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THE FLUORIDE-INDUCED REACTION OF PHENYLTHIO-, METHYLTHIO- AND METHOXY-SUBSTITUTED SILYLMETHYLAZOLES WITH CARBONYL COMPOUNDS

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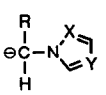
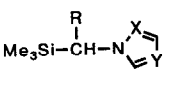
Abstract: Phenylthio-, methylthio- and methoxy-substituted silylmethylazoles, which act as substituted (N-azolyl)methylanion equivalents, were prepared and made to react with carbonyl compounds in the presence of fluoride anion to obtain 2-phenylthio-, 2-methylthio- and 2-methoxy-substituted 2-azolylethanols. Also examined in this study was the lithiation of 1-methylthiomethyl-1,2,4-triazole and 1-bis(methylthio)methyl-1,2,4-triazole.

The generation of azolylmethylanions has been attracting interest[1] because the anions are hetero-aromatic analogues of dipole-stabilized N-C_α carbanions which are being widely studied.[2] In an earlier study, we found that the azolylmethylanions **1a-c**, derived from the fluoride- or alkoxide-induced desilylation of 1-[(trimethylsilyl)methyl]azoles **2a-c**,[3] were trapped in the reaction with carbonyl compounds. We have also reported that [1,2,4-triazol-1-yl(trimethylsilyl)]methylanion (**3a**), generated from the fluoride-induced desilylation of 1-[bis(trimethylsilyl)methyl]-1,2,4-triazole (**4a**), underwent the fluoride-catalyzed Peterson reaction with carbonyl compound.[4] In connection with our program of studies on the generation of the azolylmethylanions, we now report that the equivalents of the phenylthio-, methylthio- and methoxy-susbtituted azolylmethylanions **5-7**, derived from fluoride-induced reaction of 1-[phenylthio(trimethylsilyl)-methyl]-, 1-[methylthio(trimethylsilyl)methyl]- and 1-[methoxy(trimethylsilyl)methyl]azoles (**8-10**), were trapped in the reaction with carbonyl compounds, respectively.



1 : R=H
3 : R=$SiMe_3$
5 : R=SPh
6 : R=SMe
7 : R=OMe



2 : R=H
4 : R=$SiMe_3$
8 : R=SPh
9 : R=SMe
10 : R=OMe

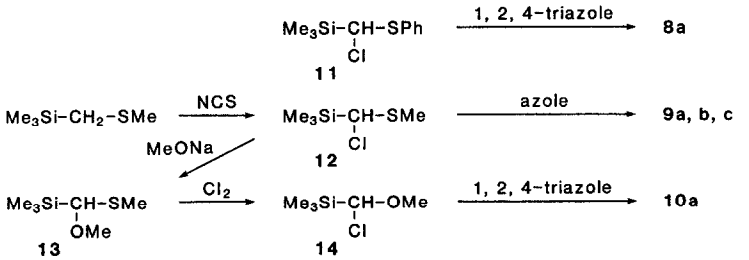
a: X=Y=N ; b: X=CH, Y=N ; c: X=N, Y=CH

RESULTS AND DISCUSSION

Preparation of 1-[Phenylthio(trimethylsilyl)methyl]-, 1-[Methylthio(trimethylsilyl)methyl]- and 1-[Methoxy(trimethylsilyl)methyl]azoles (8-10)

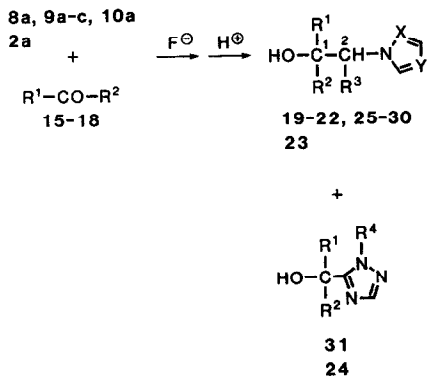
1-[Phenylthio(trimethylsilyl)methyl]-1,2,4-triazole (**8a**) was prepared by treating [chloro(phenylthio)-methyl]trimethylsilane (**11**)[5] with 1,2,4-triazole in the presence of Et_3N in CH_2Cl_2. The 1-[methylthio(tri-methylsilyl)methyl]azoles **9a-c** were prepared by the reaction of the corresponding azoles with [chloro-

