$^+$, found 285.1354.

4.4.6. 3,3-Bis-(2′,4′-dimethoxyphenyl)-propionamide (**16**)

Yield 36%; colorless needles, mp 115–117 °C; R_f (50% acetone/hexane) 0.38; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.05 (d, J=8.2 Hz, 2H), 6.44–6.39 (m, 4H), 5.66 (br s, 1H), 5.41 (br s, 1H), 4.95 (t, J=8.0 Hz, 1H), 3.77 (s, 6H), 376 (s, 6H), 2.93 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.6 159.4, 157.9, 128.8, 123.9, 104.1, 98.9, 55.6, 55.3, 36.7, 34.0; IR (CH_2Cl_2): 3347, 3194, 2957, 2938, 1663, 1610, 1587, 1504, 1208, 1034, 832, 772 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{23}NO_5$: 345.1576 [M]$^+$, found 345.1564.

4.4.7. N-Benzyl-3,3-bis-(2′,4′-dimethoxyphenyl)-propionamide (**17**)

Yield 50%; colorless needles, mp 137–138 °C; R_f (35% acetone/hexane) 0.20; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.21 (m, 1H), 7.21 (d, J=2.5 Hz, 2H), 7.09 (d, J=8.4 Hz, 2H), 6.96–6.92 (m, 2H), 6.41 (dd, J=8.4, 2.5 Hz, 2H), 6.38 (d, J=2.5 Hz, 2H), 5.97 (br s, 1H), 4.97 (t, J=8.2 Hz, 1H), 4.32 (d, J=5.5 Hz, 2H), 3.77 (s, 6H), 3.68 (s, 6H), 2.97 (d, J=8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.8, 159.3, 157.8, 138.3, 128.9, 128.4, 127.5, 127.1, 123.9, 104.1, 98.9, 55.4, 55.3, 43.4, 41.4, 33.9; IR (CH_2Cl_2): 3290, 2956, 2936, 1645, 1611, 1504, 1208, 1035, 832 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{29}NO_5$: 435.2046 [M]$^+$, found 435.2054.

4.4.8. N-Benzyl-3,3-bis(2′,4′,6′-trimethoxyphenyl)-propanamide (**18**)

Yield 37%; colorless needles, mp 148–149 °C; R_f (50% acetone/hexane) 0.44; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.23–7.20 (m, 3H), 7.06–7.02 (m, 2H), 6.22 (br s, 1H), 6.02 (s, 4H), 5.16 (t, J=8.3 Hz, 1H), 4.35 (d, J=5.5 Hz, 2H), 3.75 (s, 6H), 3.63 (s, 12H), 3.18 (d, J=8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.5, 161.6, 159.1, 138.7, 128.4, 127.7, 127.0, 113.0, 93.0, 55.3, 55.1, 43.4, 40.1, 29.1; IR (CH_2Cl_2): 3315, 2937, 2835, 1652, 1603, 1591, 1454, 1228, 1203, 1150, 1126 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{33}NO_7$: 495.2257 [M]$^+$, found 495.2246.

4.4.9. (E)-N-Benzyl-3-(2′,4′,6′-trimethoxyphenyl)-acrylamide (**19**)

Yield 23%; colorless needles, mp 162–163 °C; R_f (50% acetone/hexane) 0.56; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.04 (d, J=15.9 Hz, 1H), 7.35–7.31 (m, 4H), 7.27 (m, 1H), 6.77 (d, J=15.9 Hz, 1H), 6.11 (s, 2H), 5.82 (br s, 1H), 4.57 (d, J=5.5 Hz, 2H), 3.84 (s, 6H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.9, 162.2, 161.0, 138.9, 131.9, 128.6, 128.0, 127.3, 120.2, 106.1, 90.5, 55.7, 55.3, 43.8; IR (CH_2Cl_2): 3278, 2938, 1647, 1600, 1580, 1324, 1210, 1203, 1157, 1122, 1033, 812, 700 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{29}NO_5$: 327.1471 [M]$^+$, found 327.1458.

