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Hayashi, Masahiko
Okunaga, Ken-ichi
Nishida, Shunsuke
Kawamura, Kenjiro
Eda, Kazuo

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Department of Chemistry, Graduate School of Science,

Kobe University, Kobe 657-8501, Japan

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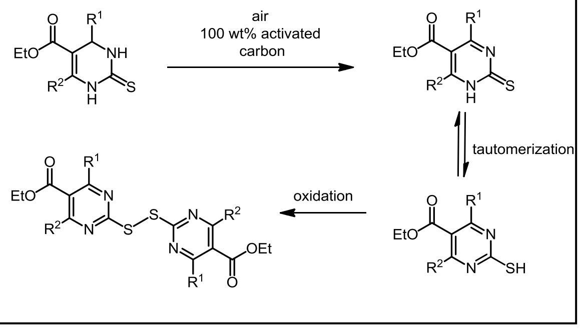

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Oxidative transformation of thiols to disulfides promoted by activated carbon—air system

Masahiko Hayashi*, Ken-ichi Okunaga, Shunsuke Nishida, Kenjiro Kawamura and Kazuo Eda

Department of Chemistry, Graduate School of Science, Kobe University, Kobe 657-8501, Japan

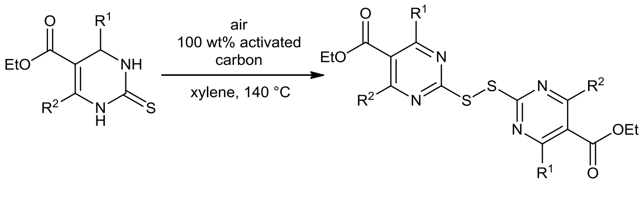
Abstract— Efficient oxidative transformation of thiols to disulfides took place in the presence of activated carbon under an oxygen (or air) atmosphere. The present oxidation method is available for a variety of thiols not only simple aromatic and aliphatic thiols, but also 3,4-dihydropyrimidin-2(1*H*)-thiones and *N*-Boc-L-cysteine.

Keywords: activated carbon; oxidation; thiol; disulfide

Transformation of thiols to disulfides is an important process in organic synthesis. Hydrogen peroxide is the most common oxidizing reagents.[1] Actually, Kirihara and his co-workers recently reported oxidation of thiols to disulfides by the combination of NaI and 30% H_2O_2.[2] Other oxidizing agents, such as $KMnO_4/CuSO_4$, Me_2SO—I_2, Br_2, t-BuOOH/$VO(acac)_2$, SmI_2, MnO_2, PCC have been also reported.[3] Recently Leino and Lönnqvist reported the use of stoichiometric amount of SO_2Cl_2 as an oxidizing agent, however, in this reaction equimolar amount of gaseous SO_2 and HCl were evolved.[4] Shirini and his co-workers reported oxidative coupling using $(NH_4)_2Cr_2O_7$ in the presence of silica chloride and wet SiO_2.[5] Sasson reported oxidative coupling of thiols to disulfides using a solid anhydrous potasium phosphate catalyst.[6] Montazerozohori and his co-workers also reported molybdate sulfuric acid (MSA) worked as a solid acid reagent for the oxidation of thiols to symmetrical disulfides.[7] In this case, the preparation of MSA is necessary in advance. Furthermore, Naimi-Jamal and Kaupp reported oxidative dimerization of 2-benzthiazolethiol and 2-pyrimidinethiol with NO_2 gas.[8] Very recently, Shaabani's group reported $H_3PW_{12}O_{40}$—$NaBrO_3$ system for the formation of disulfides from thiols.[9] Therefore, development of mild and environmentally friendly method for transformation of thiols into disulfides has been required still now. We have discovered some activated carbons work as promoter of oxidative aromatization of dihydroaromatic compounds.[10] Among them, a variety of functionalized 3,4-dihydropyrimidin-2(1*H*)-ones were converted to the corresponding pyrimidin-2(1*H*)-ones using activated carbon－molecular oxygen system.[11] During the course of this study, we discovered activated carbon also promotes the conversion of thiols to the corresponding symmetric disulfides. In this paper, we will report general synthesis of disulfides from thiols using activated carbon—air (or oxygen) system. In this paper, we will report general synthesis of disulfides from thiols using activated carbon—air (or oxygen) system.

