Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

ARTICLE

Oxidative nucleophilic strategy for synthesis of thiocyanates and trifluoromethyl sulfides from thiols†

Kazuya Yamaguchi, Konomi Sakagami, Yumi Miyamoto, Xiongjie Jin and Noritaka Mizuno*

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Thiocyanates and trifluoromethyl sulfides are very important compounds and have classically been synthesized via multistep procedures together with formation of vast amounts of byproducts. Herein, we demonstrate oxidative nucleophilic strategy for synthesis of thiocyanates and trifluoromethyl sulfides from thiols as the starting materials using nucleophilic reagents such as TMSCN and $TMSCF_3$ (TMS = trimethylsilyl). In the presence of the 2 × 2 manganese oxide-based octahedral molecular sieve (OMS-2) and potassium fluoride (KF), various kinds of structurally diverse thiocyanates and trifluoromethyl sulfides could be synthesized in almost quantitative yields (typically >90 % yields). The present cyanation and trifluoromethylation proceed through the OMS-2-catalyzed oxidative homocoupling of thiols to disulfides followed by nucleophilic bond cleavage to produce the desired compounds and thiolate species (herein *S*-trimethylsilylated thiols). OMS-2 can catalyze oxidative homocoupling of the thiolate species, thus resulting in quantitative production of thiocyanates and trifluoromethyl sulfides formally from thiols.

Introduction

Thiocyanates are an important class of compounds in chemistry as well as biochemistry and have found widespread applications such as antibacterial drugs, antiasthamatic drugs, biocidals, insenticides, vulcanization accelerators.[1] They have also found in several bioactive natural products (Fig. S1).[1] In addition, thiocyanate functionality has frequently been utilized as the synthon for various important heterocyclic and sulfur-containing compounds (Fig. S1).[1] Recently, the introduction of the trifluoromethyl group into organic molecules has prevalently been examined especially in pharmaceuticals and agrochemicals productions because the introduction can improve the lipophilicity, bioavailability, protein binding affinity, and metabolic stability.[2] To date, a large number of drugs (or drug candidates) possessing trifluoromethylthio or perfluoroalkylthio functionality (including their sulfoxide and sulfone derivatives) have been developed (Fig. S2).[3] Because of the extremely large Hansch lipophilicity parameter of the trifluoromethylthio group,[4] its introduction is expected to become more important for design of new drug candidates.

Thiocyanates and trifluoromethyl sulfides have generally been synthesized by the procedures described in Fig. 1.[5–12] The nucleophilic substitution of alkyl (pseudo)halides with stoichiometric amounts of metal thiocyanides and trifluoromethylthiolates (MSNu, Nu = CN, CF_3; M = metal) is the general procedure for synthesis of aliphatic thiocyanates and trifluoromethyl sulfides, and sometimes accompanied by elimination of hydrogen halides and/or undesirable formation of isothiocyanates (Fig. 1, A).[5] Aromatic ones can be synthesized by the Sandmeyer reaction with formation of copper salts as byproducts (Fig. 1, B).[6] With regard to synthesis of aryl trifluoromethyl sulfides, several efficient cross-coupling reactions of aryl halides or aryl boronic acids with CF_3S^- (e.g., $MSCF_3$ or $S_8 + TMSCF_3$) have recently been developed (Fig. 1, B).[7]

Although thiols are readily available starting materials, they are strong nucleophiles, and thus cyanation and trifluoromethylation of thiols using nucleophiles is intrinsically very difficult. Indeed, when we carried out the reaction of *p*-toluenethiol with TMSCN in the absence of catalysts, the corresponding *S*-trimethylsilylated thiol was quantitatively obtained without formation of the desired thiocyanate (Fig. 2).‡ Therefore, when using thiols as the starting materials, the pre-functionalization (e.g., chlorination using SO_2Cl_2) should generally be required. In this case, at least equimolar amounts of byproducts are formed not only during the nucleophilic reaction but also the pre-functionalization steps (Fig. 1, C).[8] With regard to synthesis of aryl trifluoromethyl sulfides, several radical trifluoromethylation systems using CF_3Br or CF_3I have been reported (Fig. 1, D).[9] Nucleophilic trifluoromethylation of disulfides has also been developed (Fig. 1, E).[10]

