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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

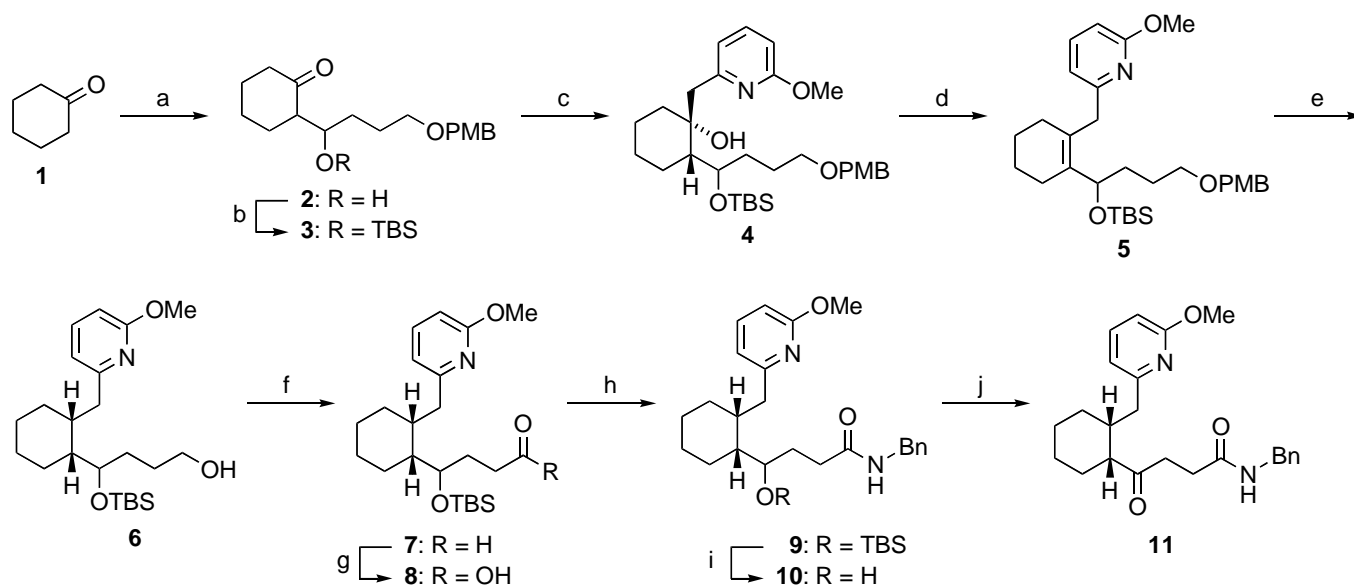
Abstract – An efficient method for the stereoselective synthesis of tetracyclic spirolactams was developed based on a spirocyclization of an *N*-acyliminium ion with 2-methoxypyridine as the aromatic π -nucleophile.

N-Acyliminium ions are an extremely important species in the synthesis of nitrogen-containing natural products.¹ A large number of reactions between *N*-acyliminium ions and nucleophiles such as olefins, allylsilanes and aromatic rings have been developed.²⁻⁸ 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, Padwa⁹ 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.¹⁰

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 **11**, a cyclic *N*-acyliminium ion precursor, starting from cyclohexanone **1**, as shown in Scheme 1. Aldol reaction of **1** with 4-(4-methoxybenzyloxy)butanal¹¹ and protection of the resulting hydroxy group of **2** as the TBS ether gave **3** in moderate yield. Treatment of 2-methoxy-6-methylpyridine¹² with *n*-BuLi in THF at 0 °C and coupling of the resulting alkylolithium with **3** gave the tertiary alcohol **4** in 93% yield. Dehydration of **4** with thionyl chloride and pyridine produced the alkene **5** in 88% yield. Catalytic hydrogenation of the double bond in **5** with palladium on carbon resulted in concomitant removal of the PMB group to yield the primary alcohol **6**. Two-step oxidation (Parikh–Doering oxidation/Pinnick oxidation) of the primary alcohol followed by condensation of the resulting acid **8** with BnNH₂ using diethyl cyanophosphonate (DEPC) provided the *N*-benzylamide **9** in 94% yield. Finally, conversion of **9** to the requisite amido ketone **11** was accomplished via cleavage of the TBS ether with TBAF followed by Swern oxidation.



Scheme 1. Synthesis of the *N*-benzylamide **11.** a) LDA, THF, –78 °C, 15 min, then 4-(4-methoxybenzyloxy)butanal, –78 °C, 10 min, 67%; b) TBSCl, Imidazole, DMF, rt, 5 h, 84%; c) 2-methoxy-6-methylpyridine, *n*-BuLi, –78 °C to 0 °C, 30 min, then **3**, 0 °C, 30 min, 93%; d) SOCl₂, pyridine, CH₂Cl₂, 0 °C, 10 min, 88%; e) H₂, 10% Pd–C, THF, rt, 48 h, 74%; f) SO₃–Py, Et₃N, DMSO, rt, 30 min; g) NaClO₂, 2-methyl-2-butene, NaH₂PO₄, *tert*-BuOH–H₂O, rt, 1 h, 96% over 2 steps; h) BnNH₂, DEPC, Et₃N, THF, rt, 12 h, 94%; i) TBAF, THF, rt, 3 h, 92%; j) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, –78 °C to rt, 30 min, 79%.