At first, we examined the oxidation of functionalized 3,4-dihydropyrimidin-2(1*H*)-thiones. We expected the corresponding pyrimidin-2(1*H*)-thiones were obtained, however, as shown in Table 1, the all products were symmetrical disulfides. The combination of xylene as a solvent, at 140 °C under an air atmosphere using 100wt% of activated carbon was the best choice we examined.[12]

Table 1. Oxidation of functionalized 3,4-dihydropyrimidin-2(1*H*)-thiones



entry	R^1	R^2	time/h	yield/%[a]
1	C_6H_5	C_6H_5	45	85
2	4-ClC_6H_4	C_6H_5	46	79
3	4-$NO_2C_6H_4$	C_6H_5	50	66
4	4-$MeOC_6H_4$	C_6H_5	43	83

5[d]	3-$MeOC_6H_4$	C_6H_5	43	82
6	2-$MeOC_6H_4$	C_6H_5	55	82
7	3-HOC_6H_4	C_6H_5	48	56
8	1-naphthyl	C_6H_5	41	91
9	C_6H_5	Me	67	54
10	Me	Me	36	57

[a] Isolated yield after silica-gel chromatography.

The structure was confirmed by MS spectra and X-ray diffractometry (Figure 1).

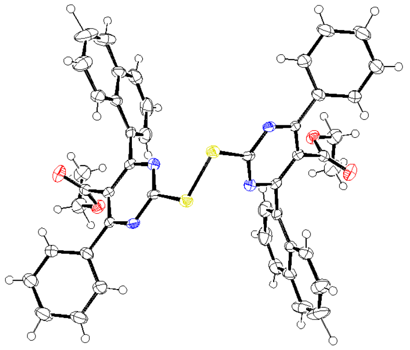
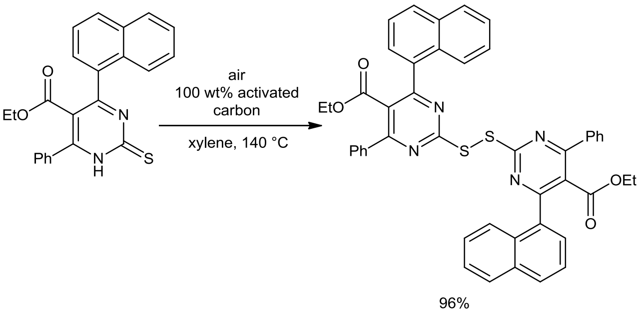


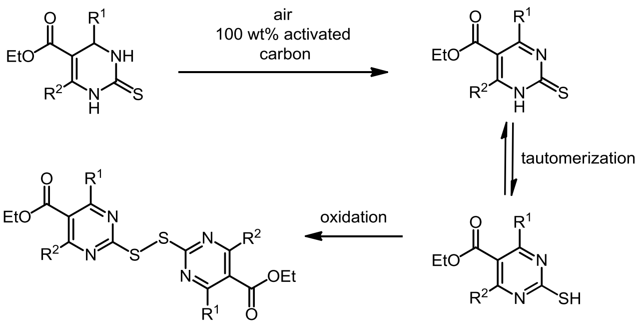
Figure 1. ORTEP diagram of 2,2'-dithiobis[4-(1-naphthyl)-6-phenyl-5-(ethoxycarbonyl)pyrimidine] with ellipsoids set at 50% probability.

It should be mentioned that in this system, the use of aliphatic group of R^1 and/or R^2 was available giving the product in moderate yields (entry 9 and 10), which was in contrast with the case of 3,4-dihydropyrimidin-2(1*H*)-ones. We proposed the mechanism of the formation of disulfides as shown in Scheme 2 based on the result of Scheme 1.



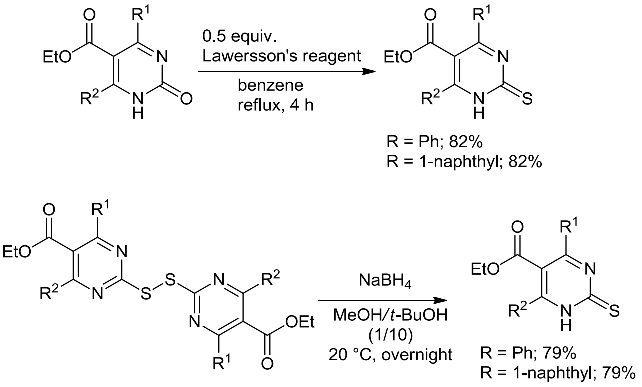
Scheme 1. Oxidation of pyrimidin-2(1*H*)-thiones

The alternative mechanism is also plausible. That is, tautomeization may occur at dihydropyrimidin-2(1*H*)-thiones stage, followed by oxidation with activated carbon—air system to form the tetrahydrodisulfide, then finally oxidation may take place again to afford functionalized bis(2-pyrimidyl) disulfides.



Scheme 2. Oxidation of functionalized 3,4-dihydropyrimidin-2(1*H*)-thiones

Reduction of functionalized bis(2-pyrimidyl) disulfide with $NaBH_4$ afforded pyrimidin-2(1*H*)-thiones (not 3,4-dihydro pyrimidin-2(1*H*)-thiones). This was confirmed by comparison with the compound that was prepared by the reaction of pyrimidin-2(1*H*)-ones with Lawesson's reagent as shown in Scheme 3.