(methylthio)methyl]trimethylsilane (12) derived from regio-selective chlorination of (methylthiomethyl)-trimethylsilane[6] under the conditions used for the preparation of 11. 1-[Methoxy(trimethylsilyl)methyl]-1,2,4-triazole (10a) was prepared as described below. The chloride 12 was treated with sodium methoxide in MeOH to give [methoxy(methylthio)methyl]trimethylsilane (13, 66%) which reacted with chlorine in the presence of Et_3N (0.3 mol equiv.) to give [chloro(methoxy)methyl]trimethylsilane (14, 69%). In the absence of Et_3N, this reaction gave a mixture of 12 and 14. The use of 0.3 mol equiv. of Et_3N effectively suppressed formation of the undesired product 12; 12 was probably formed upon reaction of 13 with hydrochloric acid. Finally, the chloride 14 was treated with 1,2,4-triazole in the presence of diisopropylethylamine in CH_3CN to obtain 1-[methoxy(trimethylsilyl)methyl]-1,2,4-triazole (10a, 69%).



Reaction of Silylmethylazoles 8-10 with Carbonyl Compounds

The phenylthio-substituted silylmethyltriazole 8a reacted at −30°C smoothly with carbonyl compound 15-18 in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) in THF to give 2-(1,2,4-triazol-1-yl)ethanols 19-22 in synthetically acceptable yields after acid-catalyzed hydrolysis (Scheme I). The results are summarized in Table 1 (entries 1-4). In the case of unsymmetrical substituted carbonyl compounds, such as 4-chlorobenzaldehyde (16), 4-chloroacetophenone (17) and phenylpropionaldehyde (18), the reaction products 20-22 were mixtures of (1R*, 2R*) and (1R*, 2S*) diastereomers, and no significant diastereoselectivity was observed.



Scheme I

Compd	R^1	R^2	R^3	R^4
15	Ph	Ph	–	–
16	4-Cl-Ph	H	–	–
17	4-Cl-Ph	Me	–	–
18	$-(CH_2)_2$-Ph	H	–	–
19	Ph	Ph	SPh	–
20	4-Cl-Ph	H	SPh	–
21	4-Cl-Ph	Me	SPh	–
22	$-(CH_2)_2$-Ph	H	SPh	–
23	Ph	Ph	H	–
24	Ph	Ph	–	Me
25	Ph	Ph	SMe	–
26	4-Cl-Ph	H	SMe	–
27	4-Cl-Ph	Me	SMe	–
28	Ph	Ph	OMe	–
29	4-Cl-Ph	H	OMe	–
30	4-Cl-Ph	Me	OMe	–
31	Ph	Ph	–	$-CH_2-O-Me$

Although the phenylthio-substituted silylmethylazole 8a selectively gave the 2-(1,2,4-triazol-1-yl)ethanols 19-22, the unsubstituted 1-[(trimethylsilyl)methyl]-1,2,4-triazole (2a) afforded the desired 2-(1,2,4-triazol-1-yl)ethanol (23) accompanied with formation of the undesired (1-methyl-1,2,4-triazol-5-yl)-methanol (24) as reported in previous literature.[3]

The formation of 24 may be explained in term of the difference in the basicity of the anions 1a and 5a. Namely, the anion 1a generated with TBAF reacts as a base to remove the proton at 5-position of 2a and give rise to the corresponding triazol-5-yl anion which may react with 15 to give 24. However, the basicity of the phenylthiosubstituted triazolylmethylanion 5a seems somewhat weak than the unsubstituted 1a due to stabilization by the phenylthio group. Thus, the anion 5a is incapable of removing the triazole ring proton in 8a and produces the 2-(1,2,4-triazol-1-yl)ethanols 19-22 selectively.

