

Oxidation of Thiols with Metal Nitrates Supported on TAFF

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ABSTRACT: Twelve thiols were readily oxidized to the corresponding disulfides by means of four metal nitrates supported on TAFF, a bentonitic clay, under mild conditions. However, in some cases, thioethers and other interesting by-products were detected. Some of the disulfides showed antimicrobial activities against *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus candidus*, *Microsporum gypseum*, *Candida albicans*, and *Cryptococcus neoformans*. © 2003 Wiley Periodicals, Inc. *Heteroatom Chem* 14:262–265, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10138

INTRODUCTION

Disulfides are an important class of molecules [1–3], e.g., they are employed as vulcanizing agents for rubber and elastomers [4]. Oxidation of thiols is the most common way to obtain the corresponding disulfides; thus, various reagents have been used, e.g., bromine [5], dimethyl sulfoxide [6], clayfen [7] and more recently trichloroisocyanuric acid [8], vanadyl acetylacetonate [9], and pyridinium chlorochromate [10], among others. However, the reported reagents suffer from one or more of the following disadvantages: availability, preparation, toxicity, and high cost, all of this in addition to cumbersome work-up procedures.

In our earlier research [11–13] on the use of TAFF, a commercial bentonitic clay [14], as a catalyst or as a support of inorganic molecules, we have provided alternative procedures to produce heterocyclic compounds [15]. Recently, experiments were performed to achieve a general alternative for the heterogeneous catalytic preparation of S,S-acetals [11].

This article reports the results of the reactions of various thiols, **1–12**, with several metal nitrates supported on TAFF.

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RESULTS AND DISCUSSION

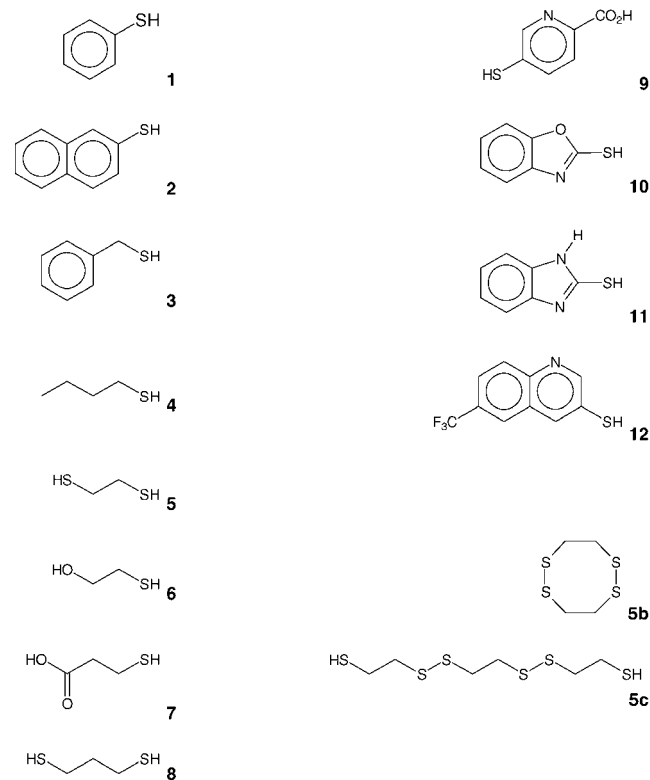
Disulfide Syntheses and Identification

The oxidative coupling of different types of mercaptans (Scheme 1) with four metal nitrates (Ag^+ , Cu^{2+} , Fe^{3+} , and Co^{2+}) supported on TAFF was investigated, Tables 1 and 2. As it can be seen in Table 1, both aromatic and aliphatic thiols **1–8** reacted efficiently to give the corresponding disulfides **1a–8a**, in good yields; however, low yields were achieved with cobalt(II) nitrate.

