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A NOVEL ONE STEP PREPARATION OF 2,6-DISUBSTITUTED PYRIDINES FROM BICYCLIC KETALS[1]

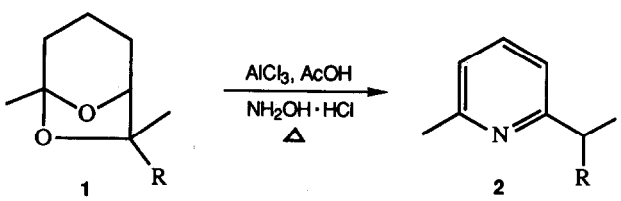
Jong-Gab Jun* and Hyun Shun Shin
Department of Chemistry, Hallym University, Chunchon 200-702, Korea

Abstract: 6,8-Dioxabicyclo[3.2.1]octanes(**1**) were readily converted to 2,6-disubstituted pyridine derivatives(**2**) in one step by treatment with $AlCl_3$-$NH_2OH{\cdot}HCl$/AcOH.

Skeletal transformation is strategically important in synthetic chemistry because it enables otherwise synthetically difficult compounds to be accessible by transformation from other, readily prepared bicyclic ketal systems. Previously, we reported the transformation of 6,8-dioxabicyclo[3.2.1]octane using AcCl-NaI and $AlCl_3$-NaI to δ,ε-unsaturated ketone[2] and 1,5-diketone[3] respectively.

Now we wish to describe the novel skeletal transformation of readily prepared 5,7-dimethyl-7-substituted-6,8-dioxabicyclo[3.2.1]octanes[4] to 2,6-disubstituted pyridines in one step (Table). In 1988, Morris and Wishka described the synthesis of a series of 2,6-disubstituted pyridine analogs of leukotriene B_4(LTB_4) which were found to bind competitively to LTB_4 receptors in human neutrophils.[5]

Table. Direct Transformation of Bicyclic Ketal Compound to Pyridine



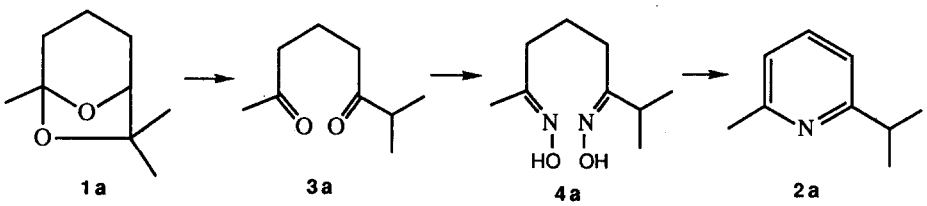
1 2

Entry	R	Yield(%)
2a	Me	83
2b	Et	99
2c	Pr	84
2d	i-Pr	63
2e	Bu	84
2f	t-Bu	73
2g	Ph	52

A solution of the 5,7,7-trimethyl-6,8-dioxabicyclo[3.2.1]octane(**1a**, 0.5 mmol) in AcOH(3 ml) was refluxed for 20h with $AlCl_3$(2 eq.) and $NH_2OH \cdot HCl$(3 eq.) to give, after basic work-up followed by short-path column chromatography, the pyridine(**2a**, 83%).[6] 1,5-Diketone(**3a**) could be involved as an intermediate for this novel rearrangement reaction.[7] In order to prove this mechanism, we prepared the 1,5-diketone(**3a**)[3] which was reacted with $NH_2OH \cdot HCl$ to give the 1,5-dioxime(**4a**). Finally, the 1,5-dioxime was transformed to pyridine(**2a**) by using $AlCl_3$ in AcOH(Scheme).

In conclusion, we prepared 2,6-disubstituted pyridine directly from bicyclic ketal in high yield.

Scheme



1a **3a** **4a** **2a**

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References and Notes:

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4) B. P. Mundy, K. B. Lipkowitz, and G. W. Dirks, *Heterocycles*, **6**, 51(1977).
5) (a) J. Morris and D. G. Wishka, *Tetrahedron Lett.*, **29**, 143(1988); (b) A. H. Lin, J. Morris, D. G. Wishka, R. R. Gorman, and N. Y. Ann, *Acad. Sci.*, **524**, 196(1988).
6) Spectral data for (**2a**): IR(neat) 2921, 1589, 1530, 1462, 1427, 1373, 790, 746 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 7.53(1H, t, J=7.7 Hz, pyridine-H_4), 6.99(2H, dd, 7.7, 1.6 Hz, pyridine-H_3 and H_5), 3.07(1H, hept, J=7.1 Hz, $CHMe_2$), 2.57(3H, s, pyridine-CH_3), 1.32(6H, d, J=7.1 Hz, $(CH_3)_2C$); ^{13}C-NMR δ ($CDCl_3$) 167.4(s), 157.9(s), 137.1(d), 121.0(d), 117.3(d), 37.0(d), 25.0(q), 23.2(q, 2 x Me); MS m/z 135(M^+), 134, 120(base), 107, 93, 77, 65.
Compounds (**2b-g**) were also characterized by ^{1}H-, ^{13}C-NMR and IR spctroscopy.
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