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A FACILE ONE-POT SYNTHESIS OF 2,3,6-TRISUBSTITUTED PYRIDINE DERIVATIVES FROM BICYCLIC KETAL BY USING TMSOMs (5 equiv.)-$BF_3 \cdot Et_2O$ (1 equiv.)[1]

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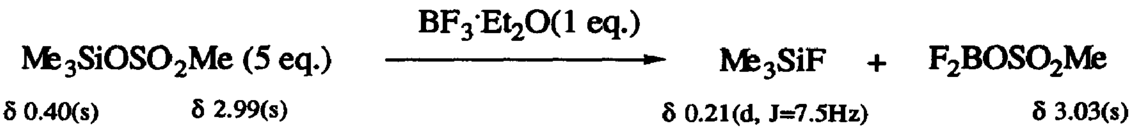
Abstract : TMSOMs (5 equiv.)-$BF_3 \cdot Et_2O$ (1 equiv.) complex was studied for the selective cleavage of bicyclic ketal and a useful method was found for the preparation of 2,3,6-trisubstituted pyridine in good yield. The bicyclic ketal was cleaved and rearranged to 1,5-diketone which was then reacted with nitrile affording pyridine as a sole product in one-flask.

Although many Lewis acids are demonstrated for the ether cleavage in organic chemistry,[2] a mild reagent system is worth to develop for selectivity. The combination of 5 equivalents of trimethylsilyl methanesulfonate (TMSOMs) and 1 equivalent of boron trifluoride etherate ($BF_3 \cdot Et_2O$) was known as a mild Lewis acid for the reductive cleavage of methylated glycans.[3] Application of this reagent system, however, was not well investigated. In our continuous research in developing the utility of bicyclic ketal in the 6,8-dioxabicyclo[3.2.1]octane skeletal system transforming to the other important structures, we developed useful methods for the synthesis of 1,5-diketone,[4] 2,6-disubstituted pyridine[5] and cis-1,2-cyclopentanediol derivatives[6] from bicyclic ketal in one-step. We report here the mild Lewis acid system, TMSOMs (5 equiv.)-$BF_3 \cdot Et_2O$ (1 equiv.), for the selective synthesis of 2,3,6-trisubstituted pyridine **2** from bicyclic ketal **1** with nitrile.

The chemical shift of ^{29}Si-NMR indicates that TMSOMs(δ_{si} 37.9) is less reactive and much milder than TMSOTf(δ_{si} 46.6) and TMSOFs(δ_{si} 52) toward basic centers.[7] TMSOMs itself had not enough reactivity for ketal cleavage, and TMSOTf or $BF_3 \cdot Et_2O$ yielded side products. Only the combination of TMSOMs (5 equiv.)-$BF_3 \cdot Et_2O$ (1 equiv.) complex gave pyridine as a single product.

The nature of the TMSOMs (5 equiv.)-$BF_3 \cdot Et_2O$ (1 equiv.) complex was studied by ^{1}H-NMR. The trimethylsilyl singlet of TMSOMs was observed at δ 0.40, and the methanesulfonyl methyl singlet at δ 2.99. The addition of 0.2 equiv. of $BF_3 \cdot Et_2O$ (relative to 1.0 equiv. of TMSOMs) gave rise to a new trimethylsilyl signal at δ 0.21 (d, J=7.5 Hz), and a new methanesulfonyl methyl singlet at δ 3.03, in addition to the expected resonances of diethyl ether. The trimethylsilyl signal at δ 0.21 was readily identified as being due to trimethylsilyl fluoride, because it was a doublet, and this assignment was confirmed by generating TMSF independenly from TMSOMs, and tetrabuthylammonium fluoride in a separate experiment.[3] A new methanesulfonyl methyl signal at δ 3.03 was identified as being due to F_2BOMs which was separated by distillation (153-155 °C at 3 torr) and showed singlet at δ -1.01 in ^{11}B-NMR. Distilled F_2BOMs showed same reactivity as the mixture of TMSOMs (5 equiv.)-$BF_3{\cdot}Et_2O$ (1 equiv.). Some related compounds, also, were reported by Olah *et al.* [8]; dissolution of TMSOTf in neat BCl_3 or BBr_3 was shown to give rise to bimolecular complexes which subsequently underwent ligand exchange to form TMSCl and Cl_2BOTf, or TMSBr and Br_2BOTf, respectively. These results therefore indicated that TMSOMs and $BF_3{\cdot}Et_2O$ react to form TMSF and F_2BOMs *via* ligand exchange.



$$\underset{\delta\ 0.40(s)\qquad\delta\ 2.99(s)}{Me_3SiOSO_2Me\ (5\ eq.)} \xrightarrow{BF_3{\cdot}Et_2O(1\ eq.)} \underset{\delta\ 0.21(d,\ J=7.5Hz)}{Me_3SiF} + \underset{\delta\ 3.03(s)}{F_2BOSO_2Me}$$

The bicyclic ketal **1** was cleaved and rearranged to 1,5-diketone **3** which was then reacted with acetonitrile affording pyridine as a sole product(**2a**-**2e** in Table) in this mild reagent system(Scheme). Butyronitrile and benzonitrile were used instead of acetonitrile to this pyridine synthesis, and the expected results were found(**2f** and **2g**). Although the cyclohexenone **4** could be the possible product from the direct aldol condensation of 1,5-diketone as shown in Scheme, it was not obtained in this reaction. In the other reagent system, Al-I_2-CH_3CN, the mixture of cyclohexenone and pyridine was found.[9] The cyclobutene **5** was not found in any case because of the structural destability.

