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## **SPIROCYCLIZATION OF AN *N*-ACYLIMINIUM ION WITH SUBSTITUTED PYRIDINE: SYNTHESIS OF TRICYCLIC SPIROLACTAMS POSSESSING PYRIDINE OR PYRIDONE NUCLEUS**

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*Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75<sup>th</sup> birthday*

**Abstract** – Spirocyclization of an *N*-acyliminium ion with pyridine activated by a 2-methoxy substituent as an aromatic  $\pi$ -nucleophile was developed. The reactions proceeded in the presence of Brønsted acids at a high temperature, producing tricyclic spirolactams that possess the ability to act as conformationally constrained nicotine analogues.

### **INTRODUCTION**

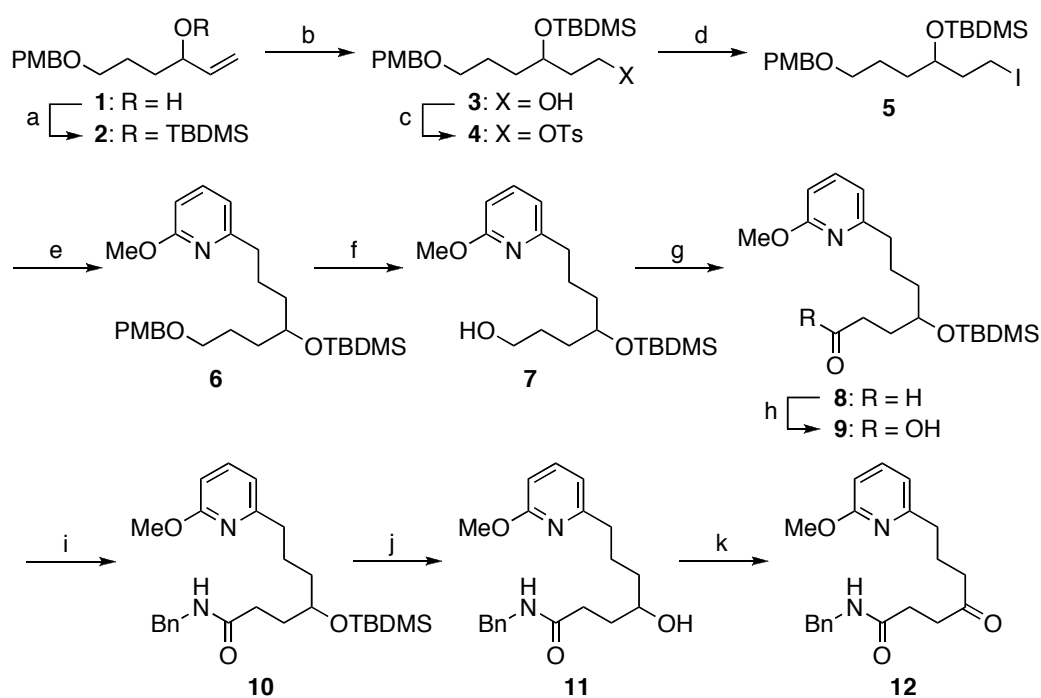
*N*-Acyliminium ions are an extremely important species in the field of the synthesis of nitrogen-containing natural products. A large number of reactions between *N*-acyliminium ions and nucleophiles have been developed to date, and have found widespread use in the total synthesis of bioactive natural products,<sup>1</sup> in which many species such as olefins, allylsilanes, and aromatic rings act as  $\pi$ -nucleophiles in inter- or intramolecular reactions involving spirocyclizations.<sup>2-8</sup> Since the electron-withdrawing pyridine ring possesses the low nucleophilicities, spirocyclizations of *N*-acyliminium ions with tethered pyridines as a  $\pi$ -nucleophile have been hardly found. However, the reaction between *N*-acyliminium ions and activated pyridines has been reported by Padwa et. al.<sup>9</sup> They demonstrated the intramolecular cyclizations of *N*-acyliminium ions derived from *N*-substituted

phthalimide tethering to 2-methoxypyridines, under refluxing benzene in the presence of TsOH, producing tetracyclic lactams in good yield, while *N*-acyliminium cyclization of  $\alpha$ -hydroxypyrrolidinones tethering to pyridines under the same conditions led to tricyclic lactams in very low yield.

Herein we report a new spirocyclization of an *N*-acyliminium ion with activated pyridine to afford spiro lactams possessing pyridine or pyridone nucleus.