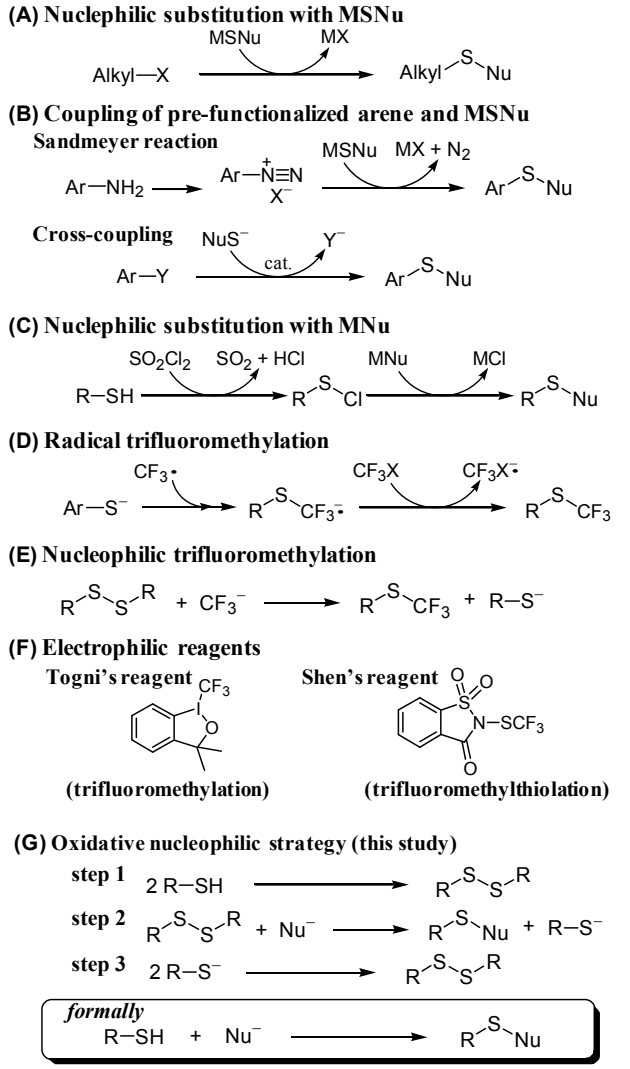


Fig. 1 Synthetic procedures for thiocyanates and trifluoromethyl sulfides. In Procedure G, the oxidant, coproducts (e.g., H_2O, TMSOH, TMS_2O), and the counter cation of nucleophiles (TMS^+) are omitted for clarity. Nu = CN, CF_3; X = halide; Y = halide or $B(OH)_2$; M = metal.

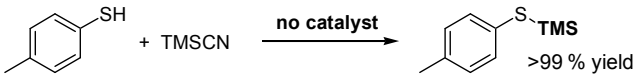


Fig. 2 Reaction of *p*-toluenethiol with TMSCN in the absence of catalysts. Reaction conditions: *p*-toluenethiol (**1h**, 0.5 mmol), TMSCN (2 mmol), DMF (2 mL), 30 °C, O_2 (1 atm), 1 h.‡

Alternatively, electrophilic trifluoromethylation reagents (e.g., Togni's reagent[11]) have been utilized for trifluoromethylation of thiols (Fig. 1, F). However, the production of disulfide byproducts (ca. 40 %) is inevitable in the case of aliphatic thiols with Togni's reagent.[11] In addition, Togni's reagent is relatively expensive in comparison with $TMSCF_3$ and has been synthesized via the multistep procedure using $TMSCF_3$ (Fig. S3).[11] Recently, several efficient electrophilic trifluoromethylthiolation reagents (e.g., Shen's reagent[12a]) have also been developed (Fig. S3).[12]

In this paper, we demonstrate oxidative nucleophilic strategy for synthesis of thiocyanates and trifluoromethyl sulfides. Various kinds of thiocyanates and trifluoromethyl sulfides can be synthesized starting from readily available thiols and nucleophilic reagents such as TMSCN and $TMSCF_3$ (TMS = trimethylsilyl) in the presence of OMS-2 and KF under mild conditions (Fig. 1, G). The catalyst/product separation is very easy, and OMS-2 can be reused.

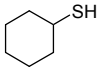
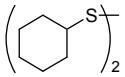
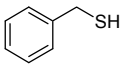
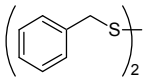
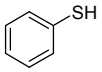
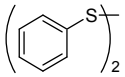
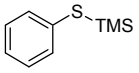
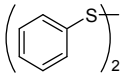
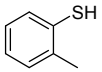
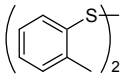
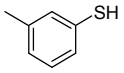
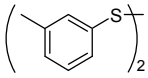
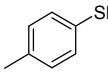
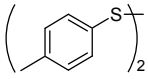
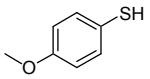
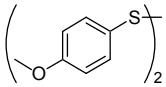
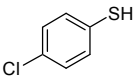
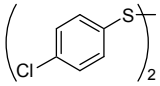
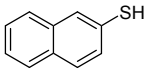
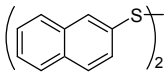
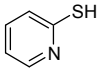
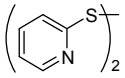
Results and discussion

Our oxidative nucleophilic strategy is the combination of three catalytic reactions in one-pot (Fig. 1, G). As above-mentioned, thiols can not react with nucleophiles. Thus, in the first step, thiols are oxidatively converted into the corresponding disulfides which can be attacked by nucleophiles. In the second step, the disulfides react with TMSNu (Nu = CN, CF_3) to form an equimolar mixture of the desired products and the thiolate species (herein *S*-trimethylsilylated thiols).[10] Finally, the thiolate species is again transformed back to the disulfides, thus resulting in quantitative production of thiocyanates and trifluoromethyl sulfides formally from thiols. In order to realize the present oxidative nucleophilic strategy, the development or finding of efficient catalysts (or reagents) effective for oxidative homocoupling of thiols (step 1 in Fig. 1, G) and thiolates (step 3 in Fig. 1, G) as well as the nucleophilic S–S bond cleavage (step 2 in Fig. 1, G) should be required.

