SYNTHESIS AND REACTION OF *N*-TRIMETHYLSILYLMETHYL-ISOTHIOUREA DERIVATIVES AS AMINONITRILE YLIDE EQUIVALENTS

Makoto Oba, Masahiro Yoshihara, and Kozaburo Nishiyama*

Department of Material Science and Technology, Tokai University, 317, Nishino, Numazu, Shizuoka 410-03, Japan

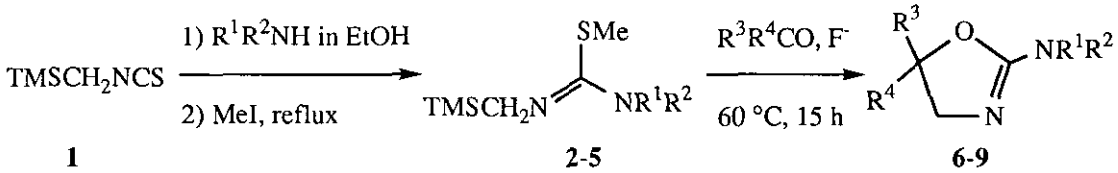
Abstract- *N*-Trimethylsilylmethylisothiourea derivatives (**2**-**5**) prepared by an addition of an amine toward trimethylsilylmethyl isothiocyanate (**1**) followed by *S*-methylation were found to react with various carbonyl compounds in the presence of fluoride ion to afford the oxazoline derivatives (**6**-**9**), the formal [3 + 2] cycloadducts, in fair yields, in which the isothiourea derivatives served as aminonitrile ylide equivalents.

Heterocyclic compounds are very widely distributed in nature, and those are essential to life in various ways and are also in use as pharmaceuticals, dyes, pesticides, plastics, and for many other purposes. Therefore, the construction of the new heterocyclic systems and the development of new synthetic protocols are desired earnestly. For the synthesis of five-membered heterocycles, 1,3-dipolar [3 + 2] cycloaddition was regarded as the most important and efficient methodology. Especially, azomethine ylides have represented attractive synthetic building blocks for the nitrogen-containing heterocycles since numerous desilylation methods of *N*-trimethylsilylmethylamine and the related compounds have been extensively studied for generating the desired ylides.[1] However, relatively little work has been done using silicon based 1,3-elimination for the generation of nitrile ylides.[2-4] As an extension of our continuing studies on the reactivity of organosilicon compounds containing heterocumulene unit such as silyl azide, silylmethyl azide, and silyl isothiocyanate,[5] we are now aiming at utilization of trimethylsilylmethyl isothiocyanate for a precursor of silyl-substituted isothiourea derivatives as aminonitrile ylide equivalents which can be obtained by a nucleophilic addition of amines across the isothiocyanate followed by *S*-alkylation. Since these compounds were expected to generate the aminonitrile ylides upon formal elimination of alkylthiosilane, we here describe the preparation and the fluoride ion promoted reaction of *N*-trimethylsilylmethylisothiourea derivatives with a variety of dipolarophiles.

Results and Discussion

As shown in the Scheme 1, *N*-trimethylsilylmethylisothiourea derivative (**2**) was readily obtained in 97%

yield by *S*-methylation of the *N*-trimethylsilylmethylthiourea prepared *in situ* from the addition of piperidine toward trimethylsilylmethyl isothiocyanate (**1**) in EtOH. Simply by changing an amine, various *N*-trimethylsilylmethylisothiourea derivatives (**3-5**) could be obtained by this one pot procedure in moderate to excellent yields (Table 1). In order to avoid the existence of the prototropic tautomers in the isothiourea framework, secondary amines were employed as nucleophiles in this work, which forced the double bond to localize on nitrogen attached to trimethylsilylmethyl moiety. Since these compounds carried a good leaving group, methylthio moiety, at γ-position with respect to the trimethylsilyl group, a fluoride ion promoted desilylation followed by an elimination of methylthio group would generate 1,3-dipolar reagents, aminonitrile ylide in this case. To the best of our knowledge, there are only a few reports concerning a utilization of silylated isothiourea derivatives as 1,3-dipolar equivalents and their structures were limited due to the synthetic restriction.[4,6] The present procedure would provide more general approach to construct the *N*-silylated isothiourea framework.