With the amido ketone **11** in hand, we examined the spirocyclization of **11** via a cyclic *N*-acyliminium ion. On the basis of our previous report,¹⁰ **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 **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

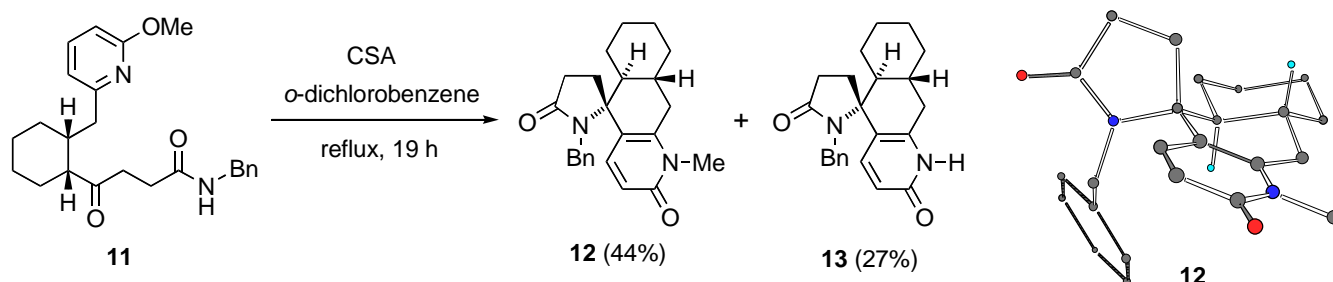
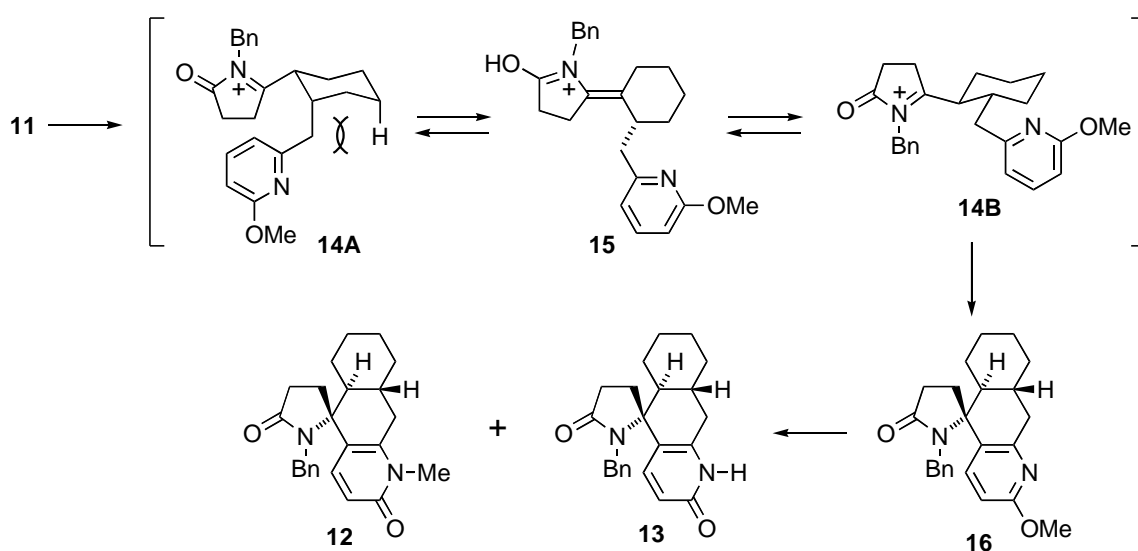


Figure 1. Spirocyclization of the amido ketone **11** and Chem3D drawing of the X-ray structure of **12**.

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 rearrangement¹⁷ or Hilbert–Johnson type reaction¹⁸ of the spiro lactam **16** formed upon spirocyclization of the *N*-acyliminium ion **14B** (Scheme 2).



Scheme 2. Plausible pathway to the spiro lactams **12** and **13** via spirocyclization of the cyclic *N*-acyliminium ions **14A**, **B**.

In conclusion, we demonstrated the stereoselective construction of tetracyclic spiro lactams 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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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. NaHCO_3 and extracted with CHCl_3 . The combined organic layers were washed with brine, dried (MgSO_4), 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[(5*S**,5*aS**,9*aR**)-1-methyl-5,5*a*,6,7,8,9,9*a*-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[(5*S**,5*aS**,9*aR**)-5,5*a*,6,7,8,9,9*a*-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.
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