REACTION OF 2-TRIMETHYLSILYLMETHYLTHIOPYRIDINE PROMOTED BY A FLUORIDE ION: THE FIRST EXAMPLE OF GENERATION OF 2-PYRIDYLTHIOMETHYLCARBANION

Shinya Kohra,*[a] Hiroshi Ueda,[b] and Yoshinori Tominaga[b]

Faculty of Liberal Arts,[a] Faculty of Pharmaceutical Science,[b] Nagasaki University,
1-14 Bunkyo-machi, Nagasaki 852, Japan

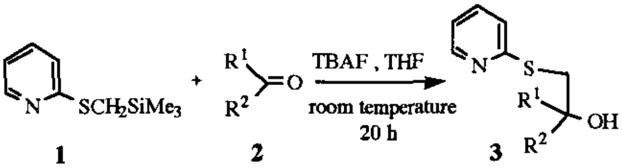
Abstract-2-Trimethylsilylmethylthiopyridine prepared readily by the reaction of 2-mercaptopyridine with chloromethyltrimethylsilane in the presence of potassium carbonate reacts with carbonyl compounds in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) to give 2-(2-pyridylthio)ethanols. This reaction is the first example of generation and introduction of 2-pyridylthiomethyl-carbanion.

The introduction of organosulfur groups into carbon skeleton is one of the most important reactions in synthetic chemistry.[1] For this purpose, in general, α-thiocarbanions, which are stabilized by the sulfur atom, are used.[2] Heterocyclic α-thiocarbanions which are generated by the lithiation of methylthio-substituted heterocycles have been useful reactants in synthetic chemistry.[3] Any expedients however have never been reported to generate 2-pyridylthiomethylcarbanion which is interesting chemical species. Recently we demonstrated a novel arylthiomethylation by using organosilicon compounds.[4] During the couse of our studies on the potential usefulness of organosilicon compounds,[5] we have found that 2-trimethylsilylmethylthiopyridine acts as 2-pyridylthiomethylcarbanion equivalent.

2-Mercaptopyridine was treated with chloromethyltrimethylsilane in the presence of one equivalent of potassium carbonate and a catalytic amount of potassium iodide in ethanol at reflux for 1 h to afford 2-trimethylsilylmethylthiopyridine (**1**)[6] as a pale yellow oil, bp 139°C/20 mmHg, in quantitative yield.

In the first place, the reaction of **1** with 4-phenylbenzaldehyde (**2f**) was taken as a model, and several conditions were examined. A mixture of **1** and two molar equivalents of **2f** in the presence of one equimolar tetrabutylammonium fluoride (TBAF) as a source of fluoride ion in THF was stirred at room temperature for 20 h to give the corresponding 2-pyridylthiomethylated product, 1-(4-biphenyl)-2-(2-pyridylthio)ethanol (**3f**),[7] in 41% yield. It should be noted that effective catalysis can be attained in this reaction. Compound (**3f**) was given in 86% yield when 10% molar equivalents of TBAF were used. On the contrary, the reaction of **1** with **2f** using other source of fluoride ion such as cesium fluoride and tris(dimethylamino)sulfur (trimethylsilyl)-difluolide (TASF) instead of TBAF gave no **3f** and **1** was recovered. As shown in Table 1, a variety of aromatic and aliphatic substrates (**2**) reacted with **1** to give the corresponding β-hydroxy-2-pyridyl sulfides (**3**) under mild and almost neutral conditions. In particular, functional groups such as methoxy, nitro, and chloro

Table 1. Reaction of 2-Trimethylsilylmethylthiopyridine (**1**) with Carbonyl Compounds (**2**)[a)]