The reaction of 1-[methylthio(trimethylsilyl)methyl]-1,2,4-triazole (**9a**), 1-[methylthio(trimethylsilyl)-methyl]imidazole (**9b**) and 1-[methylthio(trimethylsilyl)methyl]pyrazole (**9c**) with carbonyl compounds **15-17** in the presence of a catalytic amount of cesium fluoride[7] (CsF) at 60°C in diglyme selectively gave the 2-azolyl-2-methylthioethanols **25-27** in moderate yields, after acid-catalyzed hydrolysis (Scheme I, Table 1, entries 5-13). In the reaction of the methylthio-substituted imidazole **9b** and pyrazole **9c** with **16**, the product yields were higher (Table 1, entries 9 and 12) than those of the unsubstituted imidazole **1b** and pyrazole **1c**.[3] These results could be attributed to the participation of the methylthio group.

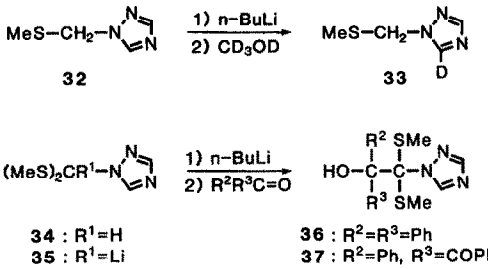
The CsF-catalyzed reaction of 1-[methoxy(trimethylsilyl)methyl]-1,2,4-triazole (**10a**) with carbonyl compound **15-17** occurred at 100°C in diglyme, and then the reaction products were desilylated with 1 mol equiv of TBAF at room temperature, giving the 2-methoxy-2-(1,2,4-triazol-1-yl)ethanols **28-30** with or without (1-methoxymethyl-1,2,4-triazol-5-yl)methanol **31** (Scheme I, Table 1, entries **14-16**). The formation of **31** can be explained by the same reason as that of **24**, namely, the methoxy(1,2,4-triazol-1-yl)methylanion (**7a**) generated from **10a** removes the proton of the triazole ring. The methoxy-substituted triazole **10a** seems somewhat less reactive than the unsubstituted **1a** due to destabilization of the carbanion **7a** by the adjacent oxygen atom.[8]

Table 1. Reactions of Silylmethylazoles **8-10** with Carbonyl Compounds **15-18**

Entry	Azoles	Carbonyl compds	Condns Temp	Time	Products	(Yields, %)[a]	Mp °C	(Recryst solv)[b]
1	**8a**	**15**	−30°C,	2 h	**19**	(83)	151 - 152	(A)
2	**8a**	**16**	−30°C,	2 h	**20**	(44)	108.5 - 110.5	(A)
						(21)	103 - 106	(A)
3	**8a**	**17**	−30°C,	2 h	**21**	(47)	167 (dec)[c]	(B)
						(39)	139 - 141[d]	(A)
4	**8a**	**18**	−30°C,	2 h	**22**	(30)	94 - 96	(A)
						(18)	106.5 - 108.5	(A)
5	**9a**	**15**	60°C,	4.5 h	**25a**	(41)	144 - 146	(A)
6	**9a**	**16**	60°C,	1.5 h	**26a**	(75)[e]	105 - 138	(A)
7	**9a**	**17**	60°C,	7 h	**27a**	(34)	120 - 122	(A)
						(30)	125.5 - 126.5	(A)
8	**9b**	**15**	60°C,	4.5 h	**25b**	(81)	208.5 - 210.5	(B)
9	**9b**	**16**	60°C,	1.5 h	**26b**	(89)[e]	130.5 - 136	(C)
10	**9b**	**17**	60°C,	7 h	**27b**	(23)	153.5 - 154.5	(A)
						(22)	180.5 - 182.5	(B)
11	**9c**	**15**	60°C,	4.5 h	**25c**	(94)	142.5 - 144.5	(A)
12	**9c**	**16**	60°C,	3 h	**26c**	(43)	97 - 99	(D)
						(45)	78 - 80	(C)
13	**9c**	**17**	60°C,	4.5 h	**27c**	(46)[e]	107.5 - 134	(A)
14	**10a**	**15**	100°C,	22 h	**28**	(34)	172 - 174	(A)
					31	(3)	128 - 129	(D)
15	**10a**	**16**	100°C,	6 h	**29**	(63)[e]	110 - 122	(A)
16	**10a**	**17**	100°C,	21 h	**30**	(5)	130 - 132	(A)
						(5)	79 - 90	(A)