In conclusion, F_2BOMs was the active catalyst, which was easily prepared from the mixture of TMSOMs (5 equiv.)-$BF_3{\cdot}Et_2O$ (1 equiv.), for the selective synthesis of pyridine from bicyclic ketal with nitrile in one step.

Typical Procedure; A mixture of 5 equivalents of trimethylsilyl methanesulfonate (0.48 ml) and 1 equivalent of boron trifluoride etherate (0.073 ml) was added to bicyclic ketal **1a** (0.1 g, 0.64 mmol) in acetonitrile (4 ml) while stirring at room temperature; the solution was refluxed for 30h. Aqueous 10% NaOH solution (10 ml) was added, and the product was extracted with ether (3 x 20 ml). The combined ether layer was washed with saturated $NaHCO_3$ (30 ml) and saturated brine (30 ml), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ether-hexane 3:7) gave the pyridine **2a** as a pale yellow oil (83 mg, 73 %).[10]

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REFERENCES AND NOTES:

1. Presented at the Seventh IUPAC Symposium on OrganoMetallic Chemistry directed towards Organic Synthesis, Kobe, Japan, September 19-23, 1993.

Scheme

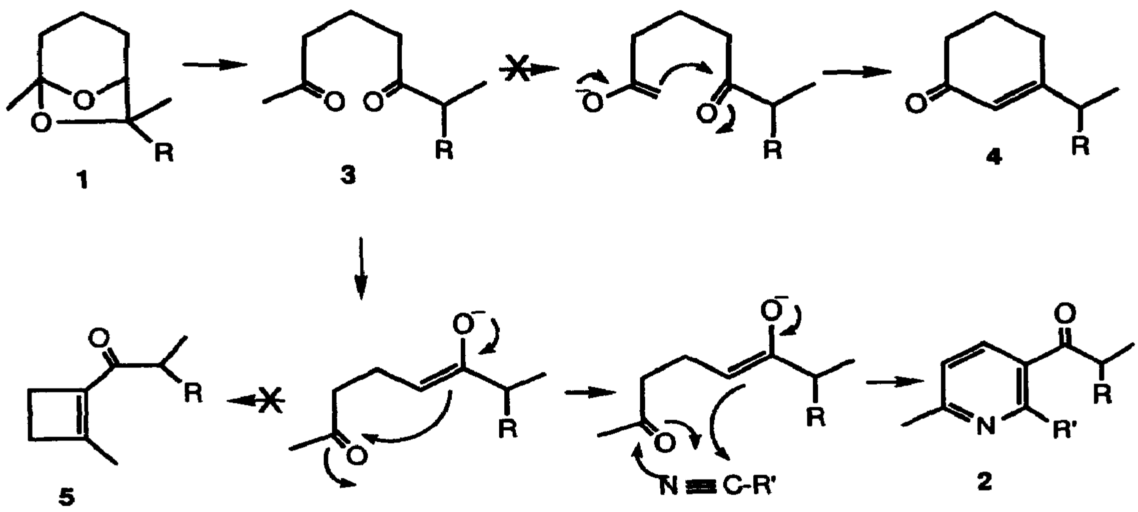
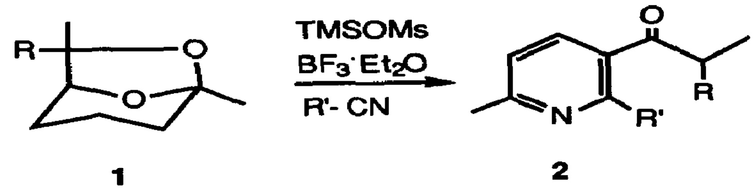


Table. Synthesis of 2,3,6-Trisubstituted Pyridine By Using TMSOMs-$BF_3 \cdot Et_2O$



Entry	R	R'	Rxn time(h)	%yield
a	Me	Me	30	73
b	i-Pr	Me	30	83
c	n-Bu	Me	30	88
d	t-Bu	Me	30	85
e	Ph	Me	48	52
f	Me	n-Pr	30	66
g	Me	Ph	30	58

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10. Spectral data for (**2a**); IR (neat) ; 1684, 1585, 905, 730 cm^{-1}.

    ^{1}H-NMR ($CDCl_3$) ; δ 7.89 (1H, d, J=8.1Hz), 7.07 (1H, d, J=8.1Hz), 3.04 (1H, septet, J=7.0Hz), 2.72 (3H, s), 2.55 (3H, s), 1.28 (6H, d, J=7.0Hz).

    ^{13}C-NMR ($CDCl_3$) ; δ 200.7 (s), 170.3 (s), 158.2 (s), 138.1 (d), 130.7 (s), 117.7 (d), 37.0 (d), 29.8 (q), 25.5 (q), 22.9 (q x 2).

    m/z ; 177 (M^+), 176, 162 (base), 149, 135, 119, 92, 74, 65, 43.

    HRMS ; Found: 177.1149. $C_{11}H_{15}NO$ requires M, 177.1154.

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