Of particular significance, no oxidation of the hydroxylic group was observed for the thiol **6** in the presence of cupric and ferric nitrate; however, the use of an excess of oxidant led to the formation of a low percentage of the corresponding dicarboxylic derivative (10%), as evidenced by GC-MS.

Another interesting case was the oxidation of **5** because in addition to the target compound **5a** (80%), the cyclic bis(disulfide) **5b** (6%), and the acyclic bis(disulfide) **5c** (5%) were also produced. **5a–c** were identified by their molecular ions in HRMS: m/z 185.9665 ($\text{C}_4\text{H}_{10}\text{S}_4$), 183.9509 ($\text{C}_4\text{H}_8\text{S}_4$), and 277.9419 ($\text{C}_6\text{H}_{14}\text{S}_6$), respectively.

As summarized in Table 2, we found that the reaction of the thiols **9–12** afforded the corresponding



SCHEME 1 Thiols used (**1–12**) and observed cyclic bis(disulfide) **5b** and acyclic bis(disulfide) **5c**.

TABLE 1 Oxidative Coupling of Thiols **1–8** by Metal Nitrates Supported on TAFF

	Disulfide Yield (%) ^{a,b}			
	Ag^+	Cu^{2+}	Fe^{3+}	Co^{2+}
1	80	90	90	50
2	75	77	85	40
3	80	80	90	50
4	75	80	90	50
5	75	80	90	40
6	75	85	85	40
7	70	75	85	50
8	80	85	95	50

^aThe resulting disulfides **1a–8a** are known products and were identified by comparison of their spectroscopical data (^1H NMR and EIMS), see Refs. [16a–e].

^bYields are of isolated pure products.

disulfides **9a–12a** as the major products. In addition, the respective thioethers **9b–12b** were also obtained. The separation of these two products by column chromatography seems to be impossible. However, they were quantified by GC-MS, and evidenced by means of HRMS and use of CID-linked scans. Thus, it was demonstrated that **9b–12b** have nothing in common with the corresponding disulfides in terms of mass spectroscopy, for example, the ion m/z 268 was not present in the CID-linked scan mass spectra of the molecular ion of **10a**.

Antifungal Activity

The biological study of the disulfides **5a–8a** was performed by assaying four filamentous fungi and two genus of yeast. The results indicate that compound **5a** acted as a fungicide against *Aspergillus fumigatus* and *Aspergillus candidus*, but appeared fungistatic with *Microsporum gypseum* and *Aspergillus niger*. The disulfide **8b** showed only fungicide activity when assayed with *A. fumigatus*, *A. niger*, and *A. candidus*.

TABLE 2 Oxidative Coupling of Thiols **9–12** and Formation of Thioethers, Using $\text{Fe}(\text{NO}_3)_3/\text{TAFF}$

	Disulfide (%) ^a	Thioether (%) ^a	HRMS	
			Disulfide	Thioethers
9	30	25	307.9925 $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_4\text{S}_2$	276.0204 $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_4\text{S}$
10	35	15	300.0027 $\text{C}_{14}\text{H}_8\text{N}_2\text{O}_2\text{S}_2$	268.0306 $\text{C}_{14}\text{H}_8\text{N}_2\text{O}_2\text{S}$
11	40	10	298.0346 $\text{C}_{14}\text{H}_{10}\text{N}_4\text{S}_2$	266.0626 $\text{C}_{14}\text{H}_{10}\text{N}_4\text{S}$
12	50	20	456.0189 $\text{C}_{20}\text{H}_{10}\text{F}_6\text{N}_2\text{S}_2$	424.0468 $\text{C}_{20}\text{H}_{10}\text{F}_6\text{N}_2\text{S}$

^aPercentage of formation acquired by GC-MS.

Finally **6a** and **7a** acted as fungicides against *M. gypseum* as well as both yeasts assayed.