[a] Isolated yields. [b] A = AcOEt/*i*-Pr_2O; B = MeOH-AcOEt; C = *i*-Pr_2O/Petr-ether; D = *i*-Pr_2O. [c] HNO_3 salts. [d] $C_{17}H_{16}ClN_3OS \cdot \frac{1}{3}H_2O$. [e] A mixture of the diastereomers.

Next, our attention was turned to the possibility of generating the methylthio-stabilized carbanion **6a** from direct lithiation of 1-methylthiomethyl-1,2,4-triazole (**32**). Treatment of **32** with 1 mol equiv. of *n*-butyllithium in 1,2-dimethoxyethane at −60°C followed by quenching with CD_3OD at −60°C, afforded the 5-monodeuteriotriazole derivative **33** (59%) and the unchanged **32** (39%). Location of the deuterium at the 5-position of the triazole ring, not in the methylene group, was established by the ^{1}NMR spectrum. The 1-bis(methylthio)methyl-1,2,4-triazole (**34**) was lithiated at the methine position and the lithio derivative **35** was trapped with carbonyl compounds to afford the 2,2-bis(methylthio)-2-(1,2,4-triazol-1-yl)ethanols **36-37**. Although the generation of the mono methylthio-stabilized anion **6a** requires fluoride-induced desilylation of **9a**, the doubly stabilized anion **35** can be prepared by direct lithiation of **34**.



Considerable attention is currently being focused on the structure of 2-(1,2,4-triazol-1-yl)- and 2-(imidazol-1-yl)-1-arylethanol from their antifungal activity. The substituted silylmethylazoles **8-10** and the bis(methylthio) derivative **34** are useful synthetic reagents for the preparation of the 2-substituted-2-azolyl-1-arylethanols which have a certain extent of antifungal activity. This reaction has been successfully applied to the synthesis of a new series of orally active antifungal azoles.[9]

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. ^{1}NMR spectra were recorded on Varian EM-360 and VXR-200 instruments with Me_4Si as an internal standard. A Hitachi 260-10 spectrophotometer was used to obtain the IR spectra. Column chromatography was performed on 230-400 mesh silica gel.

*1-[Phenylthio(trimethylsilyl)methyl]-1,2,4-triazole (**8a**).* To a solution of [chloro(phenylthio)methyl]trimethylsilane[5] (10.8 g, 46.8 mmol) in CH_2Cl_2 (100 ml), 1,2,4-triazole (6.46 g, 93.5 mmol) and triethylamine (5.68 g, 56.1 mmol) were added at room temperature, and the mixture was refluxed for 5 h. After cooling to room temperature, the reaction mixture was chromatographed on silica gel. The fraction eluted with benzene-AcOEt (3:1) gave **8a** (4.84 g, 39%). An analytical sample was recrystallized from n-hexane. **8a**: mp 39-41°C; ^{1}NMR ($CDCl_3$) δ 0.24 (s, 9H, Me_3), 5.09 (s, 1H, CH), 7.25 (s, 5H, ArH), 7.80 (s, 1H, 3-position of triazole ring), 7.91 (s, 1H, 5-position); IR (Nujol) 1262, 1245, 855, 840, 745 cm^{-1}. Anal. Calcd for $C_{12}H_{17}N_3SSi$: C, 54.71; H, 6.50; N, 15.95. Found: C, 54.69; H, 6.49; N, 15.93.