1 **2-5** **6-9**

Scheme 1

Table 1. Preparation of *N*-Trimethylsilylmethylisothiourea Derivatives (**2-5**).

entry	R^1	R^2	Compd.	Yield (%)
1	$-(CH_2)_5-$		**2**	97
2	$-(CH_2)_4-$		**3**	100
3	Et	Et	**4**	91
4	Ph	Me	**5**	48

When a mixture of isothiourea (**2**), 4-chlorobenzaldehyde (2 equiv.) and CsF (1.2 equiv.) in DMF (1 mL) was heated at 60 ℃ for 15 h, an expected cycloadduct, 2-piperidino-5-(4'-chlorophenyl)oxazoline (**6a**), was isolated by flash chromatography on silica gel in 80% yield (Table 2, run 1). The corresponding regioisomer was not detected in the reaction mixture by ^{1}H NMR spectroscopy. Similar reaction at room temperature resulted in the formation of a trace amount of the compound (**6a**). Other fluoride ion sources such as tetrabutylammoniun fluoride and KF/18-crown-6 were also effective to give the compound (**6a**) in 38 and 56% yields, respectively (runs 2 and 3). Regarding the solvents, HMPA afforded the comparable result to give 70% yield of (**6a**) whereas acetonitrile and THF gave a trace amount of the product (runs 4-6), indicating the polarity of the solvents was important for the efficient reaction.

A variety of aromatic aldehydes carrying an electron donating or withdrawing group as well as cinnamic

aldehyde were found to be reactive toward the isothiourea (**2**) to give the corresponding oxazoline derivatives (**6b-e**) in the yields as shown in Table 2 (runs 7-10). In contrast to the Kohra's report,[4] the present aminonitrile ylide equivalent (**2**) was reactive toward even aliphatic aldehyde to give the corresponding adduct (**6f**) and (**6g**) in 42 and 20% yields, respectively (runs 12 and 13). We also employed ketones as dipolarophiles. Although acetophenone gave the corresponding oxazoline derivative (**6h**) in 43% yield (run 14), only 6% yield of the product (**6i**) was obtained with cyclohexanone (run 15). Diethyl ketone gave no product at all. Furthermore, the cyclization with an activated alkene such as dimethyl fumarate was not achieved under the reaction conditions employed. In some cases, HMPA was used as reaction media for a little efficiency.

Finally, reactions of other isothiourea derivatives (**3-5**) were also examined. The exposure of the compounds (**3**, **4** or **5**) to CsF in the presence of 4-chlorobenzaldehyde resulted in the formation of the corresponding cycloadducts (**7**, **8** or **9**) in good yields (runs 16-18).

Table 2. Reaction of *N*-Trimethylsilylmethylisothiourea (**2-5**) with Carbonyl Compounds.

run	R^1	R^2	R^3	R^4	Fluoride	Solvent	Compd.	Yield (%)
1	$-(CH_2)_5-$		4-ClC_6H_4	H	CsF	DMF	**6a**	80
2	$-(CH_2)_5-$		4-ClC_6H_4	H	Bu_4NF	DMF	**6a**	38
3	$-(CH_2)_5-$		4-ClC_6H_4	H	KF[a]	DMF	**6a**	56
4	$-(CH_2)_5-$		4-ClC_6H_4	H	CsF	HMPA	**6a**	70
5	$-(CH_2)_5-$		4-ClC_6H_4	H	CsF	MeCN	**6a**	trace
6	$-(CH_2)_5-$		4-ClC_6H_4	H	CsF	THF	**6a**	trace
7	$-(CH_2)_5-$		Ph	H	CsF	DMF	**6b**	70
8	$-(CH_2)_5-$		4-$MeOC_6H_4$	H	CsF	DMF	**6c**	42
9	$-(CH_2)_5-$		4-$CF_3C_6H_4$	H	CsF	DMF	**6d**	84
10	$-(CH_2)_5-$		PhCH=CH	H	CsF	DMF	**6e**	60
11	$-(CH_2)_5-$		$Me(CH_2)_4$	H	CsF	DMF	**6f**	36
12	$-(CH_2)_5-$		$Me(CH_2)_4$	H	CsF	HMPA	**6f**	42
13	$-(CH_2)_5-$		Me_2CH	H	CsF	HMPA	**6g**	20
14	$-(CH_2)_5-$		Ph	Me	CsF	HMPA	**6h**	43
15	$-(CH_2)_5-$		$-(CH_2)_5-$		CsF	HMPA	**6i**	9
16	$-(CH_2)_4-$		4-ClC_6H_4	H	CsF	DMF	**7**	52
17	Et	Et	4-ClC_6H_4	H	CsF	DMF	**8**	73
18	Ph	Me	4-ClC_6H_4	H	CsF	DMF	**9**	73