## RESULTS AND DISCUSSION

We began our investigation by preparing the acyclic amido ketone **12**, a cyclic *N*-acyliminium ion precursor, starting from the allylic alcohol **1**<sup>10</sup> as shown in Scheme 1. Protection of the hydroxy group of **1** as the TBDMS ether and hydroboration with 9-BBN gave the primary alcohol **3** in 95% yield, which was then transformed into the iodide **5** by tosylation followed by treatment with sodium iodide. Treatment of 6-methyl-2-methoxypyridine<sup>11</sup> with *n*-BuLi in THF at 0 °C and coupling of the resulting alkyl lithium with **5** gave the heptylpyridine derivative **6** in 91% yield. Removal of the PMB group with DDQ and two-step oxidation (Parikh–Doering oxidation/Pinnick oxidation) of the resulting alcohol **7** yielded the carboxylic acid **9** in 88% yield. Condensation of **9** with BnNH<sub>2</sub> was achieved by using diethyl cyanophosphonate (DEPC) to provide the *N*-benzylamide **10** in 98% yield. Finally,

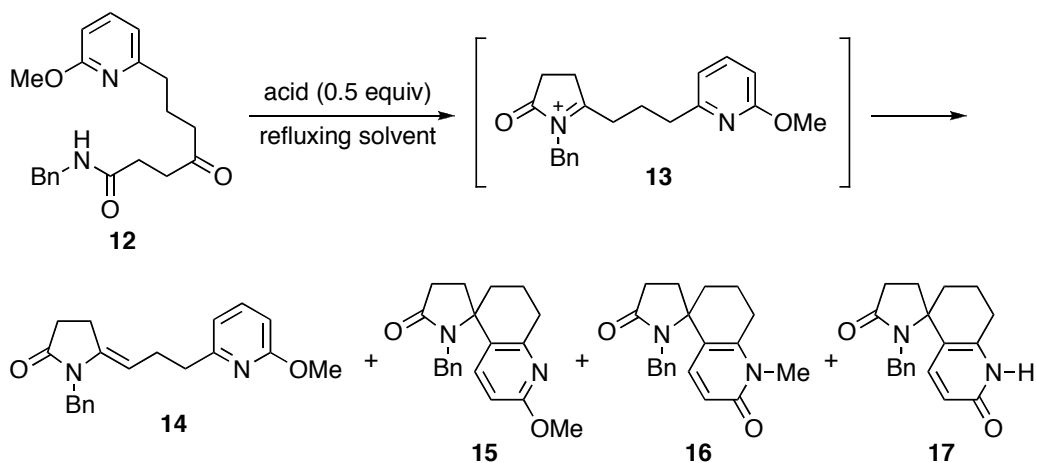


**Scheme 1. Synthesis of the *N*-benzylamide **12**** a) TBDMSCl, Imidazole, DMF, rt, 12 h, 90%; b) 9-BBN, THF, rt, 12 h, then 35% H<sub>2</sub>O<sub>2</sub> aq., 3 M NaOH aq., rt, 1 h, 95%; c) TsCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 3 h; d) NaI, 2-butanone, refl., 1 h, 88% over 2 steps; e) 2-methoxy-6-methylpyridine, *n*-BuLi, -78 °C then rt, 30 min, 91%; f) DDQ, CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O, rt, 30 min, 86%; g) SO<sub>3</sub>·Py, Et<sub>3</sub>N, DMSO, rt, 30 min; h) NaClO<sub>2</sub>, 2-methyl-2-butene, NaH<sub>2</sub>PO<sub>4</sub>, *tert*-BuOH-H<sub>2</sub>O, rt, 1 h, 86% over 2 steps; i) BnNH<sub>2</sub>, DEPC, Et<sub>3</sub>N, THF, rt, 1 h, 98%; j) TBAF, THF, rt, 12 h, 90%; k) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 1 h, 83%.

conversion of **10** to the requisite amido ketone **12** was accomplished via cleavage of the TBDMS ether with TBAF followed by Swern oxidation.

Having obtained the amido ketone **12** in an efficient way, we investigated the spirocyclization of **12** via the cyclic *N*-acyliminium ion **13**. First, on the basis of Padwa's result<sup>9</sup> (described above), **12** was treated with TsOH in refluxing toluene for 120 h (Table 1, entry 1).<sup>12</sup> TLC analysis indicated the complete disappearance of the starting material and the spirocyclization led to the desired spiro lactam **15**<sup>13</sup> containing a 2-methoxypyridine ring in 20% yield accompanied with the enamide **14**,<sup>14</sup> the *N*-methylpyridone derivative **16**,<sup>15</sup> and the *N*-norpyridone derivative **17**.<sup>16</sup> When the reaction was carried out using chlorobenzene as a solvent, the yields of all the spiro lactams increased and **15** was obtained as a major product in 34% yield (entry 2). The reaction conducted at a higher temperature in *o*-dichlorobenzene gave **15**, **16**, and **17** in 16%, 47%, and 25% isolated yields, respectively (entry 3). Similar results were obtained when PPTS or CSA was employed as an acid catalyst (entries 4, 5). Under more harsh conditions using sulfuric acid as a catalyst, complete decomposition occurred (entry 6).