Therefore, 17 kinds of metal oxides were initially examined for the homocoupling of cyclohexanethiol (**1a**) to dicyclohexyldisulfide (**2a**) in acetonitrile at 30 °C (Tables S1 and S2) because metal oxides are readily available or preparable and intrinsically possess nucleophilic nature due to the surface oxygen atoms. Among metal oxides examined, the 2 × 2 manganese oxide-based octahedral molecular sieve ($KMn_8O_{16}{\cdot}nH_2O$, OMS-2, Fig. S4)[13,14] showed the highest performance; 95 % yield of **2a** was achieved for only 5 min (Table S1, entry 8). The high performance of OMS-2 is likely due to its redox property, large surface area, and stability.[13,14] Amounts of OMS-2 could be reduced; even when the homocoupling of **1a** was carried out at 60 °C using a reduced amount of OMS-2 (10 mg, 21.4 mol% Mn with respect to **1a**), 80 % yield of **2a** was obtained for 5 min (Table S1, entry 9). Polar solvents such as acetonitrile, tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMAc) were good solvents, giving **2a** in ≥95 % yields (Table S1, entries 8–12). On the other hand, non-polar solvents such as chloroform, *n*-hexane, and toluene afforded moderate yields of **2a** (Table S1, entries 15–17).

In the presence of OMS-2, various kinds of structurally diverse aliphatic, benzylic, aromatic, and heteroaromatic thiols could be converted into the corresponding disulfides in excellent yields under mild reaction conditions (30 °C, 1 atm O_2 or air) for only 5 min (Table 1). In all cases, the corresponding disulfides were selectively produced without formation of any byproducts, e.g., oxygenated products. Besides thiols, the homocoupling of the *S*-trimethylsilylated

Table 1 Scope of the OMS-2-catalyzed oxidative homocoupling[a]

Entry	Substrate		Product		Yield (%)[b]
1		**1a**		**2a**	95
2[c]					98
3	$CH_3(CH_2)_5SH$	**1b**	$(CH_3(CH_2)_5S)_2$	**2b**	89
4	$CH_3(CH_2)_7SH$	**1c**	$(CH_3(CH_2)_7S)_2$	**2c**	>99
5		**1d**		**2d**	97
6		**1e**		**2e**	84
7[d]		**1e'**		**2e**	77
8		**1f**		**2f**	>99
9		**1g**		**2g**	>99
10		**1h**		**2h**	98
11		**1i**		**2i**	98(93)
12		**1j**		**2j**	>99
13		**1k**		**2k**	>99(96)
14		**1l**		**2l**	>99

[a] Reaction conditions: OMS-2 (50 mg), substrate (0.5 mmol), acetonitrile (2 mL), 30 °C, O_2 (1 atm), 5 min. [b] Yields were determined by GC using naphthalene as the internal standard. The values in the parentheses are the isolated yields. The corresponding disulfides were selectively produced without formation of byproducts. [c] Air (1 atm). [d] **1e** was formed in 15 %.

thiol (**1e'**) also efficiently proceeded, suggesting that OMS-2 cancatalyze the homocoupling of thiolate species (step 3 in Fig. 1, G).

The ESR analysis of the reaction mixture containing OMS-2, **1h**, and α-phenyl-*N*-*tert*-butylnitron (PBN) showed the signals assignable to the spin adduct between PBN and the corresponding thiyl radical species (Fig. S5). Therefore, the present OMS-2-catalyzed homocoupling possibly proceeds through single-electron oxidation-deprotonation of thiols followed by coupling of the two thiyl radicals. This radical pathway is commonly observed for previously reported thiol homocoupling systems.[15]

As shown in Fig. 3, di-*p*-tolyldisulfide (**2h**) could react with TMSCN to afford the corresponding thiocyanate and *S*-trimethylsilylated thiol even without the catalysts. OMS-2 could catalyze homocoupling of thiols and *S*-trimethylsilylated ones (Table 1). Thus, it is expected that thiocyanates can efficiently be synthesized from thiols using TMSCN in the presence of OMS-2.

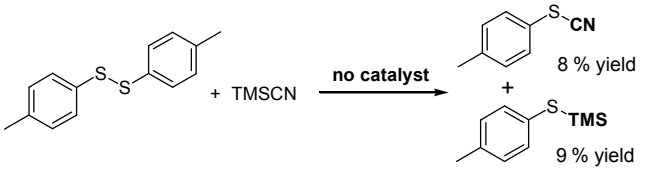


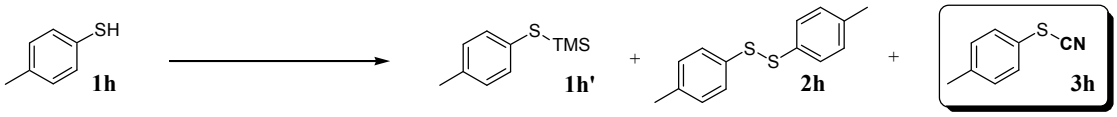
Fig. 3 Reaction of di-*p*-tolyldisulfide with TMSCN in the absence of catalysts. Reaction conditions: di-*p*-tolyldisulfide (**2h**, 0.25 mmol), TMSCN (2 mmol), DMF (2 mL), 30 °C, O_2 (1 atm), 1 h.

As we expected, *p*-toluenethiocyanate (**3h**) was obtained in 59 % yield for 1 h, when the reaction of *p*-toluenethiol (**1h**) and TMSCN was carried out in DMF (Table 2, entry 4). When prolonging the reaction time to 4 h, the yield of **3h** reached up to 90 % (Table 2, entry 6). The effect of solvents was very crucial. The cyanation efficiently proceeded in polar aprotic solvents such as DMF and DMAc (Table 2, entries 4–7 and 13–23). Acetonitrile, THF, and non-polar solvents gave low yields of **3h** (Table 2, entries 1, 3, and 9–12). In a protic solvent of ethanol, the cyanation did not proceed at all (Table 2, entry 8). Similar solvent effects are typically observed for S_N2-type reactions where polar aprotic solvents interact with the counter cations of nucleophilic reagents to promote the generation of nucleophiles; in the present case, the carbonyl oxygens in DMF and DMAc interact with the silicon center of TMSCN to promote the generation of the CN^- nucleoplile.