a) 18-Crown-6 (10 mol%) was added.

Consequently, the *N*-trimethylsilylmethylisothiourea derivatives (**2-5**) readily available from trimethylsilylmethyl isothiocyanate (**1**) and appropriate amines were found to react with various carbonyl

compounds to afford the oxazoline derivatives (**6-9**), the formal [3 + 2] cycloadducts, in fair yields, where the isothioureas served as synthetic equivalents of aminonitrile ylides.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were measured in $CDCl_3$ solution on a Varian UNITY-400 spectrometer (399.97 MHz for ^1H, 100.58 MHz for ^{13}C). All chemical shifts are reported as δ values (ppm) relative to residual chloroform (7.26 ppm for ^1H) and the central peak of deuteriochloroform (77.00 ppm for ^{13}C). HRMS (EI) were obtained on a JEOL JMS-AX-500 spectrometer with DA7000 data system. GCMS was measured with the direct combination of GC (Hewlett-Packard GC 5890 Series II with a 25 m × 0.25 mm methyl silicone capillary column) and a JEOL JMS-AX-500 spectrometer.

Most of the starting materials and reagents were commercial products and were used as supplied. Trimethylsilylmethyl isothiocyanate were prepared according to the literature, bp 89 ℃/16 mmHg (lit.,[7] 46 ℃/3 mmHg). Solvents were dried by conventional methods and were distilled before use.

Preparation of *N*-Trimethylsilylmethylisothiourea Derivatives 2-5.

Typically, to a solution of trimethylsilylmethyl isothiocyanate (**1**, 7.25 g, 50.0 mmol) in ethanol (40 mL) was added piperidine (4.25 g, 50.0 mmol), and the mixture was stirred at rt for 0.5 h. TLC analysis of the reaction mixture revealed the quantitative formation of the thiourea derivative. Then iodomethane (8.50 g, 60.0 mmol) was added, and the reaction mixture was refluxed overnight. After evaporation of the solvent, the residue was extracted with chloroform, washed with saturated aqueous Na_2CO_3, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane : ethyl acetate = 90 : 10) to afford 11.8 g (97%) of 2-methyl-1,1-pentamethylene-3-trimethylsilylmethylisothiourea (**2**) as an oil. ^1H NMR δ 0.00 (s, 9 H), 1.54 (m, 6 H), 2.24 (s, 3 H), 3.14 (m, 4 H), 3.21 (s, 2H). ^{13}C NMR δ -2.38, 15.47, 25.14, 25.91, 44.72, 50.15, 155.95. HRMS *m/z* 244.1431 (M^+ calcd for $C_{11}H_{24}N_2SSi$ 244.1429).

Other isothiourea derivatives (**3-5**) were similarly prepared from the isothiocyanate (**1**) and pyrrolidine, diethylamine, or *N*-methylaniline, respectively. With *N*-methylaniline, reflux was required to complete the addition reaction. The spectral data are as follows.

3: oil. ^1H NMR δ 0.00 (s, 9 H), 1.83 (t, 4 H, *J* = 7 Hz), 2.28 (s, 3 H), 3.21 (s, 2 H), 3.40 (t, 4 H, *J* = 7 Hz). ^{13}C NMR δ -2.56, 15.78, 24.94, 44.63, 48.74, 150.91. HRMS *m/z* 230.1293 (M^+ calcd for $C_{10}H_{22}N_2SSi$ 230.1273).

