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Electrophilic Aromatic Substitution on Pyridine Rings. Intramolecular Cyclization Using *N*-Acyliminium Ions

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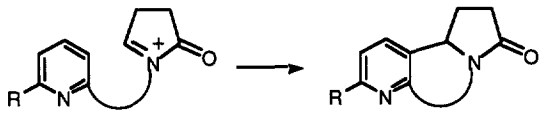
Abstract: The reaction of *N*-acyliminium ions with several activated pyridines resulted in an intramolecular cyclization to provide novel heterocycles. The reaction exhibited a regiochemical preference for cyclization *para* to the electron donating substitutent. © 1997 Elsevier Science Ltd.

The use of electron rich aromatic rings for cationic π-cyclizations[1] has emerged as a powerful method for the construction of novel heterocycles and natural products.[2] These cyclizations have been utilized as the key carbon-carbon bond forming reaction in the synthesis of several alkaloids, including the tetrahydroisoquinoline, β-carboline, and lycopodium classes.[3] From a synthetic standpoint, iminium and *N*-acyliminium ions have emerged as powerful electrophiles for these reactions, allowing for an overall α-imido alkylation.[4,5] The π-systems typically employed in these cyclizations are electron rich aromatics,[6] as well as allyl[7] and vinyl silanes.[8] In contrast, the pyridine ring has received very little attention as a potential nucleophilic partner in cationic π-cyclizations despite its prevalence in a wide variety of biologically important heterocycles.[9] This is not surprising, as the electron-withdrawing effect of nitrogen in pyridine makes this heterocycle considerably less reactive than benzene toward electrophiles.[10] Electrophilic attack at carbon is further complicated in that these reactions are often carried out in highly acidic conditions, which means that the reacting species is often the more electron-deficient conjugate acid. When electrophilic attack does occur, it is generally at the ring nitrogen. An obvious corollary of this high reactivity of electrophiles toward the ring nitrogen atom, is that electrophilic heteroaromatic substitution of the π-deficient heterocycle is exceptionally difficult. Thus, nitration, sulfonation, and halogenation of pyridine require drastic conditions, and yields of the expected 3-substituted products are very low.[11] In this paper, we describe the intramolecular cationic π-cyclization of pyridines of type **1** with tethered *N*-acyliminium ions.

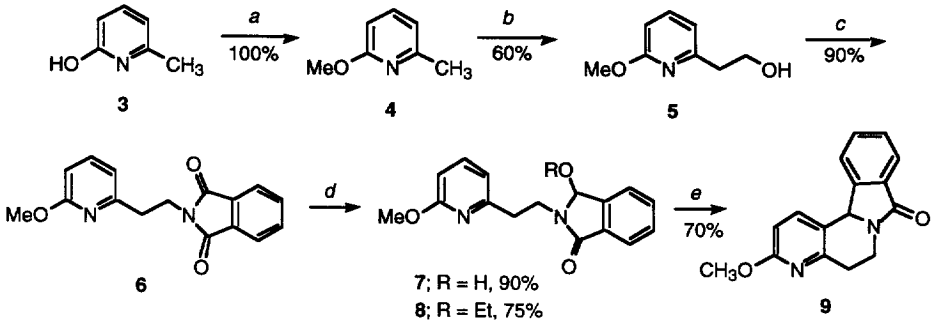


1 R=donor group **2**

Preparation of α-hydroxy lactam **7** was accomplished in four steps in good overall yield starting from the appropriate hydroxy pyridine derivative (Scheme 1). Commercially available 2-hydroxy-6-methyl pyridine (**3**) was alkylated with MeI in the presence of Ag_2CO_3 to furnish 2-methoxy-6-methyl-pyridine (**4**)

in quantitative yield.[12] Deprotonation of **4** with *n*-BuLi at -78 °C, followed by quenching with paraformaldehyde afforded the primary alcohol **5** in 60% yield. Incorporation of the phthalimide functionality was accomplished by nucleophilic substitution using Mitsunobu conditions to provide **6** in 90% yield.[13] Conversion of **6** to the α-hydroxy lactams **7** and **8** was carried out using lithium triethyl-borohydride ($Li(Et)_3BH$) at -78 °C in THF.[14] Our initial attempts to cyclize lactams **7** or **8** using a variety of Lewis acidic conditions ($BF_3{\bullet}OEt_2$, $TiCl_4$, $ZnCl_2$, $SnCl_4$, $BF_3{\bullet}2AcOH$) were unsuccessful, resulting only in the recovery of starting material or decomposition products. Cationic π-cyclization was ultimately successful when protic acids such as *p*-TsOH or CSA were used. For example, when lactam **7** was heated in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, the desired tetracyclic lactam **9** was obtained in 70% yield.[15] The same product was isolated in 55% yield when α-ethoxy amide **8** was treated under similar conditions.

