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Hydrotalcite Clay-catalysed Air Oxidation of Thiols†

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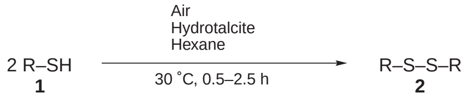
Hydrotalcite is an efficient catalyst for air oxidation of a variety of aromatic, aliphatic and alicyclic thiols in hexane, affording the corresponding disulfides in excellent to quantitative yields under mild and neutral conditions.

Use of supported reagents and catalysts for organic syntheses is current research interest, since reactions under solid–solution biphasic conditions have many practical advantages unavailable by conventional solution-phase counterparts.[1] Of support materials frequently examined, aluminosilicate clays,[2] especially bentonites, have enjoyed extensive use as solid acid catalysts. On the other hand, investigations into solid bases and their application to organic reactions have apparently been limited. It has very recently been reported, however, that the epoxidation of alkenes[3a–d] and Baeyer–Villiger oxidation of ketones[3e,f] are favorably effected by synthetic basic clays, hydrotalcites, some of which exert interesting shape-selective catalysis[3d] as observed in well-known zeolite catalysed reactions.[4]

Oxidative coupling of thiols **1** to disulfides **2** has been a subject of extensive research and many reagents and reagent systems are currently available.[5] It is well known that the ease with which thiols are oxidised is dependent on their acidities and therefore they undergo base catalysis.[6] Thus basic alumina[7] and DMSO,[8,9] for instance, can lead to efficient oxidation of a number of thiols, owing to their nucleophilic activity. Accordingly, it is reasonably expected that a hydrotalcite clay could be an efficient catalyst for the oxidation of thiols.



$$\underset{\mathbf{1}}{2\ \mathrm{R{-}SH}} \xrightarrow[30\,^{\circ}\mathrm{C},\ 0.5\text{–}2.5\ \mathrm{h}]{\text{Air, Hydrotalcite, Hexane}} \underset{\mathbf{2}}{\mathrm{R{-}S{-}S{-}R}}$$

1, 2	R	**1, 2**	R	**1, 2**	R
a	Ph	**g**	2-ClC$_6$H$_4$	**m**	C$_8$H$_{17}$
b	4-MeOC$_6$H$_4$	**h**	3-ClC$_6$H$_4$	**n**	C$_{10}$H$_{21}$
c	2-MeC$_6$H$_4$	**i**	4-ClC$_6$H$_4$	**o**	C$_{12}$H$_{25}$
d	3-MeC$_6$H$_4$	**j**	4-O$_2$NC$_6$H$_4$	**p**	C$_{14}$H$_{29}$
e	4-MeC$_6$H$_4$	**k**	PhCH$_2$	**q**	*c*-C$_5$H$_9$
f	4-BrC$_6$H$_4$	**l**	C$_6$H$_{13}$	**r**	*c*-C$_6$H$_{11}$

Scheme 1 Oxidative coupling of thiols

Attempted reactions of benzenethiol **1a** were carried out at 30 °C by simply stirring **1a** in hexane under a gentle flow of air in the absence and presence of commercial (untreated) hydrotalcite. However, reactions were sluggish and diphenyl disulfide **2a** was not obtained in a synthetically acceptable yield within a reasonable period of time; GLC analyses of crude mixtures from 30 min reactions showed that conversions of **1a** were 5.3 and 12%, respectively, giving only 2.0 and 5.0% of **2a**, respectively. On the other hand, oxidation with the use of predried hydrotalcite under otherwise identical conditions achieved 100% conversion and, after simple work-up and chromatographic isolation, gave **2a** in 97% yield (Table 1, entry 1). The higher activity of dry hydrotalcite than that of the untreated clay may be related to its increased surface area and/or enhanced basicity.[10] A control run under an inert atmosphere gave only 11% of **2a** and 86% of **1a** remained unreacted even in the presence of dry hydrotalcite (Table 1, entry 2), indicating clearly that the clay catalyses the reaction and air is essential for efficient oxidation. These observations are markedly in contrast to those from an earlier basic alumina-catalysed air oxidation[7] claiming that the dehydration of commercial alumina does not give any improvement, and also that small scale experiments (< 5 mmol of thiols) give the same results whether or not air is involved in the reaction system. Treatment of **2a** in place of **1a** under the conditions of entry 1 led to complete recovery of the disulfide, the mp of which showed no depression upon mixing with **2a**, suggesting that the dry hydrotalcite/air system lacks the ability to convert the disulfide to a higher oxidation product such as the sulfonic acid. A test reaction of **1a** at 20 °C led to decreased conversion and product yield (92 and 87%, respectively).

Table 1 Oxidative coupling of thiols **1** to disulfides **2** with air and calcined hydrotalcite[a]

Entry	Clay/g	*t*/h	Yield of disulfide(%)[b]	Entry	Clay	*t*/h	Yield of disulfide(%)[b]
1	0.5	0.5	**2a**(97)	11	0.7	2	**2i**(96)
2[c]	0.5	0.5	**2a**(11)	12	0.7	2	**2j**(90)
3[d]	15	1.5	**2a**(94)	13	0.5	2	**2k**(98)
4	0.7	2	**2b**(96)	14	0.5	2.5	**21**(95)
5	0.5	0.75	**2c**(96)	15	0.5	2.5	**2m**(quant.)
6	0.5	0.75	**2d**(95)	16	0.5	2.5	**2n**(98)
7	0.5	0.75	**2e**(97)	17	0.5	2	**2o**(98)
8	0.7	2	**2f**(92)	18	0.5	2	**2p**(96)
9	0.7	2.5	**2g**(92)	19	0.5	2.5	**2q**(98)
10	0.7	2.5	**2h**(90)	20	0.5	2.5	**2r**(95)

[a] Under a gentle flow of air (*ca.* 25 ml min^{-1}), at 30 °C; 1 mmol of thiol **1** and 5 ml of hexane were used in every run. [b] Isolated yield of chromatographically purified disulfide **2** based on the starting **1**. [c] Under a gentle flow of argon; 86% of **1a** remained unreacted. [d] **1a** (30 mmol, 3.3 g), hexane (150 ml).

