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Metal-free oxidative coupling of thiols to disulfides using guanidinium nitrate or nitro urea in the presence of silica sulfuric acid

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Abstract. Efficient combination of nitro urea or guanidinium nitrate and silica sulfuric acid (SiO_2OSO_3H) as a new oxidizing system is able to oxidize a variety of aliphatic or aromatic thiols to the corresponding disulfides. The process reported here is operationally simple, environmentally benign and reactions have been mildly and heterogeneously performed in dichloromethane at room temperature.

Keywords. Thiols; disulfides; guanidinium nitrate; nitro urea; silica sulfuric acid; oxidation; coupling.

1. Introduction

The controlled oxidative coupling of thiols to disulfides is important in organic synthesis.[1] The conversion of thiols to the corresponding disulfides is an important reaction in chemical and biological process such as vulcanization,[2] synthesis of 4H-1,4-benzothiazines,[3] carbon–carbon bond forming,[4] protein thiol oxidation in tumor cells,[5] and cysteinyl thiol oxidation in vascular smooth muscle cells.[6] Oxidation of thiols is the most exploited method for disulfide synthesis mainly because a large number of thiols are commercially available and are easily synthesized.[7] Thiols and disulfides are important in living cells being a structural feature of many biomolecules including proteins. In many biochemical redox reactions they are interconverted.[8] In recent years, several reagents or reagent systems have presented ability of thiols coupling into disulfides such as molybdate sulfuric acid/sodium nitrite,[9] monochloro poly(styrenehydantoin),[10] tetramethylammonium fluorochromate,[11] O_2/manganese(III) Schiff-base complex,[12] $I_2/CeCl_3.7H_2O$/graphite,[13] ethylenebis(*N*-methylimidazolium) chlorochromate,[14] tripropylammonium fluorochromate,[15] *N*-*tert*-Butyl-*N*-chlorocyanamide,[16] and iron(III) trifluoroacetate/air;[17] but some of these procedures are not satisfactory because of several reasons such as overoxidation to sulfoxides and other by-products, tedious work-up of products, low yields, heavy metal contamination, toxicity, and cost effective reagents or catalysts.

2. Experimental

The chemicals and solvents were purchased from Fluka, Merck and Aldrich chemical companies and used without further purifications. All products are known and were characterized by comparison of their spectral (IR, ^{1}H NMR, or ^{13}C NMR) and physical data with authentic samples.

2.1 *Preparation of nitro urea ($NH_2CONHNO_2.xH_2O$)*

In a 50 mL round-bottomed flask, 4 mL of HNO_3 (65%) and 3.46 g of urea was stirred at room temperature for 2 h, and a white crystalline solid ($NH_2CONHNO_2.xH_2O$) was obtained quantitatively. M.p. 156–158.4°C (Ref.[28] 157–159°C); MS (70 eV): m/z = 105 (M+), 91, 69, 63, 60, 46 (base peak, NO_2^+), 44.

2.1a *Oxidative coupling of 2-mercaptobenzothiazole into 1,2-bis(benzo[d]thiazol-2-yl) disulfane by nitro urea and silica sulfuric acid: As a typical procedure*: Nitro urea ($NH_2CONHNO_2.xH_2O$), (0.40 g) and silica sulfuric acid (0.60 g) was added to a solution of 2-mercaptobenzoxazole (0.167 g, 1 mmol) in CH_2Cl_2

*For correspondence

Table 1. Oxidative coupling of thiols to the corresponding disulfides using combination of guanidinium nitrate **I** or nitro urea **II** in the presence of silica sulfuric acid **III** in dichloromethane at room temperature.

