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SPIROCYCLIZATION OF AN N-ACYLIMINIUM ION WITH SUBSTITUTED PYRIDINE: STEREoselective SYNTHESIS OF TETRACYCLIC SPIROLACTAMS POSSESSING THE PYRIDONE NUCLEUS

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Dedicated to Professor Dr. Albert Eschenmoser on the occasion of his 85th birthday

Abstract – An efficient method for the stereoselective synthesis of tetracyclic spirolactams was developed based on a spirocyclization of an N-acyliminium ion with 2-methoxypyridine as the aromatic π-nucleophile.

N-Acyliminium ions are an extremely important species in the synthesis of nitrogen-containing natural products. A large number of reactions between N-acyliminium ions and nucleophiles such as olefins, allylsilanes and aromatic rings have been developed. Among various reactions of N-acyliminium ions, spirocyclizations of N-acyliminium ions with tethered pyridines as π-nucleophiles are rarely found, because electron-withdrawing pyridine rings possess low nucleophilicity. However, in 1997, Padwa reported intramolecular cyclizations of N-acyliminium ions derived from N-substituted phthalimides tethered to 2-methoxypyridines. Similarly, we reported that a spirocyclization of an N-acyliminium ion with an activated pyridine afforded spirolactams possessing pyridine or pyridone moieties leading to conformationally constrained nicotine analogues. In order to expand the scope of this methodology, we decided to examine the viability of this approach toward the synthesis of tetracyclic compounds. Herein we report an efficient synthesis of tetracyclic
aza-spiro compounds by use of a spirocyclization between an $N$-acyliminium ion and a 2-methoxypyridine moiety tethered on a cyclohexane ring.

We began our spirocyclization studies by preparing the acyclic amido ketone $\text{11}$, a cyclic $N$-acyliminium ion precursor, starting from cyclohexanone $\text{1}$, as shown in Scheme 1. Aldol reaction of $\text{1}$ with 4-(4-methoxybenzyloxy)butanal$^{11}$ and protection of the resulting hydroxy group of $\text{2}$ as the TBS ether gave $\text{3}$ in moderate yield. Treatment of 2-methoxy-6-methylpyridine$^{12}$ with $n$-BuLi in THF at 0 °C and coupling of the resulting alkylolithium with $\text{3}$ gave the tertiary alcohol $\text{4}$ in 93% yield. Dehydration of $\text{4}$ with thionyl chloride and pyridine produced the alkene $\text{5}$ in 88% yield. Catalytic hydrogenation of the double bond in $\text{5}$ with palladium on carbon resulted in concomitant removal of the PMB group to yield the primary alcohol $\text{6}$. Two-step oxidation (Parikh–Doering oxidation/Pinnick oxidation) of the primary alcohol followed by condensation of the resulting acid $\text{8}$ with BnNH$_2$ using diethyl cyanophosphonate (DEPC) provided the $N$-benzylamide $\text{9}$ in 94% yield. Finally, conversion of $\text{9}$ to the requisite amido ketone $\text{11}$ was accomplished via cleavage of the TBS ether with TBAF followed by Swern oxidation.

With the amido ketone $\text{11}$ in hand, we examined the spirocyclization of $\text{11}$ via a cyclic $N$-acyliminium ion. On the basis of our previous report,$^{10}$ $\text{11}$ was treated with CSA in refluxing $o$-dichlorobenzene for 19 h.$^{13}$ TLC analysis revealed complete disappearance of the starting material and the spirocyclization occurred to give $N$-methylpyridone derivative $\text{12}^{14}$ as the major product in 44% yield, along with the
$N$-norpyridone derivative 13$^{15}$ in 27% yield. As determination of the stereochemistry of the resulting tetracyclic compounds 12 and 13 was not possible by NMR, the relative configuration of the tetracyclic compound 12 having a *trans*-fused decalin was confirmed as depicted in Figure 1 by X-ray crystallographic analysis.$^{16}$

![Figure 1. Spirocyclization of the amido ketone 11 and Chem3D drawing of the X-ray structure of 12.](image)

The observed stereochemistry of the spirocyclization products 12 and 13 can be rationalized by considering the isomerization of *cis*-configured *N*-acyliminium ion 14A, generated from the amido ketone 11, to the thermodynamically more stable *trans*-epimer 14B through the formation of an *exo*-alkene intermediate 15. Additionally, the formation of 12 and 13 are interpreted as resulting from the thermally induced rearrangement$^{17}$ or Hilbert–Johnson type reaction$^{18}$ of the spirolactam 16 formed upon spirocyclization of the *N*-acyliminium ion 14B (Scheme 2).