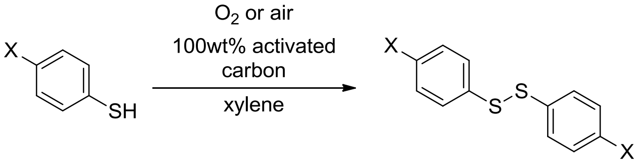


Scheme 3. Synthesis of functionalized pyrimidin-2(1*H*)-thiones

Therefore, in order to obtain substituted pyrimidin-2(1*H*)-thiones, there are two methods. One is the reaction of pyrimidin-2(1*H*)-ones with Lawesson's reagent. The other method is the reduction of substituted bis(2-pyrimidyl) disulfide with $NaBH_4$.[1] These two methods are general. Two examples to prepare functionalized pyrimidin-2(1*H*)-thiones are shown Scheme 3.

Then we examined the generality of this activated carbon—air (or oxygen) system promoted oxidation of aromatic and aliphatic thiols to disulfides. Table 2 and Table 3 show the results of the oxidation of 4-*tert*-butylbenzenethiol, 4-isopropylbenzenethiol, 4-bromobenzenethiol and 1-undecanethiol, 1-dodecanethiol, 1-tetradecanethiol, respectively. In all cases, in the absence of activated carbon, no reaction took place even at 140 °C. While, in the presence of activated carbon the reaction proceeded smoothly to give the corresponding disulfides in good to high yield (72—98% yield).

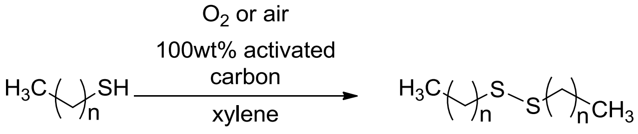
Table 2. Oxidation of aromatic thiols to disulfides[a]



X	O_2 or air	temp/°C	time/h	yield/%
t-Bu	O_2	30	24	97
	air	30	48	98
	O_2	60	12	93
	air	60	24	96
	O_2	120	6	94
	air	140	4	98
i-Pr	O_2	120	3	72
	air	140	3	76
Br	O_2	120	4	97
	air	140	4	94

[a] In the absence of activated carbon; 0% yield (O_2, 140 °C, 4 h)

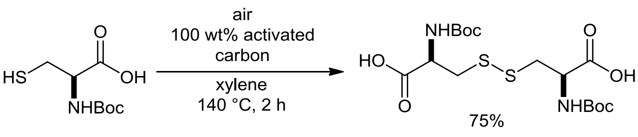
Table 3. Oxidation of aliphatic thiols to disulfides[a]



n	O_2 or air	temp/°C	time/h	yield/%
10	O_2	120	4	89
	air	140	9	92
11	O_2	120	6	86
	air	140	8	89
13	O_2	120	5	93
	air	140	5	95

[a] In the absence of activated carbon; 0% yield (O_2, 140 °C, 6 h)

Finally, we applied this method to the amino acid. That is, *N*-Boc-L-cysteine was converted to the corresponding disulfide L-cystine using activated carbon under an air atmosphere in 75% yield.



Scheme 4. Oxidation of *N*-Boc-L-cysteine

In conclusion, we revealed oxidative conversion of thiols to disulfides was promoted by activated carbon—air (or oxygen) system. The present method is applicable to both aromatic and aliphatic thiols. This method is not operationaly simple and inexpensive but also environmentally friendly method.

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Supporting Information Available: Details of experimental procedures and characterization data (^1H, ^{13}C, IR, mass spectrometry, elementary analyses for all new compounds, and the CIF file of 2,2’-dithiobis[4-(1-naphthyl)-6-phenyl-5-(ethoxycarbonyl)pyrimidine]).
CCDC 769416 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

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12 A general experimental procedure is as follow: A mixture of functionalized 3,4-dihydropyrimidin-2(1*H*)-thiones (5 mmol), 100 wt% of activated carbon (Charcoal Activated, TOKYO CHEMICAL INDUSTRY CO., LTD (TCI)), and anhydrous xylene (20 mL) was placed in a three-necked flask under an air atmosphere. The whole was heated to 140 °C and stirred for 36—67 h at this temperature. After confirmation of the completion of the reaction by TLC analysis (hexane : EtOAc = 1 : 2), activated carbon was filtered off using celite. The filtrate was evaporated then recrystalized or silica-gel column chromatographed. The obtained solid was vacuum-dried to give functionalized bis(2-pyrimidyl) disulfides.