The reaction profile for the OMS-2-catalyzed cyanation of **1h** showed that **1h** was completely converted into the corresponding disulfide **2h** at the initial stage of the reaction (within 5 min), and then the thiocyanate **3h** was gradually formed from **2h** (Fig. S6). During the reaction, the corresponding *S*-trimethylsilylated thiol was hardly detected (below 1 %). These results suggest that the nucleophilic bond cleavage of the disulfide (step 2 in Fig. 1, G) is included in the rate-limiting step. Thus, we utilized potassium fluoride (KF) as the additional nucleophilic catalyst to promote the generation of the CN^- nucleoplile from TMSCN. It is well known that silyl compounds can efficiently be activated by nucleophilic attack of F^- to silicon centers. As shown in Table S1, entry 27, the homocoupling of **1a** hardly proceeded using KF alone.

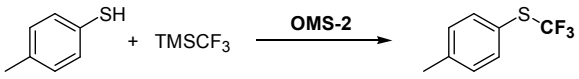
As summarized in Table 2, the effect of nucleophilic catalysts was very significant. In the presence of catalytic amounts of KF, the OMS-2-catalyzed cyanation in DMF was efficiently accelerated (Table 2, entries 13–15 and 20–23). Even in acetonitrile, **3h** was quantitatively produced when using KF (Table 2, entry 1 vs entry 2).

Table 2 Cyanation of *p*-toluenethiol (**1h**) under various reaction conditions[a]



Entry	Solvent	Nucleophilic catalyst (mmol)	TMSCN (mmol)	Time (h)	Yield (%) 1h'	2h	3h
1	Acetonitrile	—	2	1	2	95	**1**
2	Acetonitrile	KF (0.25)	2	1	<1	<1	**>99**
3	THF	—	2	1	9	82	**3**
4	DMF	—	2	1	<1	36	**59**
5	DMF	—	2	2	<1	20	**77**
6	DMF	—	2	4	<1	7	**90**
7	DMAc	—	2	1	<1	47	**53**
8	Ethanol	—	2	1	<1	99	**<1**
9	Dichloromethane	—	2	1	1	94	**5**
10	Chloroform	—	2	1	1	91	**8**
11	*n*-Hexane	—	2	1	8	87	**3**
12	Toluene	—	2	1	8	88	**4**
13	DMF	KF (0.13)	2	1	<1	7	**92**
14	DMF	KF (0.25)	2	1	<1	<1	**>99**
15	DMF	KF (0.5)	2	0.5	<1	<1	**>99**
16	DMF	Na_2CO_3 (0.25)	2	1	<1	30	**69**
17	DMF	K_2CO_3 (0.25)	2	1	<1	<1	**>99**
18	DMF	NaOAc (0.25)	2	1	<1	6	**94**
19	DMF	NaOH (0.25)	2	1	<1	33	**64**
20	DMF	KF (0.25)	0.5	1	<1	19	**78**
21	DMF	KF (0.25)	0.75	1	<1	<1	**>99**
22	DMF	KF (0.25)	1	1	<1	1	**99**
23	DMF	KF (0.25)	1.5	1	<1	<1	**>99**

[a] Reaction conditions: OMS-2 (50 mg), nucleophilic catalyst (0–0.5 mmol), **1h** (0.5 mmol), TMSCN (0.5–2 mmol), solvent (2 mL), 30 °C, O_2 (1 atm).
[b] Yields were determined by GC using naphthalene as the internal standard.



without KF: 11 % yield
with KF: 96 % yield; **with K_2CO_3:** 92 % yield

Fig. 4 Trifluoromethylation of *p*-toluenethiol with $TMSCF_3$. Reaction conditions: OMS-2 (50 mg), nucleophilic catalyst (0 or 0.25 mmol), *p*-toluenethiol (**1h**, 0.5 mmol), $TMSCF_3$ (2 mmol), DMF (2 mL), 30 °C, O_2 (1 atm), 1 h.

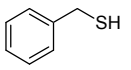
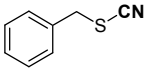
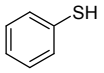
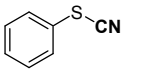
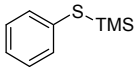
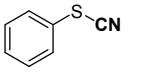
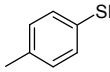
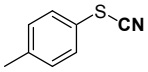
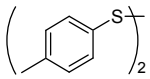
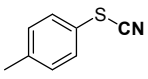
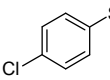
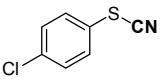
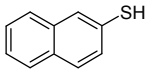
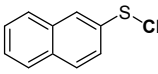
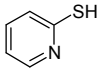
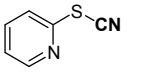
The effects of amounts of TMSCN and KF used for the cyanation of **1h** are also summarized in Table 2. Even when the cyanation was carried out with 1 equivalent TMSCN with respect to **1h**, 78 % yield of **3h** was obtained (Table 2, entry 20). Using ≥1.5 equivalents TMSCN, **3h** was quantitatively produced (Table 2, entries 21–23). The amount of KF could be reduced to 25 mol% with keeping the efficiency of the reaction (Table 2, entry 13). Under the same reaction conditions using $TMSCF_3$ instead of TMSCN, **1h** was efficiently converted into the corresponding trifluoromethyl sulfide **4h** (Fig. 4).