4.4.10. (1′R,3R,4R)-3-(1′-tert-Butyldimethylsilyloxy-ethyl)-4-(2,5-dimethoxyphenyl)-azetidin-2-one (**25**)

Compound **24** was obtained from **23** according to the general procedure described above. Yield 33%; colorless needles, mp 148–151 °C; R_f (25% acetone/hexane) 0.45; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.96 (d, J=2.3 Hz, 1H), 6.80–6.79 (m, 2H), 5.97 (br s, 1H), 5.05 (d, J=2.3 Hz, 1H), 4.31 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.10 (m, 1H), 1.27 (d, J=6.3 Hz, 3H), 0.9 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.2, 153.8, 151.2, 129.4, 113.14, 113.05, 111.4, 66.9, 65.1, 55.8, 55.6, 47.9, 25.8, 22.3, 18.0, −4.3, −5.0; IR (CH_2Cl_2): 3170, 1926, 1752, 1034, 777 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{31}NO_4Si$: 365.2022 [M]$^+$, found 365.2029.

4.5. General procedure for synthesis of *N*-substituted-4-vinyloxyazetidin-2-ones 27a–e

To a vigorously stirred mixture of alkyl–aryl bromides **26a**–**e** (17.7 mmol) and TBAB (2.85 g, 8.8 mmol) in 50% NaOH (100 mL)/toluene (100 mL) was added a solution of 4-vinyloxyazetidin-2-one (**3**) (1 g, 8.8 mmol) and a second portion of alkyl-aryl bromide (17.7 mmol) in 20 mL of toluene dropwise at 0 °C within 2 h. The

mixture was then poured into the water (200 mL) and extracted with toluene (100 mL). The organic extracts were dried over $MgSO_4$ and concentrated. Purification of residue by column chromatography on silica gel using acetone/hexane mixture as eluant afforded corresponding products as colorless oils.

*4.5.1. 1-(3′-Methoxyphenethyl)-4-vinyloxy-azetidin-2-one (**27a**)*

Yield 52%; R_f (30% acetone/hexane) 0.53; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.22 (t, J=7.8 Hz, 1H), 6.81–6.74 (m, 3H), 6.29 (dd, J=14.3, 6.7 Hz, 1H), 5.07 (dd, J=3.6, 1.0 Hz, 1H), 4.32 (dd, J=14.3, 2.2 Hz, 1H), 4.18 (dd, J=6.7, 2.2 Hz, 1H), 3.80 (s, 3H), 3.57 (ddd, J=14.2, 8.2, 6.0 Hz, 1H), 3.40 (dt, J=14.2, 7.8 Hz, 1H), 3.08 (dd, J=14.8, 3.6 Hz, 1H), 2.95–2.81 (m, 2H), 2.83 (br d, J=14.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.3, 159.9, 147.9, 139.9, 129.6, 120.9, 114.3, 112.1, 91.2, 80.6, 55.2, 44.8, 41.9, 34.5; IR (CH_2Cl_2): 2938, 1767, 1621, 1398, 1262, 1194 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{13}NO_3Na$: 270.1101 $[M+Na]^+$, found 270.1091.

*4.5.2. 1-(2′,5′-Dimethoxyphenethyl)-4-vinyloxy-azetidin-2-one (**27b**)*

Yield 20%; R_f (30% acetone/hexane) 0.49; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.79–6.73 (m, 3H), 6.29 (dd, J=12.4, 6.7 Hz, 1H), 5.09 (dd, J=3.7, 1.1 Hz, 1H), 4.33 (dd, J=14.2, 2.2 Hz, 1H), 4.16 (dd, J=6.7, 2.2 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.56 (ddd, J=14.1, 7.8, 6.4 Hz, 1H) 3.37 (dt, J=14.1, 7.5 Hz, 1H), 3.06 (dd, J=14.8, 3.7 Hz, 1H), 2.92–2.80 (m, 2H), 2.82 (dd, J=14.8, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 153.6, 151.9, 148.1, 127.8, 116.7, 112.2, 111.3, 96.1, 91.1, 80.5, 55.8, 55.7, 44.7, 40.4, 29.6; IR (CH_2Cl_2): 2935, 1767, 1640, 1502, 1224, 1046 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{19}O_4N$: 277.1314 $[M]^+$, found: 277.1321.