Entry	Substrate	Product	Substrate/Reagents (mmol)[a]			Time	Yield	Mp (°C)	Mp (°C)	Reference
			I	II	III	(Min)	(%)[b]	found	reported	
1	**1a**	**2a**	2.5	—	0.6	20	86	138–139	144–146	(9)
2	**1a**	**2a**	—	0.4	0.6	15	88	139–141		
3	**1b**	**2b**	2.5	—	0.6	17	90	89–91	90–92	(9)
4	**1b**	**2b**	—	0.4	0.6	40	87	89–91		
5	**1c**	**2c**	2.5	—	0.6	10	88	oil	oil	(27)
6	**1c**	**2c**	—	0.4	0.6	22	84	oil		
7	**1d**	**2d**	2.5	—	0.6	8	92	41–41.5	43–44	(9)
8	**1d**	**2d**	—	0.4	0.6	15	92	39–41		
9	**1e**	**2e**	2.5	—	0.6	17	92[d]	43–44	42–43	(13)
10	**1e**	**2e**	—	0.4	0.6	28	95[d]	41–43		
11	**1f**	**2f**	2.5	—	0.6	10	95	283–285	278–280	(24)
12	**1f**	**2f**	—	0.4	0.6	26	93	283–286		
13	**1g**	**2g**	2.5	—	0.6	22	96	89–91	78–92	(27)
14	**1g**	**2g**	—	0.4	0.6	51	97	77–84		
15	**1h**	**2h**	2.5	—	0.6	10	90	77.6–79	77.5–79	(24)
16	**1h**	**2h**	—	0.4	0.6	7	96	75–78		
17	**1h**	**2h**	2.5	—	—	5 h	No Reac.	—	—	—
18	**1h**	**2h**	—	0.4	—	5 h	No Reac.	—		
19	**1i**	**2i**	2.5	—	0.6	19	86	177.5–178	177–179	(9)
20	**1i**	**2i**	—	0.4	0.6	10	80	177–179		
21	**1j**	**2j**	2.5	—	0.6	39	92	68–70	70–71	(8)
22	**1j**	**2j**	—	0.4	0.6	78	88	68–70		
23	**1k**	**2k**	2.5	—	0.6	21	91	166.5–168	167–169	(13)
24	**1k**	**2k**	—	0.4	0.6	40	92	165–167		
25	**1l**	**2l**	2.5	—	0.6	22	62	oil	oil	(24)
26	**1l**	**2l**	—	0.4	0.6	16	61	oil		
27	**1m**	**2m**	2.5	—	0.6	12	63	oil	oil	(8)
28	**1m**	**2m**	—	0.4	0.6	52	64	oil		

[a]**I** refers to mmol of guanidinium nitrate and **II** and **III** refer to grams of nitro urea and silica sulfuric acid, respectively. [b]Isolated yield. [c]In the absence of silica sulfuric acid. [d]Product purified by column chromatography

(10 mL). The resulting mixture was stirred at room temperature for 10 min (the reaction progress was monitored by TLC) and then filtered. The residue was washed with CH_2Cl_2 (4 × 5 mL). Finally, CH_2Cl_2 was removed and 1,2-*bis*(2-benzoxazol)disulfane was obtained in 80% yield (0.258 g) as crystalline white solid; mp 177–179°C; H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.94 (d, J = 8 Hz, 1H), 7.80–7.78 (d, J = 8 Hz, 1H), 7.50–7.46 (t, J = 7.6 Hz, 1H), 7.39–7.35 (t, J = 7.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 154.6, 136.2, 126.6, 125.3, 122.7, 121.3 ppm. All the thiols converted into disulfides via same procedure except compounds **f**, **l** and **m**.

2.1b *General procedure for the oxidative coupling of thiols* **1f**, **1l** *and* **1m** *into disulfides* **2f**, **2l** *and* **2m** *using guanidinium nitrate or nitro urea in the presence of silica sulfuric acid*: To a mixture of guanidinium nitrate or nitro urea, (2.5 mmol or 0.4 g, respectively) and silica sulfuric acid (0.6 g) in CH_2Cl_2 (10 mL) one of the thiols **1f, 1l** or **1m** (1 mmol) was added, and the mixture was stirred at room temperature for the specified time (table 1) the reaction progress was monitored by TLC. After reaction completion CH_2Cl_2 was evaporated and ethanol (10 mL) was added to the residue, this mixture was stirred for 5 minutes then filtered. The residue was washed with CH_3CH_2OH (4 × 5 mL).

