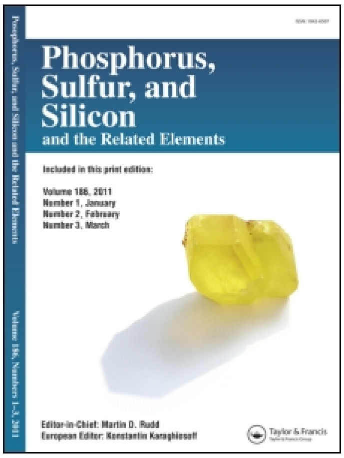

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EASY AND RAPID METHOD FOR DISULFIDE SYNTHESES USING NANOPHASE-MANGANESE (VII) OXIDE COATED CLAY

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Disulfide bond formation by the oxidation of several thiol compounds using nanophase manganese (VII) oxide coated clay (NM7O coated clay) in chlorinated, nonchlorinated (toluene), and polar solvents (water) is described. During the process, nitro and methoxy groups remain unaffected. The NM7O coated clay is easily prepared, stable, and inexpensive to manufacture. Furthermore, this and other studies prove that NM7O coated clay properties, i.e., mineralogy, chemical, and reactivity, are different from $KMnO_4$. This rapid and facile synthesis coupled with the use of the recyclable NM7O coated clay catalyst will save energy due to low temperature and rapid reaction times, as well as minimal disposal problems, thus decreasing production costs.

Keywords Catalyst; coupling; easy and rapid synthesis energy; stable

INTRODUCTION

Disulfide bond formation is important in peptide synthesis,[1] protein stabilization,[2] and in bioactive molecules.[3] Thiols are the main precursors to disulfides, but they are highly susceptible to air oxidation. Therefore, in multistep syntheses, the protection of thiols as acetates or esters and their subsequent transformation into -SS-linkages is often necessary. There are a few methods for the cleavage of thiol acetates under abnormal conditions, such as longer reaction time (12 days), argon atmosphere, and photolysis.[4] Recently, two improved methods have been reported: one requires activation by stannates,[5] while the other uses a metallic reagent[6] with a longer reaction time. The last decade has witnessed two major changes in chemical manufacturing: 1) a large interest in "green" chemistry syntheses in which toxic reagents, catalysts, and solvents have been replaced by nontoxic counterparts, and 2) energy efficient processes to decrease CO_2 footprint. This has been achieved by the use of environmentally friendly solid-supported catalysts[7] and/or in combination with microwave irradiation.[8] This modification not only increases the reaction rate, but affords

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$$2RSH \longrightarrow RSSR$$

R = a) C_6H_5-, b) $HOCH_2CH_2$- , c) 2-NH_2-C_6H_5- d) 4-H0-C_6H_5-, e) 4-NO_2-C_6H_5-, f) 4-$CH_3$0-C_6H_5-CH_2- g) CH_2=CH-CH_2-, h) $(CH_3)_2CH$-, i) $(CH_3)_3C$-
j) $(C_6H_5$-$)_3C$-, k) $HSCH_2CH_2CH_2$-

Scheme 1

a simple workup and ease of manipulation of the reaction. Herein, we report a rapid and convenient method for the oxidative coupling of thiols using a nanophase manganese (VII) oxide coated clay (NM7O coated clay)[9] catalyst as shown in Scheme 1. The NM7O coated clay properties, i.e., mineralogical, chemical, and reactivity, are distinct and unique from $KMnO_4$.[10] This method affords a rapid, low temperature method for the synthesis of disulfides that avoids the use of activating reagents or excess chlorinated solvent.

RESULTS AND DISCUSSION

To determine the optimum reaction conditions and solvent for the above thiol-coupling reactions shown in Scheme 1, we studied the conversion of benzenethiol (**1a**) to diphenyl disulfide (**2a**) in various solvents, temperatures, and reaction times. The results, shown in Table I, show that nearly quantitative yields (~98%) of **2a** were obtained when the reactions were carried out in chloroform (entry 3) at room temperature for 2 h and in toluene (entry 1) at 40°C. The other solvents listed, acetonitrile (entry 2) and dichloromethane (entry 4), required longer reaction times (3 h and 6 h, respectively) and gave significantly lower yields of **2a** (66% and 87%, respectively). Thus we decided to carry out subsequent reactions in toluene at 40°C and chloroform at room temperature.

We next used these conditions to the conversion of a variety of thiols (**1a–k**) to the corresponding disulfides (**2a–k**), and the results are listed in Table II. All products were characterized by MS, NMR, melting point, and by comparison of their R_f values to those of authentic samples.

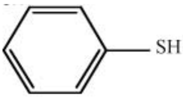
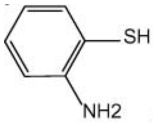
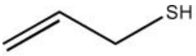
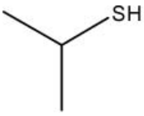
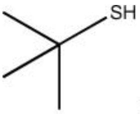
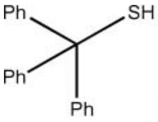
As shown in Table II, most of the listed disulfides (**2a**, **2c**, **2f**, **2g**, **2h**, **2i**, and **2k**) were obtained in essentially quantitative yields within 1–3 h when the reactions were run in toluene or chloroform. Additionally, the reaction of the water-soluble butane-1-thiol (**1a**) carried out in water at room temperature gave the corresponding disulfide **2b** in 98% yield. It is noteworthy that diallyic disulfide (**2g**) (entry 7) was obtained in 98% yield when the reaction was run in toluene; however, in chloroform the yield of **2g** was lowered to 65%.