4: oil. ^1H NMR δ 0.00 (s, 9 H), 1.04 (t, 6 H, *J* = 7 Hz), 2.23 (s, 3 H), 3.23 (s, 2 H), 3.28 (q, 4 H, *J* = 7 Hz). ^{13}C NMR δ -2.35, 13.01, 15.89, 43.29, 44.87, 153.38. HRMS *m/z* 232.1404 (M^+ calcd for $C_{10}H_{24}N_2SSi$ 232.1429).

5: oil. ^1H NMR δ 0.03 (s, 2.3 H), 0.12 (s, 6.7 H), 1.97 (s, 2.3 H), 2.35 (s, 0.7 H), 3.00 (s, 0.4 H), 3.25 (s, 2.4 H), 3.10 (s, 0.6 H), 3.33 (s, 1.6 H), 7.02 (m, 1.3 H), 7.16 (m, 3.7 H). ^{13}C NMR δ -2.13, 14.84, 40.95, 45.09, 122.08, 122.76, 128.82, 147.72, 153.73. HRMS *m/z* 266.1270 (M^+ calcd for $C_{13}H_{22}N_2SSi$ 266.1273).

Reaction of Isothiourea Derivatives (2-5) with Carbonyl Compounds.

Typically, a mixture of the compound (**2**, 0.24 g, 1.0 mmol), 4-chlorobenzaldehyde (0.28 g, 2.0 mmol), and cesium fluoride (0.18 g, 1.2 mmol) in DMF (1 mL) was stirred at 60 ℃ for 15 h. Then the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous Na_2CO_3, and dried over $MgSO_4$. After removal of the solvent, the crude product was purified by flash chromatography on silica gel (ethyl acetate) to give 2-piperidino-5-(4-chlorophenyl)-2-oxazoline (**6a**, 0.21 g, 80%) as an oil. ^{1}H NMR δ 1.57 (m, 6 H), 3.39 (m, 4 H), 3.63 (dd, 1 H, *J* = 8, 12 Hz), 4.16 (dd, 1 H, *J* = 8, 12 Hz), 5.42 (dd, 1 H, *J* = 8, 12 Hz), 7.22 and 7.31 (AA'BB'q, 4 H, *J* = 8 Hz). ^{13}C NMR δ 24.13, 25.28, 46.57, 60.94, 80.63, 126.98, 128.76, 133.78, 139.65, 161.34. HRMS *m/z* 264.1068 (M^+ calcd for $C_{14}H_{17}N_2O^{35}Cl$ 264.1029).

Reactions of various carbonyl compounds with the isothiourea (**2**) were similarly carried out, and the yields are listed in Table 2 and the spectral data are as follows.

6b: oil. ^{1}H NMR δ 1.57 (m, 6 H), 3.39 (m, 4 H), 3.68 (dd, 1 H, *J* = 8, 12 Hz), 4.17 (dd, 1 H, *J* = 9, 12 Hz), 5.45 (dd, 1 H, *J* = 8, 9 Hz), 7.33 (m, 5 H). ^{13}C NMR δ 24.25, 25.36, 46.65, 61.13, 81.46, 125.64, 128.01, 128.61, 141.22, 161.59. HRMS *m/z* 230.1394 (M^+ calcd for $C_{14}H_{18}N_2O$ 230.1419).

6c: oil. ^{1}H NMR δ 1.53 (m, 6 H), 3.34 (m, 4 H), 3.65 (dd, 1 H, *J* = 8, 12 Hz), 3.75 (s, 3 H), 4.09 (dd, 1 H, *J* = 9, 12 Hz), 5.38 (dd, 1 H, *J* = 8, 9 Hz), 6.85 and 7.22 (AA'BB'q, 4 H, *J* = 8 Hz). ^{13}C NMR δ 24.12, 25.22, 46.47, 55.12, 60.83, 81.30, 113.92, 127.18, 132.98, 159.44, 161.44. HRMS *m/z* 260.1500 (M^+ calcd for $C_{15}H_{20}N_2O_2$ 260.1525).