*[Chloro(methylthio)methyl]trimethylsilane (**12**).* To a solution of (methylthiomethyl)trimethylsilane[6] (80 g, 0.6 mol) in CCl_4 (400 ml), N-chlorosuccinimide (79.5 g, 0.6 mol) was added portionwise with stirring and cooling in ice bath for 30 min. The suspension was stirred at room temperature for 1 h. Then the insoluble materials were removed by filtration and the filtrate was evaporated. The residue was diluted with *n*-hexane (300 ml) and chilled, and the resulting precipitate was removed by filtration. The filtrate was distilled under reduced pressure to obtain **12** (60.10 g, 60%): bp 80-83°C (28 mm); ^{1}NMR ($CDCl_3$) δ 0.13 (s, 9H, Me_3), 2.25 (s, 3H, Me), 4.42 (s, 2H, CH). Anal. Calcd for $C_5H_{13}ClSSi$: C, 35.59; H, 7.76; Cl, 21.21. Found: C, 35.29; H, 7.64; Cl, 21.14.

*1-[Methylthio(trimethylsilyl)methyl]-1,2,4-triazole (**9a**).* To a solution of 1,2,4-triazole (7.87 g, 114 mmol) and diisopropylethylamine (14.72 g, 114 mmol) in dry CH_2Cl_2 (300 ml), compound **12** (19.2 g, 114 mmol) was added and the mixture was refluxed for 2 h. The reaction mixture was washed with aq. $NaHCO_3$, dried (Na_2SO_4) and evaporated. The residue was distilled under reduced pressure, giving **9a** (10.45 g, 46%): bp 84-86°C (0.2 mm); ^{1}NMR ($CDCl_3$) δ 0.17 (s, 9H, Me_3), 2.12 (s, 3H, Me), 4.86 (s, 1H, CH), 8.00 (s, 1H, 3-position of triazole ring), 8.18 (s, 1H, 5-position); IR (neat) 1275, 1255, 865, 850 cm^{-1}. Anal. Calcd for $C_7H_{15}N_3SSi$: C, 41.75; H, 7.51; N, 20.87. Found: C, 41.12; H, 7.48; N, 20.53.

*1-[Methylthio(trimethylsilyl)methyl]imidazole (**9b**).* To a solution of imidazole (12.10 g, 0.178 mol) and diisopropylethylamine (22.98 g, 0.178 mol) in CH_2Cl_2 (200 ml), compound **12** (30 g, 0.178 mol) was added and then the mixture was stirred at room temperature for 2 h. The reaction mixture was washed with aq. $NaHCO_3$, dried (Na_2SO_4) and evaporated. The residue was distilled under reduced pressure, giving **9b** (14.5 g, 41%): bp 107-109°C (0.5 mm); ^{1}NMR ($CDCl_3$) δ 0.12 (s, 9H, Me_3), 1.97 (s, 3H, Me), 4.48 (s, 1H, CH), 6.95-7.08 (m, 2H, 4 and 5-position of imidazole ring), 7.44-7.54 (m, 1H, 2-position). Anal. Calcd for $C_8H_{16}N_2SSi$: C, 47.95; H, 8.05; N, 13.98. Found: C, 47.38; H, 7.83; N, 13.99.

*1-[Methylthio(trimethylsilyl)methyl]pyrazole (**9c**).* This compound was prepared in a similar manner for **9b**. Pyrazole (12.10 g, 0.178 mol) was converted into 33.4 g of **9c** (94%): bp 111-114°C (16 mm); ^{1}NMR ($CDCl_3$) δ 0.12 (s, 9H, Me_3), 1.99 (s, 3H, Me), 4.77 (s, 1H, CH), 6.18-6.27 (m, 1H, 4-position of pyrazole ring),

7.38-7.53 (m, 2H, 3- and 5-position). Anal. Calcd for $C_8H_{16}N_2SSi$: C, 47.95; H, 8.05; N, 13.98. Found: C, 47.61; H, 8.04; 13.81.