*4.5.3. 1-(3′,4′-Dimethoxyphenethyl)-4-vinyloxy-azetidin-2-one (**27c**)*

Yield 42%; R_f (25% acetone/hexane) 0.40; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.81 (d, J=7.9 Hz, 1H), 6.74 (dd, J=7.9, 2.0 Hz, 1H), 6.73 (s, 1H), 6.31 (dd, J=14.2, 6.7 Hz, 1H), 5.06 (dd, J=3.6, 1.0 Hz, 1H), 3.42 (dd, J=14.2, 2.2 Hz, 1H), 4.18 (dd, 6.7, 2.2 Hz, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 3.55 (ddd, J=14.2, 8.4, 6.0 Hz, 1H), 3.38 (dt, J=14.2, 7.9 Hz, 1H), 3.07 (dd, J=14.8, 3.6 Hz, 1H), 2.92–2.79 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.3, 149.1, 147.84, 147.80, 130.8, 120.6, 111.9, 111.4, 91.2, 80.5, 55.92, 55.89, 44.8, 42.1, 34.0; IR (CH_2Cl_2): 2936, 1767, 1517, 1264, 1028 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{19}O_4N$: 277.1314 $[M]^+$, found: 277.1308.

*4.5.4. N-[3′-(3″,4″-Dimethoxyphenyl)-propyl]-4-vinyloxy-azetidin-2-one (**27d**)*

Yield 60%; R_f (35% acetone/hexane) 0.55; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.80 (br d, J=7.9 Hz, 1H), 6.73 (s, 1H), 6.72 (br d, J=7.9, 2 Hz, 1H) 6.38 (dd, J=14.3, 6.7 Hz, 1H), 5.21 (dd, J=3.6, 1.0 Hz, 1H), 4.34 (dd, J=14.3, 2.2 Hz, 1H), 4.20 (dd, J=6.7, 2.2 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.25 (t, J=7.1 Hz, 2H), 3.11 (dd, J=14.8, 3.6 Hz, 1H), 2.87 (br d, J=14.8 Hz, 1H), 2.66–2.55 (m, 2H), 1.97–1.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.5, 148.9, 147.7, 147.4, 133.7, 120.2, 111.9, 111.4, 91.4, 80.3, 55.9, 55.8, 44.8, 40.5, 32.8, 29.8; IR (CH_2Cl_2): 2937, 1766, 1516, 1261, 1028 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{21}O_4N$: 291.1471 $[M]^+$, found: 291.1479.

*4.5.5. N-[4′-(3″,4″-Dimethoxyphenyl)butyl]-4-vinyloxy-azetidin-2-one (**27e**)*

Yield 57%; R_f (35% acetone/hexane) 0.49; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.79 (d, J=7.8 Hz, 1H), 6.71 (dd, J=7.8, 2.0 Hz, 1H), 6.70 (s, 1H), 6.36 (dd, J=14.3, 6.7 Hz, 1H), 5.22 (dd, J=3.6, 1.0 Hz, 1H), 4.33 (dd, J=14.3, 2.2 Hz, 1H), 4.20 (dd, J=6.7, 2.2 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.30–3.18 (m, 2H), 3.11 (dd, J=14.8, 3.6 Hz, 1H), 2.86 (br d, J=14.8 Hz, 1H), 2.62–2.54 (m, 2H), 1.68–1.56 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.4, 148.88, 147.25, 134.58, 120.19, 111.81, 111.30, 91.12, 80.19, 55.93, 55.83, 44.74, 40.63, 34.81, 28.80, 27.46; IR (CH_2Cl_2): 2936, 1766, 1516, 1261, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}NO_4Na$: 328.1519 $[M+Na]^+$, found 328.1514.

4.6. Synthesis of *N*-alkyl-aryl-4-formyloxy-azetidin-2-nones 28a–e

N-Alkyl-aryl-4-formyloxy-azetidin-2-nones **28a–e** were prepared from compounds **27a–e** according to procedure described for **6**.