Besides KF, inorganic bases such as K_2CO_3 and NaOAc (OAc = acetate) could act as nucleophilic catalysts to promote the cyanation of **1h** (Table 2, entries 17 and 18). Similarly, the trifluoromethylation of **1h** using K_2CO_3 as the nucleophilic catalyst instead of KF under the conditions described in Fig. 4 gave the corresponding trifluoromethyl sulfide **4h** in 92 % yield.

Finally, we investigated the scope of the present cyanation and trifluoromethylation. In the presence of OMS-2 and KF, various kinds of structurally diverse thiols or their derivatives could be converted into the corresponding thiocyanates and trifluoromethyl sulfides in excellent yields (typically >90 % yields) in the presence of O_2 (1 atm). Notably, cyanation as well as trifluoromethylation efficiently proceeded even in air (1 atm) (Table 3, entry 8; Table 4, entry 5). Cyanation and trifluoromethylation products could easily be isolated by simple column chromatography on silica gel (see the Experimental section), and the GC yields as well as the isolated yields are summarized in Tables 3 and 4.

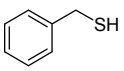
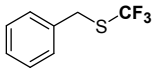
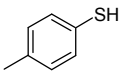
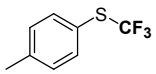
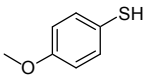
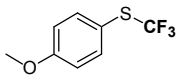
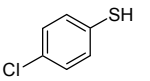
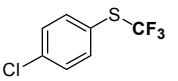
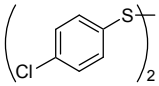
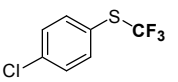
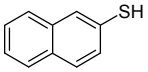
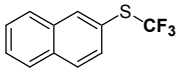
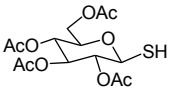
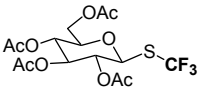
Aliphatic thiols could be converted into the corresponding thiocyanates and trifluoromethyl sulfides. The cyanation and

Table 3 Scope of the OMS-2-catalyzed cyanation[a]

Entry	Substrate	Time (h)	Product		Yield (%)[b]
1	$CH_3(CH_2)_5SH$	1.5	$CH_3(CH_2)_5S-CN$	**3b**	>99
2	$CH_3(CH_2)_7SH$	1.5	$CH_3(CH_2)_7S-CN$	**3c**	99(98)
3		1		**3d**	92(85)
4		1		**3e**	>99(89)
5		1		**3e**	>99
6		1		**3h**	>99(97)
7[c]		1			97
8[d]		1			97
9[e]		1		**3h**	>99
10		1		**3j**	98(99)
11		1		**3k**	98(97)
12		1		**3l**	>99

[a] Reaction conditions: OMS-2 (50 mg), KF (0.25 mmol), substrate (0.5 mmol), TMSCN (2 mmol), DMF (2 mL), 30 °C, O_2 (1 atm). [b] Yields were determined by GC using naphthalene as the internal standard. The values in the parentheses are the isolated yields. [c] Reuse experiment. [d] Air (1 atm). [e] Substrate (0.25 mmol).

Table 4 Scope of the OMS-2-catalyzed trifluoromethylation[a]

Entry	Substrate	Time (h)	Product		Yield (%)[b]
1	$CH_3(CH_2)_5SH$	2	$CH_3(CH_2)_5S-CF_3$	**4b**	93
2	$CH_3(CH_2)_7SH$	2	$CH_3(CH_2)_7S-CF_3$	**4c**	91(68)
3		1		**4d**	94(86)
4		1		**4h**	96(90)
5[c]		1			90
6		1		**4i**	95(90)
7[d]		1			82
8		1		**4j**	92(88)
9		1		**4j**	99
10		1		**4k**	>99(94)
11[e]		1		**4m**	90

[a] Reaction conditions: OMS-2 (50 mg), KF (0.25 mmol), substrate (0.5 mmol), $TMSCF_3$ (2 mmol), DMF (2 mL), 30 °C, O_2 (1 atm). [b] Yields were determined by GC using naphthalene as the internal standard. The values in the parentheses are the isolated yields. [c] Air (1 atm).. [d] Reuse experiment. [e] OMS-2 (25 mg), KF (0.13 mmol), substrate (0.25 mmol), $TMSCF_3$ (1 mmol).

trifluoromethylation of benzylic thiols efficiently proceeded. The reactions of benzene thiols with electron-donating as well as electron-withdrawing substituents at each position of the benzene rings also efficiently proceeded. Besides thiols, *S*-trimethylsilyl benzenethiol and disulfides could be utilized as the starting materials. The trifluoromethylation of a sugar derivative was also successful. After the reactions were completed, OMS-2 could easily be retrieved from the reaction mixtures by simple filtration (>90 % recovery). It was confirmed by ICP-AES analysis that only small amounts of manganese species were found in the filtrate (1.1 % after the cyanation of **1h**; 0.050 % after the trifluoromethylation of **1i**). The structure of OMS-2 was preserved after the reactions (Fig. S7),§ and OMS-2 could be reused for cyanation and trifluoromethylation (Table 3, entry 7; Table 4, entry 6).

