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Oxidative Coupling of Thiols to Disulfides with Ti(IV) in the Presence of NaI under Air Atmosphere

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Ti(IV) as $TiCl_3(O_3SCF_3)$ and $TiO(O_2CCF_3)_2$ are used as efficient catalysts for oxidative coupling of aliphatic, aromatic and heteroaromatic thiols to their disulfides in the presence of NaI under air atmosphere.

Keywords: Thiol; Disulfide; Oxidative coupling; Ti(IV); Sodium iodide.

INTRODUCTION

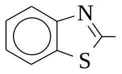
Oxidative coupling of thiols to disulfides under neutral and mild conditions is an important reaction from both biological and practical points of view.[1] Some of the reported reagents known to convert thiols to disulfides include, I_2/HI,[2] $Br_2/KHCO_3$,[3] Br_2,[4] Sm/$BiCl_3$,[5] $Tl(OAc)_3$,[6] $NaBO_3$,[7] $Zn(BiO_3)_2$,[8] $Pb(OAc)_4$,[9] $Ba(MnO_4)_2$,[10] $[Ce(NO_3)_3]_2CrO_4$,[11] pyridinium chlorochromate (PCC),[11] $[Ce(NO_3)_3]_3H_2IO_6$,[12] $Cu(NO_3)_2\cdot N_2O_4$,[13] Fe(III)/NaI,[14] $KMnO_4/CuSO_4$,[15] Fe(III)[16] or $Ca(OCl)_2$/montmorillonite,[17] $(PhCH_2PPh_3)_2Cr_2O_7$,[18] 30% H_2O_2 in fluoroalcohols,[19] silica sulfuric acid/$NaNO_2$,[20] wet HIO_3,[21] HMDS/DMSO[22] and $MoO_2Cl_2(dmso)_2$.[23] With the aim to explore new synthetic methodologies and continue our recent work for oxidative coupling of thiols to disulfides with iodine in wet acetonitrile,[24] we now wish to report an alternative procedure for this transformation.

RESULTS AND DISCUSSION

In our investigation on some new applications of Ti(IV) in organic synthesis,[25] it was observed that $TiCl_4$ in the presence of NaI can catalyze the coupling reaction of thiols to disulfides but the yields of the reactions are low.[26] In order to overcome the low efficiency, the handling problem of $TiCl_4$ and to increase the Lewis acidity of Ti(IV), we decided to prepare two known compounds of Ti(IV) as $TiCl_3(O_3SCF_3)$[27] and $TiO(O_2CCF_3)_2$ [28] which are both solid and stable compounds and their handling is easy. It was also observed that these two Ti(IV) compounds are more efficient catalysts than $TiCl_4$ for coupling reaction of thiols in the presence of sodium iodide in refluxing acetonitrile. Therefore, different aliphatic, aromatic and heteroaromatic thiols were reacted with these two Ti(IV) catalysts under air atmosphere (Scheme I).

Scheme I

$$\underset{\mathbf{1(a\text{-}j)}}{\mathrm{RSH}} \xrightarrow[\text{Air, Reflux, 45-99\%}]{\text{Ti(IV) cat., NaI, } CH_3CN} \underset{\mathbf{2(a\text{-}j)}}{\mathrm{RSSR}}$$

Entry	R groups	Entry	R groups
1a	C_6H_5	**1f**	n-Butyl
1b	3-MeC_6H_4	**1g**	C_2H_5
1c	4-MeC_6H_4	**1h**	Cyclohexyl
1d	4-MeOC_6H_4	**1i**	$HS(CH_2)_3$
1e	$PhCH_2$	**1j**	

The possibility of performing this coupling reaction with catalytic amounts of Ti(IV) as $TiCl_3(O_3SCF_3)$ and $TiO(O_2CCF_3)_2$ was studied. It was observed that 0.1-0.3 molar equivalents of Ti(IV) are enough to complete the dimerization of thiols accompanied by 2 molar equivalents of NaI. The results obtained from the reaction of different thiols under air atmosphere are listed in Table 1.