*4.6.1. N-[2′-(3″-Methoxyphenyl-ethyl)-4-formyloxy-azetidin-2-one (**28a**)*

Yield 57%; colorless oil; R_f (30% acetone/hexane) 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, J=0.6 Hz, 1H), 7.21 (t, J=7.8 Hz, 1H), 6.80–6.74 (m, 3H), 5.93 (ddd, J=3.9, 1.2, 0.6 Hz, 1H), 3.80 (s, 3H), 3.60 (ddd, J=14.2, 8.4, 6.8 Hz, 1H), 3.35 (ddd, J=14.2, 8.3, 6.3 Hz, 1H), 3.21 (dd, J=15.0, 3.9 Hz, 1H), 2.93 (ddd, J=13.7, 8.4, 6.3 Hz, 1H), 2.92 (br d, J=15.0, 1H), 2.85 (ddd, J=13.7, 8.3, 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.9, 160.3, 159.8, 139.6, 129.6, 121.0, 114.3, 112.2, 76.0, 55.2, 44.6, 42.5, 34.3; IR (CH_2Cl_2): 2939, 1771, 1727, 1262, 1397, 1154, 1100, 1009 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{15}O_4N$: 249.1001 $[M]^+$, found: 249.1008.

*4.6.2. N-[2′-(2″,5″-Dimethoxyphenyl-ethyl)]-4-formyloxy-azetidin-2-one (**28b**)*

Yield 63%; colorless oil; R_f (30% acetone/hexane) 0.46; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (d, J=0.7 Hz, 1H), 6.78–6.71 (m, 2H), 6.72 (s, 1H), 5.97 (dt, J=3.9, 0.7 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.58 (dt, J=14.1, 7.4 Hz, 1H), 3.34 (ddd, J=14.1, 7.2, 6.6 Hz, 1H), 3.19 (dd, J=15.0, 3.9 Hz, 1H), 2.91–2.86 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.9, 160.2, 153.5, 151.9, 127.6, 116.8, 112.2, 111.3, 76.0, 55.8, 55.7, 44.6, 41.1, 29.5; IR (CH_2Cl_2): 2939, 1773, 1728, 1503, 1225, 1158, 1089, 1046 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{17}O_5N$: 279.1107 $[M]^+$, found: 279.1102.

*4.6.3. N-[2′-(3″,4″-Dimethoxyphenyl-ethyl)]-4-formyloxy-azetidin-2-one (**28c**)*

Yield 67%; colorless oil; R_f (25% acetone/hexane) 0.36; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.03 (s, 1H), 6.80 (br d, J=8.8 Hz, 1H), 6.74 (dd, J=8.8, 2.0 Hz, 1H), 6.73 (s, 1H), 5.93 (br d, J=4.0, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.59 (ddd, J=14.2, 8.4, 6.8 Hz, 1H), 3.33 (ddd, J=14.2, 8.4, 6.2 Hz, 1H), 3.20 (dd, J=15.0, 4.0 Hz, 1H), 2.93 (br d, J=15.0 Hz, 1H), 2.91 (ddd, J=13.8, 8.4, 6.2 Hz, 1H), 2.82 (ddd, J=13.8, 8.4, 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.0, 160.4, 149.1, 147.8, 130.5, 120.7, 111.9, 111.4, 76.0, 55.90, 55.87, 44.6, 42.7, 33.8; IR (CH_2Cl_2): 2937, 1771, 1725, 1517, 1264, 1158, 1143, 1027 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}NO_5Na$: 302.1012 $[M+Na]^+$, found 302.1013.

*4.6.4. N-[3′-(3″,4″-Dimethoxyphenyl-propyl)]-4-formyloxy-azetidin-2-one (**28d**)*

Yield 73%; colorless oil; R_f (35% acetone/hexane) 0.51; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 6.79 (d, J=7.8 Hz, 1H), 6.73 (s, 1H), 6.72 (dd, J=7.8, 2 Hz, 1H), 6.03 (d, J=3.9 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.34 (dt, J=14.2, 7.4 Hz, 1H), 3.22 (dd, J=15.0, 3.9 Hz, 1H), 3.13 (dt, J=14.2, 6.8 Hz, 1H), 2.93 (d, J=15.0 Hz, 1H), 2.59 (t, J=7.5 Hz, 2H), 1.97–1.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.0, 160.3, 148.9, 147.4, 133.5, 120.1, 111.8, 111.4, 76.0, 55.9, 55.8, 44.7, 40.8, 32.7, 29.5; IR (CH_2Cl_2): 2937, 1770, 1726, 1516, 1261, 1156, 1027 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}NO_5Na$: 316.1155 $[M+Na]^+$, found 316.1154.