*[Methoxy(methylthio)methyl)]trimethylsilane (**13**).* To a solution of sodium methoxide (11.53 g, 0.21 mol) in MeOH (115 ml), compound **12** (30 g, 0.18 mol) was added dropwise under 20 °C. The reaction mixture was stirred at room temperature for 1 h and then poured into ice water. The mixture was extracted with pentane and the pentane layer was washed with water and dried (Na_2SO_4). The pentane solution was allowed to evaporate under atmosphere to remove pentane and then was distilled under reduced pressure to obtain **13** (19.3 g, 66%): bp 88-93°C (93 mm); ^{1}NMR ($CDCl_3$) δ 0.11 (s, 9H, Me_3), 2.17 (s, 3H, S-Me), 3.40 (s, 3H, O-Me), 4.01 (s, 1H, CH). Anal. Calcd for $C_6H_{16}OSSi$: C, 43.85; H, 9.81. Found: C, 43.22; H, 9.82.

*[Chloro(methoxy)methyl]trimethylsilane (**14**).* A solution of **13** (16.4 g, 0.1 mol) and triethylamine (3.03 g, 0.03 mol) in CCl_4 (82 ml) was added dropwise at <20°C to a solution of Cl_2 in CCl_4 (124 ml, 1.21 M, 0.15 mol) and then the reaction mixture was stirred at room temperature for 15 min. The resulting precipitate was removed by filtration. The filtrate was evaporated under atmosphere to remove CCl_4 and distilled under reduced pressure to give **14** (10.44 g, 69%): bp 84-87°C (155 mm); ^{1}NMR ($CDCl_3$) δ 0.13 (s, 9H, Me_3), 3.53 (s, 1H, OMe), 4.34 (s, 1H, CH); MS m/z 137 ($M^+ - Me$), 79 ($M^+ - SiMe_3$), 73 ($SiMe_3^+$).

*1-[Methoxy(trimethylsilyl)methyl]-1,2,4-triazole (**10a**).* To a solution of 1,2,4-triazole (13.7 g, 0.198 mol) and diisopropylethylamine (8.46 g, 65 mmol) in dry acetonitrile (274 ml), compound **14** (10 g, 65 mmol) was added at room temperature. The mixture was refluxed for 1 h and then evaporated to remove acetonitrile. Ice and aq. $NaHCO_3$ were added to the residue and the mixture was extracted with ether. The ether layer was washed with water, dried (Na_2SO_4) and evaporated. Distillation of the residue under reduced pressure gave **10a** (8.32 g, 69%): bp 102-103°C (12 mm); ^{1}NMR ($CDCl_3$) δ 0.15 (s, 9H, Me_3), 3.31 (s, 3H, Me), 5.02 (s, 1H, CH), 7.98 (s, 1H, 3-position of triazole ring), 8.16 (s, 1H, 5-position). Anal. Calcd for $C_7H_{15}N_3OSi$: C, 45.37; H, 8.16; N, 22.68. Found: C, 44.95; H, 8.03; N, 22.64.

*General Procedure for TBAF-Catalyzed Reaction of 1-[Phenylthio(trimethylsilyl)methyl]-1,2,4-triazole (**8a**) with Carbonyl Compounds.* Anhydrous TBAF[10] (0.1 molar equiv/mol of carbonyl compound) was added to a solution of carbonyl compound (200 or 300 mg, 1.1-2.2 mmol) and **8a** (1.2 molar equiv/mol of carbonyl compound) in dry THF (3.2 ml/mmol of carbonyl compound) under nitrogen atmosphere at −30°C. The mixture was stirred at the same temperature for 2 h. Next, 6 N HCl (2 ml) was added and the mixture was stirred at room temperature for 15 h. The reaction mixture was poured into aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography and recrystallization, and the results are summarized in Table 1 (entries 1-4). Elemental analysis results of the products **19-22** were within ±0.3% of the calculated values for the C, H, Cl and N elements.