![Scheme 2. Plausible pathway to the spirolactams 12 and 13 via spirocyclization of the cyclic *N*-acyliminium ions 14A, B.](image)

In conclusion, we demonstrated the stereoselective construction of tetracyclic spirolactams having the 2-pyridone nucleus, based on intramolecular spirocyclization between an *N*-acyliminium ion and the internal pyridine ring activated by a 2-methoxy substituent.
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REFERENCES (AND NOTES)
13. Experimental procedure: A mixture of the amido ketone 11 (38.0 mg, 96.3 µmol) and CSA (11.0 mg, 48.2 µmol) in o-dichlorobenzene (4 mL) was heated at reflux for 19 h, and then allowed to cool to room temperature. This mixture was basified by the addition of sat. aq. NaHCO₃ and extracted with CHCl₃. The combined organic layers were washed with brine, dried (MgSO₄), and
concentrated in vacuo. The residue was purified by column chromatography (CHCl₃–MeOH, 30:1) to give 12 (16.1 mg, 44%) and 13 (9.4 mg, 27%), respectively.

14. Data for spiro[(5S*,5aS*,9aR*)-1-methyl-5,5a,6,7,8,9,9a-octahydrobenz[g]quinoline-5,5'-1-benzyl]pyrrolidin-2'-one] (12): colorless prism after recrystallization from EtOH–AcOEt. mp 258–260 °C; IR (KBr): 1678, 1656 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.48–1.36 (6H, m), 1.52–1.90 (5H, m), 2.15 (1H, A part of ABX, J = 17.8, 10.3 Hz), 2.20–2.51 (3H, m), 2.70 (1H, B part of ABX, J = 17.8, 5.5 Hz), 3.50 (3H, s), 3.63 and 4.84 (2H, ABq, J = 14.8 Hz), 6.43 (1H, d, J = 9.5 Hz), 6.96 (1H, d, J = 9.5 Hz), 7.19–7.28 (5H, m); ¹³C NMR (100.6 MHz, CDCl₃): δ 25.0, 25.1, 25.3, 30.4, 30.5, 30.7, 32.7, 34.3, 35.3, 43.7, 44.2, 69.4, 118.7, 118.9, 127.5, 128.3 (2C), 129.1 (2C), 137.2, 138.2, 143.9, 162.7, 175.9; HRMS (ESI–TOF): calcd for C₂₄H₂₉N₂O₂ (M⁺ + H) 377.2229, found 377.2229.

15. Data for spiro[(5S*,5aS*,9aR*)-5,5a,6,7,8,9,9a-octahydrobenz[g]quinolin-2(1H)-one-5,5-(1-benzyl)pyrrolidin-2-one] (13): white crystals. mp 293–295 °C; ¹H NMR (400 MHz, CDCl₃): δ 0.49–1.41 (6H, m), 1.53–1.91 (5H, m), 2.23–2.52 (4H, m, including 1H, A part of ABX, J = 17.8, 11.0 Hz), 2.71 (1H, B part of ABX, J = 17.8, 5.3 Hz), 3.73 and 4.79 (2H, ABq, J = 14.7 Hz), 6.35 (1H, d, J = 9.4 Hz), 7.07 (1H, d, J = 9.5 Hz), 7.21–7.52 (5H, m), 12.8 (1H, br s); ¹³C NMR (100.6 MHz, CDCl₃): δ 25.1, 25.2, 25.3, 30.5, 30.9, 32.8, 34.0, 34.3, 44.2, 44.7, 68.8, 118.4, 118.9, 127.5, 128.4 (2C), 129.1 (2C), 138.2, 140.1, 164.8, 176.0.

16. Crystal data for 12: Crystal size: 0.48 × 0.43 × 0.30 mm; Cell dimension: a = 9.4640 (4) Å, b = 15.2930 (5) Å, c = 15.4750 (5) Å; Cell volume: 1924.13 (12) Å³; Z = 4.