Conclusions

In summary, we have successfully developed the novel catalytic systems for formal nucleophilic cyanation and trifluoromethylation of thiols. Various kinds of structurally diverse thiocyanates and trifluoromethyl sulfides could successfully be synthesized. The present results will provide the efficient synthetic routes to chemically and biochemically important thiocyanates and trifluoromethyl sulfides starting from readily available thiols and nucleophilic reagents such as TMSCN and $TMSCF_3$. This strategy will also be extended to functionalization of thiols and their derivatives using other nucleophiles.

Experimental

General

GC analyses were performed on Shimadzu GC-2014 with FID detector equipped with InertCap 5 (0.25 mm ID × 60 m) or Rtx-1 (0.25 mm ID × 30 m) capillary column. GC-MS spectra were recorded on Shimadzu GCMS-QP2010 equipped with InertCap 5 (0.25 mm ID × 30 m) capillary column at an ionization voltage of 70 eV. Liquid-state NMR spectra were recorded on JEOL JNM-ECA-500. ^1H, ^{13}C, and ^{19}F NMR spectra were measured at 500.16, 125.77, and 470.62 MHz, respectively, using tetramethylsilane (TMS) as an internal reference ($\delta = 0$ ppm) for ^1H and ^{13}C, and trifluorotoluene as an internal reference ($\delta = -63.72$ ppm) for ^{19}F. ICP-AES analyses were performed on Shimadzu ICPS-8100. XRD patterns were recorded on Rigaku SmartLab using Cu Kα radiation (45 kV, 200 mA). BET surface areas were measured on micromeritics ASAP 2010 and calculated from the N_2 adsorption isotherm with the BET equation. ESR spectra (X-band) were measured on JEOL JES-RE-1X. OMS-2 (see the ESI†)[13,14] and Birnessite-type MnO_2[16] were prepared according to the literature procedures. Other metal oxides were commercially

available (Table S2). Solvents and substrates were obtained from Kanto Chemical, TCI, Wako, or Aldrich (reagent grade) and typically used as received (purified prior to the use, if required).

Oxidative homocoupling of thiols

OMS-2 (50 mg), **1** (0.5 mmol), acetonitrile (2 mL), napthalene (0.1 mmol, internal standard for GC analysis), and a Teflon-coated magnetic stir bar were charged to a Pyrex glass reactor (volume: ca. 20 mL), and the reaction mixture was vigorously stirred (ca. 600 rpm) at 30 °C in 1 atm of O_2 (or air). After the reaction was completed, the conversion of **1** and the yield of **2** were determined by GC analysis, and then OMS-2 was retrieved by filtration (>99 % recovery). As for isolation of disulfide products, the internal standard was not used for the reaction. After the reaction was completed, the reaction mixture containing the crude product and OMS-2 was directly subjected to column chromatography on silica gel (using 1.5 cm ID × 5 cm short silica column; using *n*-hexane/ether (7/3 v/v) as the eluent), giving the pure disulfide. The GC and isolated yields are summarized in Table 1. The products were identified by GC-MS analyses (see the ESI†).

Cyanation of thiols

OMS-2 (50 mg), **1** (0.5 mmol), TMSCN (2 mmol), DMF (2 mL), napthalene (0.1 mmol, internal standard for GC analysis), and a Teflon-coated magnetic stir bar were charged to a Pyrex glass reactor (volume: ca. 20 mL), and the reaction mixture was vigorously stirred (ca. 600 rpm) at 30 °C in 1 atm of O_2 (or air). After the reaction was completed, the conversion of **1** and the yield of **3** were determined by GC analysis, and then OMS-2 was retrieved by filtration (>95 % recovery). The retrieved catalyst was washed with acetone and water, and then dried at 150 °C for 1 h before being used for the reuse experiment. As for isolation of thiocyanate products, the internal standard was not used for the reaction. After the reaction was completed, the reaction mixture containing the crude product and OMS-2 was directly subjected to column chromatography on silica gel (using 4.5 cm ID × 15 cm silica column; typically using *n*-hexane/ether (7/3 v/v) as the eluent; using *n*-hexane/ether (9/1 v/v) as the eluent for isolation of **3e**; using *n*-hexane/ethyl acetate (7/2 v/v) as the eluent for isolation of **3l**), giving the pure thiocyanate. The GC and isolated yields are summarized in Table 3. The products were identified by GC-MS and NMR (^{1}H and ^{13}C) analyses (see the ESI†).

Trifluoromethylation of thiols

OMS-2 (50 mg), **1** (0.5 mmol), $TMSCF_3$ (2 mmol), DMF (2 mL), napthalene (0.1 mmol, internal standard for GC analysis), and a Teflon-coated magnetic stir bar were charged to a Pyrex glass reactor (volume: ca. 20 mL), and the reaction mixture was vigorously stirred (ca. 600 rpm) at 30 °C in 1 atm of O_2 (or air). After the reaction was completed, the conversion of **1** and the yield of **4** were determined by GC analysis, and then OMS-2 was retrieved by filtration (>90 % recovery). The retrieved catalyst was washed with acetone and water, and then dried at 150 °C for 1 h before being used for the reuse experiment. As for isolation of trifluoromethyl sulfide products, the internal standard was not used for the reaction. After the reaction was completed, the reaction mixture containing the crude product and OMS-2 was directly subjected to column chromatography on silica gel (using 4.5 cm ID × 15 cm silica column; using *n*-pentane as the eluent), giving the pure trifluoromethyl sulfide. The GC and isolated yields are summarized in Table 4. The products were identified by GC-MS and NMR (^{1}H, ^{13}C, and ^{19}F) analyses. As for identification of **4m**, we synthesized the authentic sample using Togni's reagent according to ref. 11 and confirmed that the GC retention time as well as the GC-MS pattern of **4m** obtained by the present system were the same as those of the authentic sample (see the ESI†).