EXPERIMENTAL

Toluene and *n*-hexane (Aldrich) were dried prior to use (Na/benzophenone). The mercaptans (Aldrich) were used as received. The bentonitic material was obtained from Tonsil Mexicana and analyzed prior to use with a Siemens D-5000 X-ray diffractometer using Cu K α_1 radiation. Purified products were characterized by spectroscopic means: ^1H NMR spectra were recorded on a Varian Mercury-300 spectrometer, using CDCl_3 as solvent and TMS as internal reference; EIMS (70 eV) spectra, the HRMS and the CID-linked scans data were obtained using JEOL MS AX 505 HA and MS-SM 102 mass spectrometers. Thin layer chromatographic analyses were performed using Merck precoated plates (silica gel 60 F $_{254}$, 0.25 mm); for the corresponding column chromatography (flash), silica gel Merck 230-400 mesh was employed. The melting points were determined on a Fisher-Johns apparatus and are uncorrected. The supported reagents were prepared according to a previously reported procedure [15]. All the known compounds (see Tables 1 and 2) were identified by comparison with authentic samples, using physical (mp) and spectroscopical data (^1H NMR and EIMS) [16].

Oxidative Coupling of Mercaptans

One hundred milligrams of each mercaptan and 100 mg of $\text{M}(\text{NO}_3)_n/\text{TAFF}$ in 20 ml of toluene were placed in a round-bottomed flask (50 ml) equipped with a condenser and gently refluxed for 3–12 h. The reaction was monitored by TLC (*n*-hexane/EtOAc) each hour. At the end of each reaction, the reaction mixture was filtered over celite and washed with hot toluene. Once the solvent had been evaporated under vacuum, some of the residue (substrates **1–8**) were purified by preparative film chromatography and crystallized from toluene.

Biological Assay

The following filamentous fungi were employed: *A. fumigatus*, *A. niger*, *A. candidus*, and *M. gypseum*. The yeast strains used were *Candida albicans* and *Cryptococcus neoformans*. They were obtained from Laboratorio de Microbiología, FESC-UNAM, México.

Filamentous fungi were inoculated in 250 ml Erlenmeyer flasks with 50 ml growth medium malt extract broth (15 g malt extract and 5 g peptone in 1 l distilled water). Then, each solution was incubated at 30°C until a strong mycelial growth was obtained

(8 days). Yeasts were grown in the same medium and were incubated at 30°C for 36 h. Fungal cultures were maintained on malt extract broth plus 15 g antibiotic medium (Bioxon) number 3 (Becton Dickinson of México, S.A. of C.V. Cuautitlán Izcalli, Carretera México Queretaro Km. 37.5, Estado de México). The biological activity was assessed on the basis of the growth rate for both filamentous fungi and yeasts aqueous solutions [17].

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- [14] (a) Tonsil Actisil FF (TAFF), a commercial Mexican bentonitic clay, is available from Tonsil Mexicana S. A. de C. V. Mexico City, Mexico at US\$ 1.30/kg. When examined with X-ray fluorescence, this clay proved to have the following composition (in percent): SiO $_2$, 74.5; Al $_2$ O $_3$, 9.3; MgO, 0.4; Fe $_2$ O $_3$, 1.3; CaO, 4.0; K $_2$ O, 0.4; TiO $_2$, 0.4; H $_2$ O, 9.7. When X-ray thermogravimetric analysis was run, the laminar structure was found to be unstable above 150°C. Quartz and cristobalite are also important components in the clay

composition, as observed by powder X-diffraction. The corresponding BET surface area was $198.718 \text{ m}^2 \text{ g}^{-1}$ and the pore volume and average pore diameter were $32.04 \times 10^{-2} \text{ cm}^3 \text{ g}^{-1}$ and $77.8 \text{ \AA}$, respectively. It is worth mentioning that a detailed characterization of the clay (^{29}Si and ^{27}Al MAS-NMR, SEM, IR-Py, DTA, and TG, H_2O) is in galley proof; (b) Miranda, R.; Ríos, H.; Salmón, M.; Cogordán, J. A.; Castro, M. *J Appl Catal* 2002.

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