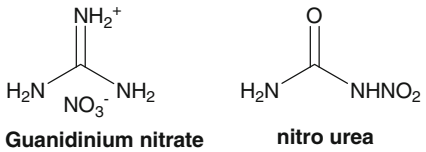
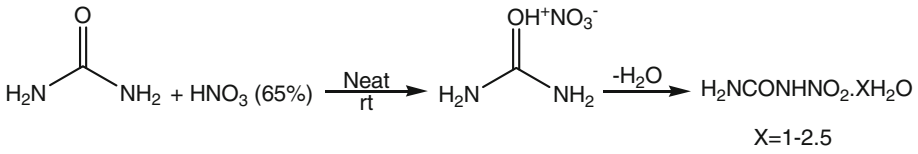


Figure 1. Chemical structures of guanidinium nitrate and nitro urea.



Scheme 1. Preparation of nitro urea.

Finally, CH_3CH_2OH was removed by rotary evaporator and resulting sediment was washed with H_2O (4 × 20 mL) and dried under vacuum to give pure disulfides **2f, 2l** or **2m**.

2.2 *Representative NMR Data*

2.2a *1,2-Bis(4-bromophenyl)disulfane 2b*: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, J = 8.4 Hz, 4H), 7.36 (d, J = 7.9 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.8, 132.3, 129.5, 121.6 ppm.

2.2b *1,2-Dip-tolyldisulfane 2d*: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, J = 7.9 Hz, 4 H), 7.42 (d, J = 7.9 Hz, 4 H), 2.35 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.5, 134.0, 129.8, 128.6, 21.1 ppm.

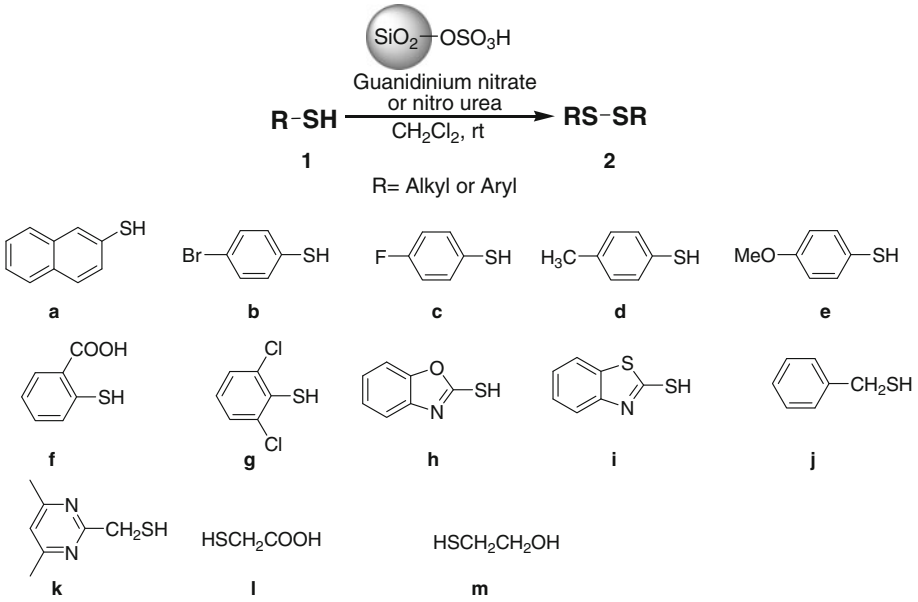
2.2c *1,2-Bis((4,6-dimethylpyrimidin-2-yl)methyl)disulfane 2k*: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.76 (s, 2H), 2.39 (s, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0, 167.6, 117.1, 23.8 ppm.