Table I Thiophenol reaction conditions using NM7O coated clay

Entry	Substrate	Solvent	Time	Temperature	% Yield
1	Thiophenol	Toluene	2 h	40°C	98
2	Thiophenol	Acetonitrile	3 h	rt	66
3	Thiophenol	Chloroform	2 h	rt	98
4	Thiophenol	Dichloromethane	6 h	rt	87

rt = room temperature.

Table II Syntheses of disulfide compounds using NM7O coated clay

Entry No.	Thiol	Solvent	Time	Reaction Conditions	Product	Yield (%)	Ref.[†]
1	 **1a**	Toluene $CHCl_3$	2h 2h	40°C rt	**2a**	97 98	11
2	 **1b**	Water	2 h	rt	**2b**	98	12
3	 **1c**	Toluene $CHCl_3$	1 h	40°C rt	**2c**	97 99	13
4	 **1d**	Toluene	2h	40°C	**2d**	98	14
5	 **1e**	Toluene	2 h	40°C	**2e**	94	15
6	 **1f**	Toluene $CHCl_3$	2 h	40°C rt	**2f**	98 97	16
7	 **1g**	Toluene $CHCl_3$	3 h	40 °C rt	**2g**	99 65	17
8	 **1h**	Toluene $CHCl_3$	2 h	40°C rt	**2h**	98 97	18
9	 **1i**	Toluene CH_3Cl	2 h	40°C rt	**2i**	99 98	19
10	 **1j**	Toluene	3 h[‡]	40°C	**2j**	60	20
11	 **1k**	Toluene $CHCl_3$	2 h	40°C rt	**2k**	99	21

[†] References.

[‡] Reaction incomplete even with additionalNM70 (1:3) and longer reaction time (18 h).

rt = room temperature.

Interestingly, both the electron-withdrawing 4-nitro group and electron-donating 4-hydroxy group on the respective phenylthiols (entries 5 and 4) gave respective coupling products **2e** and **2d** in 94% and 98% yields. However, despite the utility and simplicity of these reactions, limitations were encountered. For example, ditrityl disulfide **2j** (entry 10) was obtained in 60% when the reaction was run for 3 h in toluene at 40°C; attempts to increase the yield of **2j** by prolonged heating for 18 h failed. However, even though the yield of ditrityl disulfide was low (60%), to the best of our knowledge, it is the highest yield reported to date.

The kinetics and mechanism of the oxidation of a thiol to a disulfide by the one-equivalent oxidants neptunium (VI) and cobalt (III) have been reported.[22] The major features of that proposed mechanism involve an initial 1-equiv oxidation of a thiol to a thiol radical in the rate determining step (RDS). The resulting radical then is thought to react with another thiol to give the stable disulfide radical, which presumably is converted to the disulfide. It is possible that the nanophase Mn(VII)O used in our study behaves similarly. We, however, have insufficient evidence for the role of Mn(VII)O in the process. Studies are underway, and the results will be submitted in due course.

CONCLUSION

In summary, we have developed a convenient and practical alternative to disulfide synthesis by coupling various types of thiol groups using NM7O coated clay. The lower temperature and rapid syntheses of disulfides coupled with the use of recyclable NM7O coated clay catalyst will save energy and decrease production costs. Furthermore, the reaction appears to be surface-based and catalytic, since the NM7O coated clay can be reused multiple times for making additional disulfide compounds. We are carrying out mechanistic studies and will report the conclusions in due course.

EXPERIMENTAL

Thiophenol and trityl thiol were obtained from Acros and Aldrich, respectively. The natural montmorilinite clay, Bentonite L-10, was purchased from Southern Clay Products, Gonzalez, TX, USA. All other materials were reagent grade unless otherwise specified. ^{1}H and ^{13}C NMR spectra were obtained on a 400-MHz Bruker Advance NMR spectrometer. Melting points were collected on a TA Instruments DSC 2010 Differential Scanning Calorimeter using a heating rate of 10 °C min^{-1} and nitrogen as a purge gas. Thin layer chromatography was done on precoated silica gel 60f 254 (0.5 mm) glass plates. The NM7O coated clay (Bentonite-L-10) was prepared by adding $MnCl_2$ $4H_2O$ (720 g) to water (500 mL), and stirring for 5 min to dissolve the salt to yield a solution (termed Solution A). Then montmorillonite clay (2000 g) was added to water (8 L) and stirred for 30 min, or until a uniform suspension was achieved (termed Suspension B). Solution A and Suspension B were added and mixed in another vessel to make a beige-colored suspension of $Mn(OH)_2$. After 30 min of stirring, 1.5 L, 5.2 M NaOH (1.5 L) was added, and the resultant pH of the suspension was 13. Subsequently, 1,4-phenylenediamine (PDA, 40 g) was added to the suspension and stirred for 30 min. The PDA-added suspension was lowered to pH 7.8 by the addition of 6 N HCl, during which time the color of the suspension changed from green to violet within 1 h. The violet color is the indication of NM7O coated clay. The oxidation states were characterized and confirmed by cyclic voltametric techniques and visible spectroscopy.[10] The suspension contained 22% by weight NM7O coated clay with a Mn content of 7%. Unless otherwise indicated, the compounds were obtained commercially and used without further purification.

In a typical experimental procedure, the thiol compounds were treated with excess NM7O coated clay, i.e., 1:2 molar ratio of thiol compounds and Mn (based on its content in NM7O coated clay) in chloroform at room temperature or in toluene at 40°C in the presence of air for 2 h. After completion of the reaction, the NM7O coated clay was filtered, and the filtrate was concentrated using a rotary evaporator under reduced pressure. Thin layer chromatography was done on precoated silica gel 60f 254 (0.5 mm) glass plates. Column chromatography was used to yield the pure disulfide.

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