Commercially available and functionalized aromatic thiols **1a-d** were first chosen to test our procedure. The reactions were carried out under reflux condition and air atmosphere, using CH_3CN as a solvent. Under these conditions, the mercaptans efficiently oxidized to the corresponding disulfides (Table 1). Next we turned our attention to aliphatic

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Table 1. Catalytic Oxidative Coupling of Thiols to Disulfides with $TiCl_3(O_3SCF_3)$ and $TiO(O_2CCF_3)_2$ in the Presence of NaI under Air Atmosphere[a]

Entry	Thiol	Disulfide	$TiCl_3(O_3SCF_3)$			$TiO(O_2CCF_3)_2$			Mp or Bp (°C)[14,18,20,23]	
			Molar Ratio Cat./NaI/Thiol	Time (h)	Yield (%)[b]	Molar Ratio Cat./NaI/Thiol	Time (h)	Yield (%)[b]	Found	Reported
1	**1a**	**2a**	0.1/2/1	0.3	95	0.2/2/1	2.5	94	59-60	60
2	**1b**	**2b**	0.1/2/1	1.3	93	0.3/2/1	3	95	45-46	45-47
3	**1c**	**2c**	0.1/2/1	1.4	94	0.1/2/1	3.1	96	45-46	45-46
4	**1d**	**2d**	0.2/2/1	2.3	94	0.3/2/1	10	93	43	43-44
5	**1e**	**2e**	0.1/2/1	4	93	0.1/2/1	6	93	71-72	72
6	**1f**	**2f**	0.2/2/1	2.5	93	0.2/2/1	5	94	224-226(760)	226(760)
7	**1g**	**2g**	0.2/2/1	2.2	94	0.2/2/1	6	92	153-154(760)	154(760)
8	**1h**	**2h**	0.2/2/1	8	96	0.2/2/1	10	94	124-129	125-130
9[c]	**1i**	**2i**	0.2/2/1	12	45	----	--	--	----	----
10	**1j**	**2j**	0.2/2/1	2	96	0.3/2/1	24	15	180-182	182-183

[a] All reactions were performed in CH_3CN under reflux conditions. [b] Yields referred to isolated products. [c] The reaction was performed between 1,3-propanedithiol (1 mmol), $TiCl_3(O_3SCF_3)$ (0.2 mmol) and NaI (2 mmol) in acetonitrile (100 mL) under reflux condition. After 12 h, 1,2-dithiacyclopentane was isolated according to the procedure and identified by its spectral data.

thiols **1e-h**, and these compounds could also be efficiently oxidized to their disulfides under the mentioned conditions for 2.2-10 hrs. The ability of this procedure for conversion of heteroaromatic thiols was demonstrated by the oxidation of 2-benzothiazolthiol (**1j**) to 2,2′-benzothiazol disulfide (**2j**) by two Ti(IV) compounds in 15-96% yields.

In order to show the necessity of Ti(IV), the role of NaI and air oxygen in this transformation, a set of experiments was undertaken by performing the coupling reaction of thiophenol under different reaction conditions (Table 2). The reaction of thiophenol with an equimolar amount of sodium iodide was carried out in refluxing acetonitrile. After 4 h, unreacted starting material was recovered (Entry 9). The possibility of formation of disulfides was also examined by using I_2 or I_2/NaI in refluxing acetonitrile. Under these conditions the yields of disulfides after 3 hrs were 10-50%. (Entries 7,8). The presence of I_2 and absence of NaI with two Ti(IV) catalysts in the formation of diphenyl disulfide were also studied (Entries 5,6). After 4-5 hrs, the disulfides have 0-45% yields. So, from the obtained results in Table 2, it can be concluded the presence of $TiCl_3(O_3SCF_3)$ or $TiO(O_2CCF_3)_2$ as catalyst and NaI are necessary for completion of the reaction. The actual mechanism of the present protocol and the precise role of Ti(IV) are not clear at this stage, but it could be proposed that the following catalytic cycle may play a role in formation of the disulfides (Scheme II).