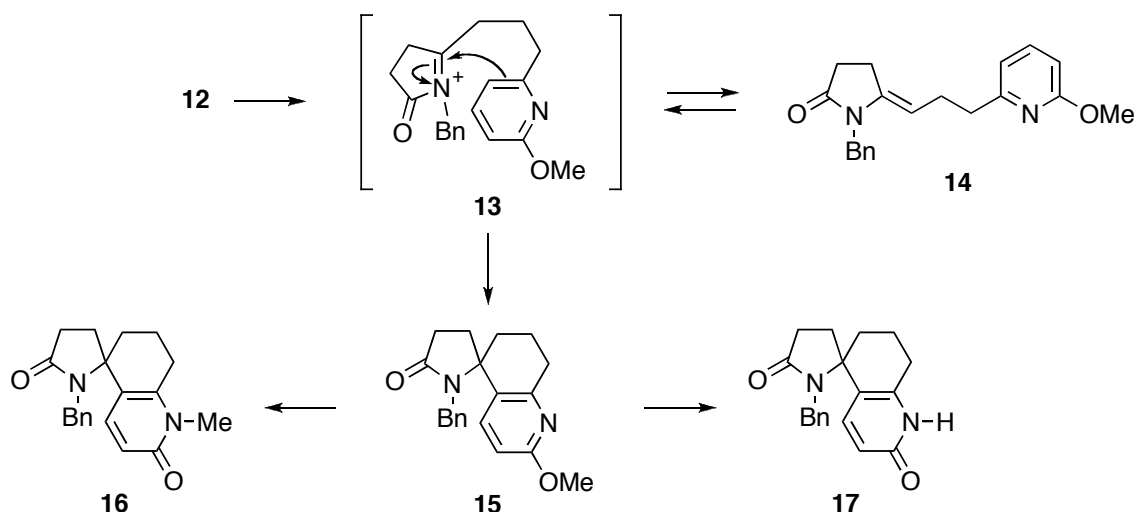
**Table 1.** Spirocyclization of the *N*-benzylamido ketone **12** under acidic conditions



Entry	Acid	Solvent <sup>a</sup> (bp)	Time (h)	Yield (%) <sup>b</sup>			
				<b>14</b>	<b>15</b>	<b>16</b>	<b>17</b>
1	TsOH	toluene (110 °C)	120	31	20	5	16
2	TsOH	chlorobenzene (132 °C)	100	7	34	21	29
3	TsOH	<i>o</i> -dichlorobenzene (180 °C)	20	–	16	47	25
4	PPTS	<i>o</i> -dichlorobenzene (180 °C)	20	–	24	38	35
5	CSA	<i>o</i> -dichlorobenzene (180 °C)	20	–	18	52	24
6	H <sub>2</sub> SO <sub>4</sub>	<i>o</i> -dichlorobenzene (180 °C)	11	complex mixture			

<sup>a</sup> All reactions were carried out in 25 mM solution. <sup>b</sup> Isolated yield.

The formations of **16** and **17** are interpreted as resulting from the thermally induced rearrangement<sup>17</sup> and/or Hilbert–Johnson type reaction<sup>18</sup> of the spirolactam **15** formed upon the spirocyclization of the *N*-acyliminium ion **13**, which is in equilibrium with the enamide **14**, derived by dehydration of the amido ketone **12** (Scheme 2).



**Scheme 2.** Plausible pathways to spirolactams **15**, **16**, and **17** via spirocyclization of the cyclic *N*-acyliminium ion **13**

In conclusion, we have developed an efficient methodology for the synthesis of spirolactams fused with 2-methoxypyridine or 2-pyridone nucleus, based on the spirocyclization between an *N*-acyliminium ion and the side-chain pyridine ring activated by 2-methoxy substituent. The obtained spirolactams possess the ability to act as conformationally constrained nicotine analogues.