6d: oil. ^{1}H NMR δ 1.60 (m, 6 H), 3.41 (m, 4 H), 3.66 (dd, 1 H, *J* = 7, 12 Hz), 3.75 (s, 3 H), 4.22 (dd, 1 H, *J* = 9, 12 Hz), 5.52 (dd, 1 H, *J* = 7, 9 Hz), 7.43 and 7.62 (AA'BB'q, 4 H, *J* = 8 Hz). ^{13}C NMR δ 24.21, 25.37, 46.75, 61.04, 80.53, 124.00 (q, *J* = 270 Hz), 125.64 (q, *J* = 3 Hz), 125.77, 130.40 (q, *J* = 32 Hz), 145.38, 161.38. HRMS *m/z* 298.1286 (M^+ calcd for $C_{15}H_{17}N_2OF_3$ 298.1293).

6e: oil. ^{1}H NMR δ 1.57 (m, 6 H), 3.39 (m, 4 H), 3.61 (dd, 1 H, *J* = 8, 12 Hz), 4.00 (dd, 1 H, *J* = 9, 12 Hz), 5.13 (m, 1 H), 6.24 (dd, 1 H, *J* = 8, 16 Hz), 6.62 (d, 1 H, *J* = 16 Hz), 7.34 (m, 5 H). ^{13}C NMR δ 24.26, 25.37, 46.63, 58.79, 81.15, 126.70, 127.81, 128.06, 128.62, 132.25, 136.31, 161.63. HRMS *m/z* 256.1622 (M^+ calcd for $C_{16}H_{20}N_2O$ 256.1576).

6f: oil. ^{1}H NMR δ 0.84 (t, 3 H, *J* = 7 Hz), 1.50 (m, 6 H), 1.45 (m, 8 H), 3.27 (m, 4 H), 3.32 (dd, 1 H, *J* = 7, 12 Hz), 3.78 (dd, 1 H, *J* = 9, 12 Hz), 4.45 (m, 1 H). ^{13}C NMR δ 13.81, 22.42, 24.26, 24.88, 25.31, 31.58, 35.12, 46.50, 58.01, 80.58, 161.71. HRMS *m/z* 224.1861 (M^+ calcd for $C_{13}H_{24}N_2O$ 224.1889).

6g: oil. ^{1}H NMR δ 0.83 (d, 3 H, *J* = 7 Hz), 0.90 (d, 3 H, *J* = 7 Hz), 1.50 (m, 6 H), 1.73 (m, 1 H), 3.27 (m, 4 H), 3.40 (dd, 1 H, *J* = 7, 12 Hz), 3.71 (dd, 1 H, *J* = 9, 12 Hz), 4.17 (m, 1 H). ^{13}C NMR δ 17.38, 17.91, 24.17, 25.23, 32.46, 46.34, 55.65, 85.25, 161.75. HRMS *m/z* 196.1616 (M^+ calcd for $C_{11}H_{20}N_2O$ 196.1576).

6h: oil. ^{1}H NMR δ 1.56 (m, 6 H), 1.66 (s, 3 H), 3.39 (m, 4 H), 3.82 and 3.85 (ABq, 2 H, *J* = 12 Hz), 7.26 (m, 5 H). ^{13}C NMR δ 24.29, 25.36, 28.03, 46.58, 66.81, 86.78, 124.20, 127.08, 128.36, 145.88, 160.61. HRMS *m/z* 244.1526 (M^+ calcd for $C_{15}H_{20}N_2O$ 244.1576).

6i: oil. ^{1}H NMR δ 1.49 (m, 10 H), 1.54 (m, 6 H), 3.30 (m, 4 H), 3.45 (s, 2 H). ^{13}C NMR δ 23.04, 24.26, 25.03 (2C), 25.28, 29.63, 36.30, 46.50, 62.74, 86.15, 168.89. HRMS *m/z* 222.1696 (M^+ calcd for $C_{13}H_{22}N_2O$ 222.1732).

Other isothiourea derivatives (**3**-**5**) reacted also with 4-chlorobenzaldehyde to afford the corresponding oxazoline derivatives (**7**-**9**). Yields are also compiled in Table 2 and the spectral data are follows.