Scheme 1

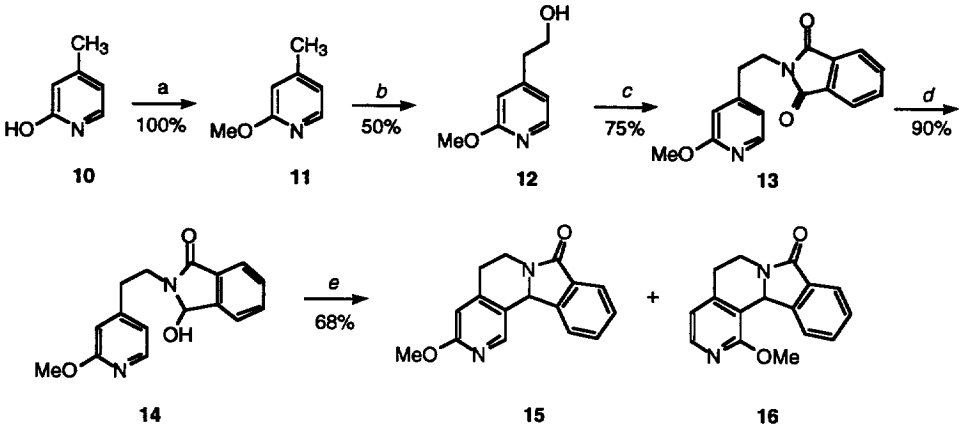


Conditions: (a) $Ag_2(CO)_3$, MeI, CH_2Cl_2; (b) *n*-BuLi, THF, 0 °C, $(CH_2O)_n$, rt; (c) PPh_3, DEAD, phthalimide, THF, rt; (d) $Li(Et)_3BH$, THF, -78 °C, HCl/H_2O (or HCl/EtOH); (e) *p*-TsOH, C_6H_6, Δ

In order to probe the regiochemical preference of the reaction, α-hydroxy lactam **14** was synthesized in an analogous manner to that described above (Scheme 2). 2-Hydroxy-4-methyl-pyridine (**10**) was converted to the methoxy derivative and then transformed into the phthalimide derivative **13** in 38% overall yield. Reduction with $Li(Et)_3BH$ provided α-hydroxy lactam **14** in 90% yield. Treatment of **14** with a catalytic amount of *p*-TsOH in benzene at reflux afforded a 3.5:1 mixture of regioisomers in 68% isolated yield. Silica gel chromatography of the mixture furnished tetracyclic lactam **15** as the major product arising from electrophilic aromatic substitution *para* to the electron donating methoxy substituent. The minor product **16** arises from attack of the *N*-acyliminium ion *ortho* to the methoxy substituent on the pyridine ring.

A final example involved the cyclization of hydroxy-lactam **18**. 2-(6-Methoxy-pyridin-2-yl)-ethanol (**5**) was converted under Mitsunobu conditions to the succinimide derivative **17** in 70% yield (Scheme 3).

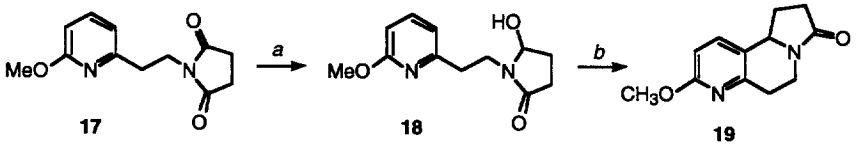
Scheme 2



Conditions: (a) $Ag_2(CO)_3$, MeI, CH_2Cl_2; (b) *n*-BuLi, THF, 0 °C, $(CH_2O)_n$, rt; (c) PPh_3, DEAD, phthalimide, THF, rt; (d) $Li(Et)_3BH$, THF, -78 °C, HCl/H_2O; (e) *p*-TsOH, C_6H_6, Δ

Reduction of **17** to **18** followed by acid catalyzed cyclization led to the tricyclic lactam **19** in only 20% yield. All attempts to improve the yield of the cyclization were unsuccessful. The low yield of **19** may be due to proton loss from the *N*-acyliminium ion, followed by some alternate reaction pathway. Clearly, the best results are obtained when a β-hydrogen is not present on the *N*-acyliminium ion precursor.