## ACKNOWLEDGEMENTS

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12. Typical experimental procedure (ex. table 1, entry 1): A mixture of the amido ketone **12** (90.9 mg, 0.267 mmol) and TsOH (25.4 mg, 0.134 mmol) in toluene (11 mL) was heated at reflux for 120 h, and then allowed to cool to room temperature. This mixture was basified by the addition of sat. NaHCO<sub>3</sub>, and extracted with CHCl<sub>3</sub>. The combined organic layers were washed with Brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo. The residue was purified by column chromatography (CHCl<sub>3</sub>-MeOH, 50:1) to gave **14** (26.9 mg, 31%), **15** (16.9 mg, 20%), **16** (4.5 mg, 5%), and **17** (13.1 mg, 16%), respectively.
13. The data of spiro[2-methoxy-5,6,7,8-tetrahydroquinoline-5,5-(1-benzyl)pyrrolidin-2-one] (**15**): colorless oil. UV λ<sub>max</sub> (MeCN) 280 nm; IR (neat) 3465, 1693, 1682 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.63–1.94 (4H, m), 2.05 (1H, A part of ABXX', *J* = 13.2, 8.9, 8.2 Hz), 2.22 (1H, B part of ABXX', *J* = 13.2, 9.3, 6.3 Hz), 2.58 (1H, A' part of A'B'X'X'', *J* = 17.6, 9.3, 5.6 Hz), 2.61 (1H, B' part of A'B'X'X'', *J* = 17.6, 8.3, 8.3 Hz), 2.63–2.83 (2H, m), 3.75 (1H, d, *J* = 15.6 Hz), 3.91 (3H, s), 4.70 (1H, d, *J* = 15.1 Hz), 6.48 (1H, d, *J* = 8.8 Hz), 7.12–7.25 (6H, m, including 1H, d, *J* = 8.8 Hz, at δ 7.17); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 19.7, 29.3, 32.2, 34.4, 35.9, 44.1, 53.4, 66.3, 109.0, 127.05, 127.08, 127.9 (2C), 128.4 (2C), 137.0, 138.5, 155.3, 162.7, 175.8; HRMS (EI) calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>) 322.1681, found 322.1681.

14. The data of (*5E*)-1-benzyloxy-5-[3-(6-methoxypyridin-2-yl)propylidene]pyrrolidin-2-one (**14**): pale yellow oil. IR (neat) 1671  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.37 (2H, q,  $J = 7.4$  Hz), 2.50–2.56 (4H, m), 2.64 (2H, t,  $J = 7.3$  Hz), 3.78 (3H, s), 4.55–4.75 (3H, m, including 2H, s, at  $\delta$  4.63), 6.44 (1H, d,  $J = 7.2$  Hz), 6.52 (1H, q,  $J = 8.2$  Hz), 7.15–7.30 (5H, m), 7.38 (1H, dd,  $J = 8.2, 7.2$  Hz);  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  21.2, 26.6, 28.9, 38.2, 43.7, 53.2, 101.2, 107.5, 115.5, 127.3 (2C), 128.5 (2C), 136.3, 138.6, 139.4, 159.0, 163.8, 175.7; HRMS (ESI-TOF) calcd for  $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2$  ( $[\text{M} + \text{H}]^+$ ) 323.1760, found 323.1771.
15. The data of spiro[1-methyl-5,6,7,8-tetrahydroquinolin-2(*1H*)-one-5,5-(1-benzyl)pyrrolidin-2-one] (**16**): colorless plates. mp 210–212  $^\circ\text{C}$ , UV  $\lambda_{\text{max}}$  (MeCN) 318 nm; IR (KBr) 3422, 1685, 1647  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.58–1.89 (3H, m), 1.93–2.29 (3H, m), 2.50–2.78 (4H, m), 3.55 (3H, s), 3.84 and 4.72 (2H, ABq,  $J = 15.4$  Hz), 6.43 (1H, d,  $J = 9.5$  Hz), 7.01 (1H, d,  $J = 9.5$  Hz), 7.15–7.32 (5H, m);  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  19.1, 27.4, 29.2, 30.6, 32.7, 34.6, 43.9, 65.5, 117.2, 118.4, 127.2, 127.9 (2C), 128.4 (2C), 136.9, 138.1, 145.7, 162.6, 175.5; HRMS (EI) calcd for  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ) 322.1681, found 322.1693.
16. The data of spiro[5,6,7,8-tetrahydroquinolin-2(*1H*)-one-5,5-(1-benzyl)pyrrolidin-2-one] (**17**): colorless plates. mp 253–255  $^\circ\text{C}$ , UV  $\lambda_{\text{max}}$  (MeCN) 312 nm; IR (KBr) 3419, 1654, 1618  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.60–2.08 (5H, m), 2.15–2.23 (1H, m), 2.51–2.74 (4H, m), 3.91 and 4.60 (2H, ABq,  $J = 15.3$  Hz), 6.27 (1H, d,  $J = 9.4$  Hz), 7.05 (1H, d,  $J = 9.4$  Hz), 7.12–7.25 (5H, m), 13.1 (1H, br s);  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  19.0, 26.8, 29.3, 33.4, 34.8, 44.0, 65.0, 117.2, 118.1, 127.3, 128.1 (2C), 128.5 (2C), 138.1, 140.1, 145.3, 164.8, 175.5; HRMS (EI) calcd for  $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ) 308.1525, found 308.1514.
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