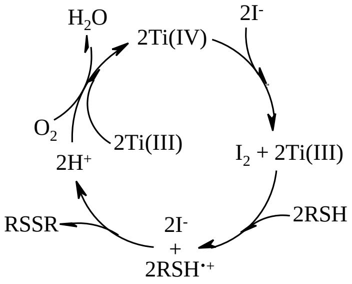
Although oxidative coupling of thiols has been widely studied, the reports on coupling of dithiols due to the ready polymerization are rare.[29] We studied the possibility of coupling 1,3-propanedithiol (**1i**) with our method under high di-

Table 2. Oxidative Coupling of Thiophenol under Different Reaction Conditions[a]

Entry	Reaction Components	Molar Ratio	Time (h)	Conversion (%)[b]
1	$TiCl_4$/NaI/thiol	0.1/1/1	10	40
2	$TiCl_4/I_2$/thiol	0.1/1/1	4	30
3[c]	$TiCl_3(O_3SCF_3)$/NaI/thiol	0.1/2/1	0.3	100
4[c]	$TiO(O_2CCF_3)$/NaI/thiol	0.2/2/1	2.5	100
5	$TiCl_3(O_3SCF_3)$ or $TiO(O_2CCF_3)_2/I_2$/thiol	0.2/2/1	4	45
6	$TiCl_3(O_3SCF_3)$ or $TiO(O_2CCF_3)_2$/thiol	0.1/1	5	0
7	I_2/thiol	1/1	3	50
8	NaI/I_2/thiol	1/0.5/1	3	10
9	NaI/thiol	1/1	4	0

[a] All reactions were performed in CH_3CN under reflux conditions. [b] Conversions referred to GC yields.
[c] When these reactions were performed in oxygen free solvent under N_2 atmosphere, only 6-8% of conversion to disulfide were observed after 3 hrs.

Scheme II



lution conditions (Table 1, footnote c). Although some polymeric materials were formed, 1,2-dithiacyclopentane (**2i**) was also obtained in 45% yield (Table 1, entry 9). In order to see the efficiency of other Lewis acids for this catalytic transformation, different metal halides such as Fe(III), Ni(II), Cr(III), Zn(II), Al(III), Ce(III), Pb(II), Mn(II), Hg(I), Co(II), Nb(VI), Sn(II), Cd(II), Mg(II), Zr(IV) and W(IV) were studied. In addition to Ti(IV) which was found to be very efficient, Fe(III), Ni(II), Cr(III), Co(II) and Sn(II) also showed this catalytic activity.[26] For showing the advantage and limitation of our method, we compared some of our results with those reported for other reagents (Table 3).

The results show that the oxidative couplings of thiols to their disulfides with Ti(IV)/NaI/air oxygen system, with respect to the rates and efficiencies of the reactions, have good to excellent results and between two Ti(IV) catalysts, $TiCl_3(O_3SCF_3)$ is more efficient than $TiO(O_2CCF_3)_2$.

In summary, we have presented a mild, catalytic and efficient method for oxidation of thiols to disulfides by Ti(IV)/NaI/air oxygen system. The present procedure could be attractive because of a new application of Ti(IV), simplicity, general applicability and high to excellent yields of the products, thus making this method a useful addition to the existing methodologies.

EXPERIMENTAL SECTION

Products were characterized by comparison of their physical data with those of authentic samples (IR, NMR, mp or bp). All yields refer to isolated pure products. TLC accomplished the purity determination of the substrates, products and reactions monitoring over silica gel PolyGram SILG/UV 254 plates. Compounds **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **2i** and **2j** are known and their mp or bp are listed in Table 1.