*4.6.5. N-[4′-(3″,4″-Dimethoxyphenyl-butyl)]-4-formyloxy-azetidin-2-one (**28e**)*

Yield 64%; colorless oil; R_f (35% acetone/hexane) 0.52; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.07 (d, J=0.6 Hz, 1H), 6.79 (d, J=8.7 Hz, 1H), 6.72–6.68 (m, 2H), 6.05 (ddd, J=3.9, 1.1, 0.6 Hz, 1H), 3.87 (s, 3H), 3.85

(s, 3H), 3.31 (m, 1H), 3.26 (dd, *J*=15.0, 3.9 Hz, 1H), 3.14 (m, 1H), 2.94 (d, *J*=15.0 Hz, 1H), 2.61–2.54 (m, 2H), 1.67–1.55 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.0, 160.3, 148.9, 147.3, 134.5, 120.2, 111.8, 111.3, 75.9, 55.9, 55.8, 44.7, 41.1, 34.8, 28.7, 27.4; IR (CH_2Cl_2): 2937, 1770, 7127, 1516, 1261, 1237, 1156, 1144, 1028, 1011 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{21}O_5N$: 307.1420 [M]$^+$, found: 307.1414.

4.7. General procedure for intramolecular alkylation in *N*-alkyl-aryl-4-formyloxy-azetidin-2-ones 29–34

To a solution of compounds **28a**–**e** (0.3 mmol) in anhydrous CH_2Cl_2 (5 mL) a 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 the 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 **29**–**33**.

*4.7.1. 7-Methoxy-4,5-dihydro-1H-azeto[2,1-a]isoquinolin-2(9bH)-one (**29**)*

Yield 65% ($BF_3\cdot OEt_2$), 83% ($SnCl_4$), 52% (TMS-OTf); colorless needles, mp 100–103 °C; R_f (30% acetone/hexane) 0.47; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.07 (d, *J*=8.5 Hz, 1H), 6.82 (dd, *J*=8.5, 2.7 Hz, 1H), 6.69 (d, *J*=2.7 Hz, 1H), 4.51 (dd, *J*=5.0, 2.1 Hz, 1H), 3.90 (ddd, *J*=12.9, 6.5, 4.7 Hz, 1H), 3.80 (s, 3H), 3.44 (ddd, *J*=14.7, 5.0, 1.0 Hz, 1H), 3.13 (dddd, *J*=12.9, 8.7, 5.3, 1.0 Hz, 1H), 3.04 (m, 1H), 2.77 (dd, *J*=14.7, 2.1 Hz, 1H), 2.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.6, 158.6, 135.5, 128.1, 127.1, 114.1, 113.1, 55.3, 47.1, 44.8, 37.8, 28.5; IR (CH_2Cl_2): 2938, 1755, 1611, 1503, 1355, 1245, 1036 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{13}NO_2$: 203.0946 [M]$^+$, found 203.0950.

*4.7.2. 9-Methoxy-4,5-dihydro-1H-azeto[2,1-a]isoquinolin-2(9bH)-one (**30**)*

Yield 10% ($BF_3\cdot OEt_2$), 17% ($SnCl_4$), 15% (TMS-OTf); colorless needles, mp 56–57 °C; R_f (30% acetone/hexane) 0.44; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.19 (t, *J*=7.9 Hz, 1H), 6.77–6.72 (m, 2H), 4.53 (br d, *J*=5.0 Hz, 1H), 4.03 (m, 1H), 3.83 (s, 3H), 3.47 (dd, *J*=15.1, 5.0 Hz, 1H), 3.10–2.96 (m, 2H), 2.75–2.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.9, 156.8, 135.1, 128.0, 124.1, 121.6, 107.8, 55.3, 44.91, 44.90, 37.2, 28.0; IR (CH_2Cl_2): 2935, 1755, 1583, 1471, 1260, 1084 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{13}NO_2$: 203.0946 [M]$^+$, found 203.0940.