*General Procedure for CsF-Catalyzed Reaction of 1-[Methylthio(trimethylsilyl)methyl]azoles (**9a-c**) with Carbonyl Compounds.* Under nitrogen atmosphere, a mixture of carbonyl compound (1000-500 mg, 2.7-7.2 mmol), **9a-c** (1.2 molar equiv/mol of carbonyl compound) and powdered anhydrous CsF (0.1 molar equiv/mol of carbonyl compound, dried 150°C under vacuum) in dry diglyme (2.3 ml/mmol of carbonyl compound) was stirred under the conditions described in Table 1 (entries 5-13). The reaction mixture was worked up in a similar manner to that described above, and purified by flash chromatography and recrystallization to obtain **25-27**, as shown in Table 1 (entries 5-13). Elemental analysis results of the products **25-27** were within ±0.3% of the calculated values for the C, H, Cl and N elements.

*General Procedure for CsF-Catalyzed Reaction of 1-[Methoxy(trimethylsilyl)methyl]-1,2,4-tiazole (**10a**) with Carbonyl Compounds.* Under nitrogen atmosphere, a mixture of carbonyl compound (500 mg, 2.7-3.6 mmol), **10a** (1.2 molar equiv/mol of carbonyl compound), CsF (0.1 molar equiv/mol of carbonyl compound) and dry diglyme (2.2 ml/mmol of carbonyl compound) was stirred at 100°C for the period shown in Table 1 (entries 14-16). After cooling to room temperature, TBAF (1.0 molar equiv/mol of carbonyl compound, 1 M in aq. THF) was added and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography and recrystallization to give **28-30** with or without **31**, as shown in Table 1 (entries 14-16). Elemental analysis results of the products **28-30** and **31** were within ±0.5% of the calculated values for the C, H, Cl and N elements.

*1-Methylthiomethyl-1,2,4-triazole (**32**).* A mixture of 1,2,4-triazole (10 g, 145 mmol), diisopropylethylamine (18.7 g, 145 mmol), chloromethylmethylsulfide (14.0 g, 145 mmol) and acetonitrile (200 ml) was refluxed for 1 h and then evaporated to remove acetonitrile. NaCl-saturated water was added to the residue and the mixture was extracted with ether. The ether layer was dried (Na_2SO_4) and evaporated. The residue

was distilled under reduced pressure to give **32**, (3.28 g, 18%): bp 112-113°C (10 mm); ^{1}NMR ($CDCl_3$) δ 2.19 (s, 3H, Me), 5.18 (s, 2H, CH_2), 7.96 (s, 1H, 3-position of triazole ring), 8.29 (s, 1H, 5-position). Anal. Calcd for $C_4H_7N_3S$: C, 37.19; H, 5.46; N, 32.53; S, 24.82. Found: C, 36.75; H, 5.54; N, 32.01; S, 25.11.

*5-Deuterio-1-methylthiomethyl-1,2,4-triazole (**33**).* *n*-BuLi (2.5 ml, 1.6 M in hexane, 4.0 mmol) was added to a solution of **32** (500 mg, 3.87 mmol) in 1,2-dimethoxyethane (15 ml) at −60°C, and the mixture was stirred at the same temperature for 20 min. CD_3OD (0.5 ml) was added to this solution at −60°C. The solution was warm to room temperature, then the solvent was evaporated. To the residue, NaCl-saturated water was added and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated to give **33** (490 mg, 97% recovery): ^{1}NMR ($CDCl_3$) δ 2.19 (s, 3H, Me), 5.18 (s, 2H, CH_2), 7.96 (s, 1H, 3-position), 8.29 (s, 0.4H, 5-position).