Preparation of Diphenyl Disulfide with $TiCl_3(O_3SCF_3)$; A Typical Procedure

A round bottom flask was charged with thiophenol (10 mmol, 1.1 g) (**1a**), acetonitrile (30 mL), NaI (20 mmol, 3 g) and $TiCl_3(O_3SCF_3)$ (1 mmol, 0.303 g). The resulting mixture was stirred under reflux condition for 18 min. After completion of the reaction, a solution of 1% aqueous sodium thiosulfate (30 mL) was added and the mixture was stirred for 10 min. The mixture was extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. The organic solution was evaporated to dryness and the residue was chromatographed on a short column of silica gel using n-hexane as eluent. The pure diphenyl disulfide (**2a**) was obtained as colorless crystals (1.03 g, 95% yield). Mp. 59-60 °C (Ref. 14, 60 °C); IR (KBr) ν/cm^{-1}: 3051, 1572, 1475, 1435, 734, 688, 459;

Table 3. Comparison of Oxidative Coupling of Thiols to Their Disulfides with Ti(IV)/NaI/Air Atmosphere and some other Reported Reagents

Entry	Thiol	Disulfide	Molar Ratio of Reaction Components/Time (h)/Yields (%)								
			I	II	III[22]	IV[23]	V[13]	VI[20]	VII[10]	VIII[11]	IX[11,a]
1	**1a**	**2a**	(0.1/2/1) (0.3)(95)	(0.1/2/1) (2.5)(94)	(1.2/3/1) (0.75)(96)	(0.01/1/1) (0.3)(98)	(0.2/1) (0.17)(98)	(2/2/1) (0.75)(95)	(1/1) (2)(92)	(2/1) (4)(80-90)	(1/1) (2)(82-92)
2	**1b**	**2b**	(0.1/2/1) (1.3)(93)	(0.3/2/1) (3)(95)	(1.2/3/1) (1.3)(90)	(0.01/1/1) (0.5)(96)	(0.2/1) (0.12)(98)	----	(2/1) (1.5)(95)	(2/1) (9)(55-60)	(1/1) (2)(67)
3	**1e**	**2e**	(0.1/2/1) (4)(93)	(0.1/2/1) (6)(93)	(1.2/3/1) (1.5)(97)	(0.05/1/1) (6)(94)	(0.2/1) (0.08)(96)	(2/2/1) (2)(97)	(2/1) (2.5)(88)	(2/1) (8)(70-80)	(1/1) (2)(75)
4	**1f**	**2f**	(0.2/2/1) (2.5)(93)	(0.2/2/1) (5)(94)	(1.2/3/1) (4.2)(82)	----	(0.2/1) (0.17)(92)	(2/2/1) (1.5)(98)	(2/1) (2)(85)	(2/1) (6)(80-85)	(1/1) (4)(45-50)
5	**1h**	**2h**	(0.2/2/1) (8)(96)	(0.2/2/1) (10)(94)	(1.2/3/1) (1.6)(96)	----	(0.2/1) (2.17)(95)	(2/2/1) (3)(99)	----	(2/1) (6)(75-80)	(1/1) (120)(0)

[I] $TiCl_3(O_3SCF_3)$/NaI/Thiol; [II] $TiO(O_2CCF_3)_2$/NaI/Thiol; [III] HMDS/DMSO/Thiol; [IV] $MoO_2Cl_2(dmso)_2$/DMSO/Thiol; [V] $Cu(NO_3)_2.3H_2O$; [VI] Silica sulfuric acid/$NaNO_2$/Thiol; [VII] $Ba(MnO_4)_2$; [VIII] $[Ce(NO_3)_3]_2CrO_4$/Thiol; [IX] PCC/Thiol; [a] Time as minutes.

^{1}H-NMR ($CDCl_3$): δ 7.64-7.5 (m, 4H), 7.43-7.21 (m, 6H).

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