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Science, Sports, and Technology of Japan (MEXT).

Notes and references

Department of Applied Chemistry, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan. E-mail: tmizuno@mail.ecc.u-tokyo.ac.jp; Fax:+81-3-5841-7220; Tel: +81-3-5841-7272

† Electronic Supplementary Information (ESI) available: Spectral data of disulfides, thiocyanates, and trifluoromethyl sulfides (GC-MS, NMR), Tables S1 and S2, Figs. S1–S7. See DOI: 10.1039/b000000x/

‡ **Caution:** The reaction of thiols with TMSCN in the absence of catalysts produces the corresponding *S*-trimethylsilylated thiols with the equimolar amount of HCN. Thus, the reaction should be carried out using appropriate experimental setups.

§ The BET surface areas of OMS-2 somewhat decreased when used for the cyanation (74.6 $m^2\ g^{-1}$) and trifluoromethylation (75.3 $m^2\ g^{-1}$).

1 (*a*) V. A. Kokorekin, A. O. Terent'ev, G. V. Ramenskaya, N. É. Grammatikova, G. M. Rodionova and A. I. Ilovaiskii, *Pharm. Chem. J.*, 2013, **47**, 422–425; (*b*) W. Zheng, A. Ariafard and Z. Lin, *Organometallics*, 2008, **27**, 246–253; (*c*) J. R. Falck, S. Gao, R. N. Prasad and S. R. Koduru, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1768–1771; (*d*) I. Kamiya, J.-I. Kawakami, S. Yano, A. Nomoto and A. Ogawa, *Organometallics*, 2006, **25**, 3562–3564; (*e*) E. Elhalem, B. N. Bailey, R. Docampo, I. Ujváry, S. H. Szajnman and J. B. Rodriguez, *J. Med. Chem.*, 2002, **45**, 3984–3999; (*f*) A. W. Erian and S. M. Sherif, *Tetrahedron*, 1999, **55**, 7957–8024; (*g*) C. Gerson, J. Sabater, M. Scuri, A. Torbati, R. Coffey, J. W. Abraham, I. Lauredo, R. Forteza, A. Wanner, M. Salathe, W. M. Abraham and G. E. Conner, *Am. J. Respir. Cell. Mol. Biol.*, 2000, **22**, 665–671; (*h*) B. Batanero, F. Barba and A. Martín, *J. Org. Chem.*, 2002, **67**, 2369–2371; (*i*) R. Riemschneider, F. Wojahn and G. Orlick, *J. Am. Chem. Soc.*, 1951, **73**, 5905–5907; and references cited therein.

2 (*a*) H. Egami, M. Sodeoka, *Angew. Chem., Int. Ed.*, DOI: 10.1002/anie.201309260; (*b*) L. Chu and F.-L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1312–1316; (*c*) X.-F. Wu, H. Neumann and M. Beller, *Chem. Asian J.*, 2012, **7**, 1744–1754; (*d*) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529–2591; (*e*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369; (*f*) F. Leroux, P. Jeschke and M. Schlosser, *Chem. Rev.*, 2005, **105**, 827–856; (*g*) A. Tlili and T. Billard, *Angew. Chem., Int. Ed.*, 2013, **52**, 6818–6819; and references cited therein.

3 (*a*) L. Hu, C. Liu, C. Shang, X. Yang, J. Yang, *J. Vet. Pharmacol. Thei.*, 2010, **33**, 503; (*b*) C. McInnes, in *Frontiers in Drug Design and Discovery*, ed., Atta-ur-Rahman, G. W. Caldwell, M. I. Choudhary and M. R. Player, Bentham Science Publishers Ltd., 2007, vol. 3, pp. 145–170; (*c*) R. M. Demarinis, J. R. E. Hoover, G. L. Dunn, P. Actor, J. V. Uri, J. A. Weisbach, *J. Antibiot.*, 1975, **28**, 463–470.

4 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165–195.

5 (*a*) D. J. Bound, B. K. Bettadaiah, P. Srinivas, *Synth. Commun.*, 2013, **43**, 1312–1316; (*b*) Y. Liu, Y. Xu, S. H. Jung and J. Chae, *Synlett*, 2012, **23**, 2692–2698; (*c*) H. M. Meshram, P. B. Thakur, B. M. Babu and V. M. Bangade, *Tetrahedron Lett.*, 2012, **53**, 1780–1785; (*d*) J. Li, J.-J. Cao, J.-F. Wei, X.-Y. Shi, L.-H. Zhang, J.-J. Feng and Z.-G. Chen, *Eur. J. Org. Chem.*, 2011, 229–233; (*e*) Z. Benfodda, F. Guillen, H. Arnion, A. Dahmani and H. Blancou, *Heteroatom Chem.*, 2009, **20**, 355–361; (*f*) N. Watanabe, M. Onaka and S. Uemura, *Bull. Chem. Soc. Jpn.*, 1974, **47**, 1312–1316.