*4.7.3. 6,9-Dimethoxy-4,5-dihydro-1H-azeto[2,1-a]isoquinolin-2(9bH)-one (**31**)*

Yield 14% ($BF_3\cdot OEt_2$), 79% ($SnCl_4$), 41% (TMS-OTf); colorless needles, mp 127–128 °C; R_f (30% acetone/hexane) 0.47; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.72 (d, *J*=8.9 Hz, 1H), 6.67 (d, *J*=8.9 Hz, 1H), 4.50 (dd, *J*=5.1, 2.3 Hz, 1H), 4.06 (ddd, *J*=13.5, 7.4, 1.4 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.47 (ddd, *J*=15.1, 5.1, 1.0 Hz, 1H), 2.96–2.84 (m, 2H), 2.74 (m, 1H), 2.69 (dd, *J*=15.1, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.4, 151.2, 150.8, 125.3, 124.2, 108.7, 107.2, 55.8, 55.5, 45.1, 44.6, 36.6, 21.7; IR (CH_2Cl_2): 2943, 1754, 1482, 1258, 1086 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{15}NO_3$: 233.1052 [M]$^+$, found 233.1045.

*4.7.4. 7,8-Dimethoxy-4,5-dihydro-1H-azeto[2,1-a]isoquinolin-2(9bH)-one (**32**)*

Yield 79% ($BF_3\cdot OEt_2$), 88% ($SnCl_4$), 70% (TMS-OTf); colorless oil; R_f (30% acetone/hexane) 0.33; ^{1}H NMR (500 MHz, C_6D_6) δ: 6.27 (s, 1H), 6.25 (s, 1H), 3.99 (dd, *J*=5.2, 2.2 Hz, 1H), 3.80 (ddd, *J*=13.0, 6.2, 3.5 Hz, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 3.01 (ddd, *J*=14.6, 5.2, 1.0 Hz, 1H), 2.69 (m, 1H), 2.60 (m, 1H), 2.43 (dd, *J*=14.6, 2.2 Hz, 1H), 2.07 (dt, *J*=15.4, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.5, 148.3, 148.2, 127.5, 126.1, 112.1, 108.7, 56.0, 55.9, 47.3, 45.0, 37.7, 27.7; IR (CH_2Cl_2): 2936, 1750, 1515, 1253, 1130 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{15}NO_3$: 233.1052 [M]$^+$, found 233.1059.

*4.7.5. 8,9-Dimethoxy-1,5,6,10b-tetrahydroazeto[1,2-a]benzo[c]azepin-2(4H)-one (**33**)*

Yield 33% ($BF_3\cdot OEt_2$), 97% ($SnCl_4$), 97% (TMS-OTf); colorless needles, mp 129–131 °C; R_f (40% acetone/hexane) 0.36; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.66 (s, 1H), 6.57 (s, 1H), 4.78 (dd, *J*=5.1, 2.3 Hz, 1H), 4.04 (dt, *J*=13.4, 4.8 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.39 (ddd, *J*=14.3, 5.1, 1.6 Hz, 1H), 3.17–3.10 (m, 2H), 2.92 (m, 1H), 2.84 (m, 1H), 1.93 (m, 1H), 1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.1, 147.7, 147.0, 133.7, 130.7, 113.9, 110.7, 56.2, 56.0, 53.8, 43.4, 43.1, 34.6, 26.4; IR (CH_2Cl_2): 2937, 1746, 1519, 1347, 1212, 1115 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}NO_3Na$: 270.1092 [M+Na]$^+$, found 270.1101.

*4.7.6. 2,3-Dimethoxy-7,8,11,11a-tetrahydro-5H-azeto[1,2-a]benzo[c]azocin-10(6H)-one (**34**)*

Yield 28% ($SnCl_4$), 19% (TMS-OTf); colorless needles, mp 143–144 °C; R_f (35% acetone/hexane) 0.49; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.66 (s, 1H), 6.62 (s, 1H), 4.72 (dd, *J*=5.1, 2.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (m, 1H), 3.29 (ddd, *J*=14.5, 5.1, 1.5 Hz, 1H), 3.16–3.08 (m, 2H), 2.92 (dd, *J*=14.5, 2.4 Hz, 1H), 2.65 (dt, *J*=14.0, 5.6 Hz, 1H), 1.88 (m, 1H), 1.71 (m, 1H), 1.60 (m, 1H), 1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.7, 148.6, 147.0, 131.0, 129.1, 114.4, 110.7, 56.0, 55.9, 55.2, 44.3, 41.6, 30.4, 29.4, 22.0; IR (CH_2Cl_2): 2926, 1742, 1517, 1347, 1256, 1228, 1117 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{19}NO_3$: 261.1365 [M]$^+$, found 261.1358.

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