Scheme 3



Conditions: (a) $Li(Et)_3BH$, THF, -78 °C, HCl/H_2O; (b) *p*-TsOH, C_6H_6, Δ

In summary, we have shown that the pyridine nucleus can be utilized as a suitable nucleophilic partner in cationic π-cyclizations. Although unactivated pyridine rings do not cyclize well, pyridines containing an electron donating substituent cyclize in good yield. The results presented herein demonstrate the potential of using such cyclizations for the synthesis of novel heterocycles. We are currently investigating further applications of this work for the synthesis of pyridine and pyridone containing natural products.

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References and Notes:

1. Mondon, A.; Hansen, K. F.; Boehme, K.; Faro, H. P.; Nestler, H. J.; Vilhuber, H. G.; Böttcher, K. *Chem. Ber.* **1970**, *103*, 615. Mondon, A.; Seidel, P. R. *Chem. Ber.* **1971**, *104*, 2937. Mondon, A.; Nestler, H. J. *Chem. Ber.* **1979**, *112*, 1329.
2. Hiemstra, H.; Speckamp, W. N. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047-1082.
3. Kametani, T.; Fukumoto, K. *The Chemistry of Heterocyclic Compounds, Isoquinoline Part 1*; Grethe, G., Ed.; Wiley: New York; pp 170-182. Jones, G. *Comprehensive Heterocyclic Chemistry;* Katritzky, A. R., Rees, C. W., Eds. Pergamon: Oxford, 1984; Vol. 2, pp 438-440. Padwa, A.; Brodney, M. A.; Marino, J. P.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78.
4. Speckamp, W. N. *Recl. Trav. Chim. Pays Bas.* **1981**, *100*, 345. Veenstra, S.; Speckamp, W.N. *J. Am. Chem. Soc.* **1981**, *103*, 4645. Wijnberg, B.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, *22*, 5079.
5. Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367. Hart, D. J. *J. Org. Chem.* **1981**, *46*, 3576. Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555. Hart, D. J.; Yang, T. K. *Tetrahedron Lett.* **1982**, *23*, 2671. Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255.
6. Whaley, W. H.; Govindachari, T. R. *Org. React.*, Wiley: New York, 1951, pp 151-206.
7. Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375. Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028. Ofial, A. R.; Mayr, H. *J. Org. Chem.* **1996**, *61*, 5823.
8. Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505. Blumankopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, 86, 857.
9. Reviews: (a) Gellert, E. *In Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley and Sons; New York, 1987; Vol. 5. (b) Suffness, M.; Cordell, G. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, FL, 1983; Vol. 25, p 156. (c) Bick, R. C.; Sinchai, W. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 19, p 193. (d) Govindachari, T. R. In *The Alkaloids*; Manske, R.H.F., Ed.; Academic Press: New York, 1967; Vol. 9, p 517.
10. Reviews: (a) *Pyridine and its Derivatives*, Supplemental ed., Abramovitch, R. A.; Wiley-Interscience: New York, 1974. (b) Smith, D. M. In *Comprehensive Organic Chemistry*, Sammes, P. G., Ed. Pergamon: Oxford, 1979 Vol. 4. (c) *Heterocyclic Chemistry*, Gilchrist, T. L.; Pitman Publ. Ltd.: London, 1985.
11. Comins, D. L.; Joseph, S. P. In *Comprehensive Heterocyclic Chemistry 2nd Edition*, Mckillop, A.; Ed.; Elsevier: Oxford, 1996.
12. Gray, M. A.; Konopski, L.; Langlois, Y. *Synth. Commun.* **1994**, *24*, 1367.
13. Mitsunobu, O. *Synthesis*, **1981**, 1.
14. Fisher, M. L.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447.
15. All new compounds were fully characterized (IR; ^{1}H-NMR; ^{13}C-NMR and analytical data).

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