6 (*a*) G. Danoun, B. Bayarmagnai, M. F. Gruenberg and L. J. Goossen, *Chem. Sci.*, 2014, **5**, 1312–1316; (*b*) A. S. Sigeev, I. P. Beletskaya, P. V. Petrovskii and A. S. Peregudov, *Russ. J. Org. Chem.*, 2012, **48**, 1055−1058; (*c*) I. P. Beletskaya, A. S. Sigeev, A. S. Peregudov and P. V. Petrovskii, *Mendeleev Commun.*, 2006, **16**, 250–251.

7 (*a*) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2012, **51**, 2492–2495; (*b*) C.-P. Zhang and D. A. Vicic, *Chem. Asian J.*, 2012, **7**, 1756–1758; (*c*) N. Sun, H. Zhang, W. Mo, B. Hu, Z. Shen and X. Hu, *Synlett*, 2013, **24**, 1443–1447; (*d*) G. Teverovskiy, D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 7312–7314; (*e*) C.-P. Zhang and D. A. Vicic, *J. Am. Chem. Soc.*, 2012, **134**, 183–185.

8 (*a*) I. W. J. Still and I. D. G. Watson, *Synth. Commun.*, 2001, **31**, 1355–1359; (*b*) D. N. Harpp, B. T. Friedlander and R. A. Smith, *Synthesis*, 1979, 250–251.

9 (*a*) V. I. Popov, V. N. Boiko and L. M. Yagupolskii, *J. Fluorine Chem.*, 1982, **21**, 365–369; (*b*) C. Wakselman and M. Tordeux, 1985, **50**, 4047–4051; (*c*) V. G. Koshechko, L. A. Kiprianova, L. I. Fileleeva, *Tetrahedron Lett.*, 1992, **33**, 6677–6678.

10 (*a*) C. Pooput, W. R. Dolbier, Jr. and M. Médebielle, *J. Org. Chem.*, 2006, **71**, 3564–3568; (*b*) C. Pooput, M. Medebielle and W. R. Dolbier, Jr., *Org. Lett.*, 2004, **6**, 301–303; (*c*) G. Blond, T. Billard and B. R. Langlois, *Tetrahedron Lett.*, 2001, **42**, 2473–2475; (*d*) B. Quiclet-Sire, R. N. Saicic and S. Z. Zard, *Tetrahedron Lett.*, 1996, **37**, 9057–9058; (*e*) T. Billard and B. R. Langlois, *Tetrahedron Lett.*, 1996, **37**, 6865–6868.

11 (*a*) I. Kieltsch, P. Eisenberger and A. Togni, *Angew. Chem., Int. Ed.*, 2007, **46**, 754–757; (*b*) P. Eisenberger, S. Gischig and A. Togni, *Chem. Eur. J.*, 2006, **12**, 2579–2586.

12 (*a*) C. Xu, B. Ma and Q. Shen, *Angew. Chem., Int. Ed.* DOI: 10.1002/anie.201403983; (*b*) S. Alazet, L. Zimmer and T. Billard, *Chem. Eur. J.* **2014**, *20*, 8589–8593; (*c*) X.-X. Shao, X.-Q. Wang, T. Yang, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2013, **52**, 3457–3460; (*d*) Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro and N. Shibata, *J. Am. Chem. Soc.*, 2013, **135**, 8782–8785; and references cited therein.

13 (*a*) S. L. Suib, *Acc. Chem. Res.*, 2008, **41**, 479–487; (*b*) R. N. DeGuzman, Y.-F. Shen, E. J. Neth, S. L. Suib, C.-L. O'Young, S. Levine and J. M. Newsam, *Chem. Mater.*, 1994, **6**, 815–821.

14 Our recent works on OMS-2 catalysis: (*a*) T. Oishi, K. Yamaguchi and N. Mizuno, *ACS Catal.*, 2011, **1**, 1351-1354; (*b*) K. Yamaguchi, H. Kobayashi, T. Oishi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2012, **51**, 544–547; (*c*) Y. Wang, H. Kobayashi, K. Yamaguchi and N. Mizuno, *Chem. Commun.*, 2012, **48**, 2642–2644; (*d*) K. Yamaguchi, H. Kobayashi, Y. Wang, T. Oishi, Y. Ogasawara and N. Mizuno, *Catal. Sci. Technol.*, 2013, **3**, 318–327; (*e*) K. Yamaguchi, Y. Wang, T. Oishi, Y. Kuroda and N. Mizuno, *Angew. Chem., Int. Ed.*, 2013, **52**, 5627–5630; (*f*) K. Yamaguchi, Y. Wang and N. Mizuno, *ChemCatChem*, 2013, **5**, 2835–2838; (*g*) X. Jin, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2014, **53**, 5356–5360.

15 Examples of heterogeneously catalyzed aerobic thiol homocoupling systems: (*a*) A. Corma, T. Ródenasa and M. J. Sabater, *Chem. Sci.*, 2012, **3**, 398–404; (*b*) L. Menini, M. C. Pereira, A. C. Ferreira, J. D. Fabris and E. V. Gusevskaya, *Appl. Catal. A*, 2011, **392**, 151–157; (*c*) A. Saxena, A. Kumar and S. Mozumdar, *J. Mol. Catal. A*, 2007, **269**, 35–40.

16 O. Ghodbane, J.-L. Pascal and F. Favier, *ACS Appl. Mater. Interfaces*, 2009, **1**, 1130–1139.