1 **2** **3**

Entry	R^1, R^2 (**2**)	Yield(%)
1	$R^1=C_6H_5$, $R^2=H$ (**2a**)	53 (**3a**)
2	$R^1=4\text{-}MeOC_6H_4$, $R^2=H$ (**2b**)	20 (**3b**)
3	$R^1=4\text{-}O_2NC_6H_4$, $R^2=H$ (**2c**)	30 (**3c**)
4	**2c**	54[b)] (**3c**)
5	$R^1=4\text{-}ClC_6H_4$, $R^2=H$ (**2d**)	86 (**3d**)
6	$R^1=2,6\text{-}Cl_2C_6H_3$, $R^2=H$ (**2e**)	91 (**3e**)
7	$R^1=4\text{-}C_6H_5C_6H_4$, $R^2=H$ (**2f**)	86 (**3f**)
8	R^1=1-naphthyl , $R^2=H$ (**2g**)	65 (**3g**)
9	$R^1=Me(CH_2)_{10}$, $R^2=H$ (**2h**)	37 (**3h**)
10	$R^1=(E)\text{-}C_6H_5CH{:}CH$, $R^2=H$ (**2i**)	61 (**3i**)
11	$R^1=C_6H_5$, $R^2=Me$ (**2j**)	29 (**3j**)
12	$R^1=CH_3(CH_2)_5$, $R^2=Me$ (**2k**)	14 (**3k**)
13	$R^1=(E)\text{-}C_6H_5CH{:}CH$, $R^2=C_6H_5$ (**2l**)	27 (**3l**)
14	$R^1+R^2=(CH_2)_5$ (**2m**)	13 (**3m**)

a) All reactions were carried out in a system of **1** (0.5 mmol), **2** (1.0 mmol) and TBAF (10 mol%) in THF (5 ml).

b) An equivalent of TBAF was used.

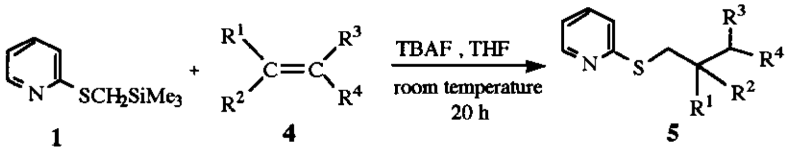
are intact under the present conditions and chemoselective 2-pyridylthiomethylation occurs. The reaction of α,β-unsaturated aldehyde with **1** proceeded entirely in the 1,2-addition mode.

Also we have found that compound (**1**) reacts with active alkenes (**4**) such as acrylates under the similar conditions to afford the corresponding Michael type adducts (**5**) (Table 2).[8]

A general experimental procedure is given as the following. Under nitrogen a solution of compound (**1**) (0.5 mmol, 99 mg), 4-phenylbenzaldehyde (**2f**) (1.0 mmol, 182 mg), and TBAF (1.0 M in THF, 0.05 ml, 0.05 mmol) in dry THF (5 ml) was stirred at room temperature for 20 h. The solvent was removed and the crude product was purified by silica gel column chromatography using a mixture of hexane and ethyl acetate (3 : 1) as eluents to give **3f** (0.43 mmol, 132 mg) in 86% yield.

In conclusion, we have devised the first procedure of generation of 2-pyridylthiomethylcarbanionic species using 2-trimethylsilylmethylthiopyridine. A synthetic utility of the present reaction was mostly displaed by the ready accessibility of the starting materials, easy manipulation of the conversion, and mild conditions. The products of the present reaction, β-hydroxy-2-pyridyl sulfides, will be versatile synthetic intermediates.

Table 2. Reaction of 2-Trimethylsilylmethylthiopyridine (**1**) with Alkenes (**4**)[a]



Entry	R^1, R^2, R^3, R^4	Yield(%)
1	R^1=H, R^2=H, R^3=H, R^4=COOMe (**4a**)	21 (**5a**)
2	R^1=H, R^2=H, R^3=H, R^4=COOEt (**4b**)	16 (**5b**)
3	R^1=COOMe, R^2=H, R^3=COOMe, R^4=H (**4c**)	28 (**5c**)
4	R^1=COOEt, R^2=H, R^3=COOEt, R^4=H (**4d**)	18 (**5d**)
5	R^1=COOMe, R^2=H, R^3=H, R^4=COOMe (**4e**)	19 (**5e**)
6	R^1=COOEt, R^2=H, R^3=H, R^4=COOEt (**4f**)	27 (**5f**)

a) All reactions were carried out in a system of **1** (1.0 mmol), **4** (2.0 mmol) and TBAF (10 mol%) in THF (5 ml).