*1-Bis(methylthio)methyl-1,2,4-triazole (**34**).* A mixture of 1,2,4-triazole (18 g, 260 mmol), tris(methylthio)methane (5 g, 32 mmol) and *p*-toluenesulfonic acid (100 mg) was refluxed for 5 days. The solvent was evaporated and the residue was triturated with ether (300 ml) and filtered. The filtrate was evaporated to remove ether. The residue was purified by flash chromatography (4% MeOH-CH_2Cl_2) to give **34** (1.59 g, 28%). An analytical sample was distilled under reduced pressure: bp 107-109°C (0.5 mm); mp 29-33°C; ^{1}NMR ($CDCl_3$) δ 2.18 (s, 6H, Me_2), 6.22 (s, 1H, CH), 7.97 (s, 1H, 3-position of triazole ring), 8.54 (s, 1H, 5-position). Anal. Calcd for $C_5H_9N_3S_2$: C, 34.27; H, 5.18; N, 23.98; S, 36.58. Found: C, 34.05; H, 5.17; N, 23.73; S, 36.85.

*2,2-Dimethylthio-1,1-diphenyl-2-(1,2,4-triazol-1-yl)ethanol (**36**).* *n*-BuLi (0.423 ml, 1.6 M in *n*-hexane, 0.68 mmol) was added to a solution of **34** (108 mg, 0.62 mmol) in dry THF (2 ml) at −45°C under nitrogen atmosphere, and the mixture was stirred at the same temperature for 1 h. Benzophenone (168 mg, 0.92 mmol) was added to the solution at −45°C and then the mixture was stirred at the same temperature for 4 h and then at −20°C for 16 h. The reaction mixture was poured into ice water and the mixture was extracted with ether. The ether layer was washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (10% AcOEt-benzene) to give **36** (133 mg, 65%). An analytical sample was recrystallized from AcOEt-*i*-Pr_2O to obtain pure **36**: mp 149.5-150.5°C; ^{1}NMR (Me_2SO-d_6) δ 1.91 (s, 6H, Me_2), 6.71 (s, 1H, 3-position of triazole ring), 7.25-7.30 (m, 10H, phenyl), 7.42 (s, 1H, OH), 7.93 (s, 1H, 5-position of triazole ring); IR (Nujol) 3190 cm^{-1}. Anal. Calcd for $C_{18}H_{19}N_3OS_2$: C, 60.48; H, 5.36; N, 11.75; S, 17.94. Found: C, 60.68; H, 5.31; N, 11.74; S, 17.91.

*1-Benzoyl-2,2-dimethylthio-1-phenyl-2-(1,2,4-triazol-1-yl)ethanol (**37**).* *n*-BuLi (0.784 ml, 1.6 M in hexane, 1.25 mmol) was added to a solution of **34** (200 mg, 1.14 mmol) in dry THF (4 ml) at −45°C under nitrogen atmosphere, and the mixture was stirred at the same temperature. After cooling to −78°C, benzil (480 mg, 2.28 mmol) was added portionwise at < −70°C for 5 min. The mixture was stirred at −20°C for 20 h. The reaction mixture was poured into ice water, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (20% AcOEt-benzene) to give **37** (277 mg, 63%). An analytical sample was recrystallized from AcOEt-*i*-Pr_2O to obtain pure **37**: mp 131-132°C; ^{1}NMR ($CDCl_3$) δ 1.44 (s, 3H, Me), 1.70 (s, 3H, Me), 6.99 (s, 1H, OH), 7.03-7.85 (m, 10H, phenyl), 7.88 (m, 3-position of triazole ring), 8.82 (s, 1H, 5-position); IR (Nujol) 3310, 1681 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_3O_2S_2$: C, 59.20; H, 4.97; N, 10.90; S, 16.63. Found: C, 59.19; H, 5.01; N, 10.89; S, 16.60.

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7 In general, CsF catalyst is preferable to TBAF one for the formation of 2-(1,2,4-triazol-1-yl)ethanols. For example, TBAF catalyzed reaction of **2a** with **15** afforded considerable amounts of **24** (**23**/**24**: 0.5).[3]

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