3. Results and discussion

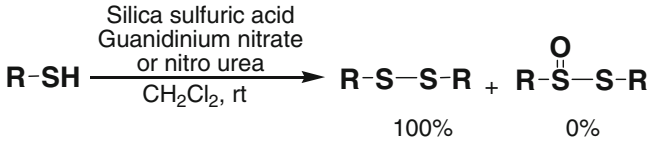
Recently we have introduced several heterogeneous procedures for the *in situ* generation of nitronium ion (NO_2^+) and nitrosonium ion (NO^+) for different organic functional group transformations.[18–26] In continuation of our investigation we became interested to delineate a new protocol to convert different types of thiols to the corresponding disulfides by guanidinium nitrate or nitro urea (figure 1) in the presence of silica sulfuric acid.

Guanidinium nitrate as commercially available reagent is a natural source of nitronium ion. While nitro urea could be easily prepared by the reaction of urea with nitric acid to produce urea nitrate, which immediately dehydrated to nitro urea (scheme 1).[27,28]

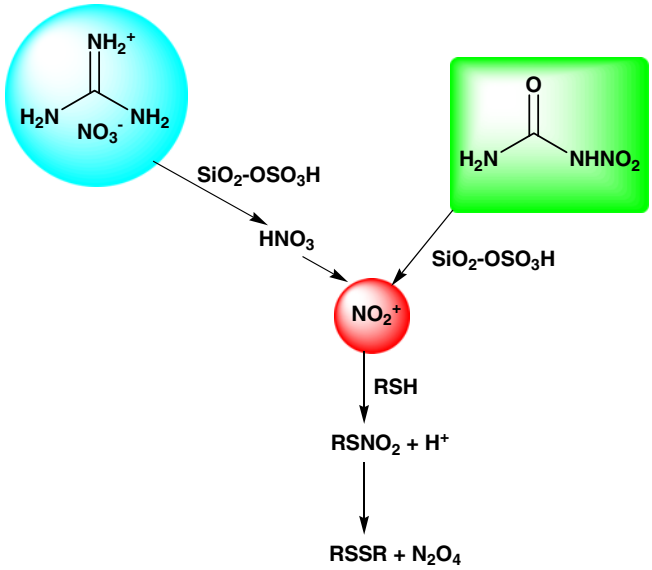
Consequently, we decided to use guanidinium nitrate and nitro urea in the presence of silica sulfuric acid for the oxidative coupling of aliphatic and aromatic thiols to prepare corresponding disulfide derivatives. Therefore, a variety of aliphatic and aromatic thiols **1** converted into corresponding disulfides **2** by combination of guanidinium nitrate **I** or nitro urea **II** and silica sulfuric acid **III** in dichloromethane as solvent at room temperature (scheme 2 and table 1).



Scheme 2. Oxidative coupling of thiols by guanidinium nitrate or nitro urea in the presence of silica sulfuric acid.



Scheme 3. Chemoselectivity in the oxidative coupling of thiols.



Scheme 4. Mechanism of oxidative coupling of thiols.

All the coupling reactions were performed easily by mixing of a thiol, guanidinium nitrate or nitro urea and silica sulfuric acid in dichloromethane and stirring this mixture for appropriate time at room temperature. Finally, pure product readily obtained by simple filtration, washing by appropriate solvent (CH_2Cl_2 or CH_3CH_2OH) and evaporation of the solvent. Because of mild properties of these heterogeneous systems, there is no overoxidation to sulfone was observed (scheme 3).

Silica sulfuric acid has a critical role in the coupling reaction by described reagents. Entries 17 and 18 from table 1 show that the coupling of 2-mercaptobenzoxazole into 1,2-*bis*(2-benzoxazol)disulfane using guanidinium nitrate and nitro urea, as a standard reaction, in the absence of silica sulfuric acid does not occur after 5 h.

A suggested mechanism of this oxidation is outlined in scheme 4 based on our previously reported works,[19,21,22,24] our observations and obtained results.

4. Conclusion

In summary, in this investigation an effective and new oxidizing media has been introduced for the preparation of disulfides under mild, metal-free and heterogeneous conditions. Furthermore, this method exhibits substrate versatility, non-toxic conditions, cost effective reagents, easy and clean work-up of products.

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