REFERENCES AND NOTES

1. D. J. Peterson, Organomet. Chem. Rev. A, 7, 295 (1972); J. C. Stowell, "Carbanion in Organic Synthesis," Wiley, New York, 1979, pp. 90-115.
2. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353; E. J. Corey and D. Seebach, *J. Org. Chem.*, 1966, **31**, 4097; D. J. Peterson, *ibid.*, 1967, **32**, 1717; T. M. Dolac and T. A. Bryson, *Tetrahedron Lett.*, **1977**, 1961; W. H. Pirkle and P. L. Rinaldi, *J. Org. Chem.*, 1978, **43**, 3803.
3. C. R. Johnson, A. Nakanishi, and K. Tanaka, *Tetrahedron Lett.*, **1975**, 2865; K. Soai and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3371; A. I. Mayer and M. E. Ford, *J. Org. Chem.*, 1976, **41**, 1735.
4. A. Hosomi, K. Ogata, K. Hoashi, S. Kohra, and Y. Tominaga, *Chem. Pharm. Bull.*, 1988, **36**, 3736.
5. Y. Tominaga, H. Ueda, K. Ogata, S. Kohra, M. Hojo, M. Ohkuma, K. Tomita, and A. Hosomi, *Tetrahedron Lett.*, 1992, **33**, 85.

6. **1** : Yield 98%; bp 139°C/20 mmHg. Ir (neat) vmax: 1580, 1418, 1250, 852, 779 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.16 (9H, s, $SiMe_3$), 2.36 (2H, s, -CH_2-), 6.94 (1H, ddd, J = 7.0, 4.8, 1.2 Hz, 4'-H), 7.18 (1H, ddd, J = 8.0, 1.2, 1.0 Hz, 3'-H), 7.45 (1H, ddd, J = 8.0, 7.0, 1.9 Hz, 5'-H), 8.41 (1H, ddd, J = 4.8, 1.9, 1.0 Hz, 6'-H). Ms m/z: 197 (M^+, 11), 182 (100), 150 (14), 78 (12), 73 (25). *Anal.* Calcd for $C_9H_{15}NSSi$: C, 54.77; H, 7.66; N, 7.10. Found: C, 54.51; H, 7.54; N, 7.10.
7. **3f** : Yield 86%; mp 100-102°C (n-hexane-ethyl acetate). Ir (KBr) vmax: 3220 (OH), 1580, 1417, 1122, 760 cm^{-1}. ^{1}H-Nmr ($CDCl_3$)δ: 3.47 (2H, dd, J = 3.4 and 4.0 Hz, -CH_2-), 5.14 (1H, dd, J = 6.4 and 4.2 Hz, -C$\underline{H}$(OH)-), 6.50 (1H, bs, OH), 6.97-7.66 (12H, m, aromatic protons), 8.43 (1H, m, 6'-H on pyridine ring). FAB-ms m/z: 308 (M^++1, 75). *Anal.* Calcd for $C_{19}H_{17}NOS$: C, 74.23; H, 5.58; N, 4.56; S, 10.43. Found: C, 74.36; H, 5.67; N, 4.50; S, 10.16.

   Other **3** were fully characterized by ^{1}H-nmr (90 MHz), ir, HR-ms.
8. **5a** : Yield 21%. Ir (neat) vmax: 2860, 1738, 1579, 1418, 1124, 760 cm^{-1}. ^{1}H-Nmr ($CDCl_3$)δ: 1.68-2.38 (2H, m, -$CH_2C\underline{H_2}CH_2$-), 2.48 (2H, t, J = 7.0 Hz, $C\underline{H_2}CO_2CH_3$), 3.22 (2H, t, J = 6.9 Hz, SCH_2), 3.66 (3H, s, OCH_3), 6.87-7.55 (3H, m, 3',4',5'-H), 8.39 (1H, ddd, J = 4.8, 1.9, 1.0 Hz, 6'-H). HR-ms Calcd for $C_{10}H_{13}NO_2S$ m/z 211.066. Found m/z 211.066.

   Other **5** were fully characterized by ^{1}H-nmr (90 MHz), ir, HR-ms.

Received, 18th February, 1993