7: oil. ^{1}H NMR δ 1.88 (t, 4 H, J = 7 Hz), 3.40 (t, 4 H, J = 7 Hz), 3.64 (dd, 1 H, J = 8, 12 Hz), 4.16 (dd, 1 H, J = 9, 12 Hz), 5.45 (dd, 1 H, J = 8, 9 Hz), 7.24 and 7.31 (AA'BB'q, 4 H, J = 9 Hz). ^{13}C NMR δ 25.47, 47.14, 60.87, 81.06, 127.07, 128.80, 133.92, 139.48, 159.93. HRMS *m/z* 250.0865 (M^+ calcd for $C_{13}H_{15}N_2O^{35}Cl$ 250.0873).

8: oil. ^{1}H NMR δ 1.15 (t, 6 H, J = 7 Hz), 3.32 (q, 2 H, J = 7 Hz), 3.35 (q, 2 H, J = 7 Hz), 3.36 (dd, 1 H, J = 8, 12 Hz), 4.17 (dd, 1 H, J = 9, 12 Hz), 5.43 (dd, 1 H, J = 8, 9 Hz), 7.24 and 7.33 (AA'BB'q, 4 H, J = 9 Hz). ^{13}C NMR δ 13.60 (2 C), 42.58 (2 C), 60.86, 80.91, 127.05, 128.86, 133.94, 139.76, 160.95. HRMS *m/z* 252.1033 (M^+ calcd for $C_{13}H_{17}N_2O^{35}Cl$ 252.1029).

9: oil. ^{1}H NMR δ 3.41 (s, 3 H), 3.74 (dd, 1 H, J = 8, 13 Hz), 4.25 (dd, 1 H, J = 9, 13 Hz), 5.49 (dd, 1 H, J = 8, 9 Hz), 7.14 (m, 1 H), 7.23 (m, 2 H), 7.30 (m, 6 H). ^{13}C NMR δ 38.96, 61.28, 81.45, 124.58, 125.25, 127.10, 128.83, 128.89, 134.02, 139.49, 144.18, 160.35. HRMS *m/z* 286.0873 (M^+ calcd for $C_{16}H_{15}N_2O^{35}Cl$ 286.0888).

REFERENCES

1. N. Imai, Y. Terao, and K. Achiwa, *J. Synth. Org. Chem., Jpn.*, 1985, **43**, 862; E. Vedejs and F. G. West, *Chem. Rev.*, 1986, **86**, 941; Y. Tominaga, M. Hojo, and A. Hosomi, *J. Synth. Org. Chem., Jpn.*, 1992, **50**, 48.
2. A. Padwa, J. R. Gasdaska, G. Haffmanns, and H. Rebello, *J. Org. Chem.*, 1987, **52**, 1027.
3. O. Tsuge, S. Kanemasa, T. Yamada, and K. Matsuda, *Hetrocycles*, 1985, **23**, 2489; O. Tsuge, S. Kanemasa, and K. Matsuda, *J. Org. Chem.*, 1986, **51**, 1997; O. Tsuge, S. Kanemasa, T. Yamada, and K. Matsuda, *J. Org. Chem.*, 1987, **52**, 2523.
4. S. Kohra and Y. Tominaga, *Heterocycles*, 1994, **38**, 1217; S. Kohra, K. Ueda, and Y. Tominaga, *Chem. Pharm. Bull.*, 1995, **43**, 204.
5. K. Nishiyama and N. Tanaka, *J. Chem. Soc., Chem. Commun.*, 1983, 1322; K. Nishiyama, M. Oba, and A. Watanabe, *Tetrahedron*, 1987, **43**, 693; K. Nishiyama and M. Oba, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2289; K. Nishiyama and M. Oba, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2692.
6. Y. Tominaga, K. Ogata, S. Kohra, M. Hojo, and A. Hosomi, *Tetrahedron Lett.*, 1991, **32**, 5987; Y. Tominaga, K. Ogata, H. Ueda, S. Kohra, and A. Hosomi, *Chem. Pharm. Bull.*, 1995, **43**, 1425.
7. O. Tsuge, S. Kanemasa, and K. Matsuda, *J. Org. Chem.*, 1984, **49**, 2688.

Received, 11th April, 1997