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† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Another set of comparative experiments showed that hexane is superior as solvent to ethanol, dichloromethane, carbon or tetrachloride, acetonitrile or diethyl ether.

The dry hydrotalcite/air system successfully gave the high-yielding oxidation of benzenethiols **1a**–**j**, regardless of electronic properties of substituents (Table 1, entries 1, 4, 7, 8, 11 and 12) and their positions on the benzene ring (entries 5–7 and 9–11). Aralkyl **1k** (entry 13), aliphatic **1l**–**p** (entries 14–18), and alicyclic thiols **1q**,**r** (entries 19 and 20) also underwent smooth oxidation. In addition, although a prolonged period of time was required to effect the multigram scale oxidation of **1a** as compared with the 1 mmol scale experiment in entry 1, it can easily be achieved without appreciable decrease in the yield of **2a** (entry 3).

Commercial hydrotalcites are readily available and inexpensive and safe to handle, some of which, including the one examined here, are used as pharmaceuticals, *e.g.* antiacid agents,[11] and thus non-toxic. The present hydrotalcite-based procedure can favorably be compared to a similar basic alumina/air oxidation system in benzene[7] in terms of smaller quantities of the solid catalyst, slightly superior yields of disulfides and especially shorter reaction times. Indeed, oxidations of **1a**, **k**, **l** and **r** (Table 1, entries 1, 13, 14 and 20, respectively) with 0.5 g of dry hydrotalcite per mmol of thiol for 0.5–2.5 h gave **2a**, **k**, **l** and **r** in 97, 98, 95 and 95% yields, respectively, whereas the latter system required 1 g of the alumina per mmol of thiol and gave 96, 91, 89 and 93% yields of **2a**, **k**, **l** and **r**, respectively, from 4–6 h reactions. In addition, from economical and environmental points of view, hexane is a more favorable solvent than the aromatic solvent.

In conclusion, the dry hydrotalcite/air system in hexane gives a mild, inexpensive and high-yielding oxidation of a wide range of thiols. Interesting results demonstrated here coupled with the ability of hydrotalcites to effect various oxidations[3] and easy reaction performance might make hydrotalcites practically attractive as basic solid catalysts and/or supports, providing a new strategy for organic synthesis.

Experimental

^{1}H NMR spectra were recorded with a JEOL PMX-60 (60 MHz) spectrometer for solutions in $CDCl_3$ using TMS as an internal standard. Analytical GLC was performed on a Shimadzu GC-4CM instrument, equipped with a FID *via* a 2 m × 5 mm diameter glass column packed with 3% Silicone OV-17 on Uniport HP and interfaced with a Shimadzu Chromatopac C-R6A integrator, with temperature programming. Melting points were determined on a Yanagimoto MP-S3 melting point apparatus and are uncorrected. Mass spectra were determined on a JEOL SX-102A mass spectrometer coupled to a Hewlett Packard GC5890 Series II GC apparatus *via* a heated capillary column. Thiols **1a**–**r** were used as received from commercial sources. A free-flowing synthetic hydrotalcite powder, Kyowaad® 500SH [formulated as $Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O$],[12] was a gift from Kyowa Chemical Industry, which was oven-dried (500 °C, 1 h; dry hydrotalcite) and stored in a desiccator, the activity of which was maintained at least for a month.

Oxidation Procedure.—A general procedure is described for the oxidation of benzenethiol **1a** (Table 1, entry 1). To a mixture of **1a** (0.110 g, 1 mmol) and hexane (5 ml) in a 30 ml two-necked roundbottom flask was added dry hydrotalcite (0.5 g) in a dry box. The flask was quickly equipped with a Teflon-coated stirrer bar, a gas-inlet tubing connected to a dry air supplier[‡] and a reflux condenser, the top of the latter was linked to a liquid paraffin trap *via* a flexible silicone-rubber tubing. The cloudy heterogeneous mixture was kept at 30 °C for 30 min under a gentle flow of air (*ca.* 25 ml min^{-1}) while efficient stirring was continued in order to ensure smooth reaction and to attain reproducible results. After cooling to room temp., the reaction mixture was filtered through a sintered glass funnel and the filter cake was washed thoroughly with portions of dry diethyl ether (total 50 ml). Rotary evaporation of the combined solvent left diphenyl disulfide **2a**, which was immediately chromatographed on a silica gel column (Merck silica gel 60; hexane–AcOEt, 10:1) to afford pure (^{1}H NMR, GLC and TLC) **2a** in 97% yield (0.106 g, mp 57.5–58 °C; lit.,[13] 58–60 °C).

Oxidations of the other thiols **1b**–**r** were carried out as above, the conditions (quantities of dry hydrotalcite and reaction periods) of which were determined on the basis of the reactivity of **1** and yield of disulfides **2**. Each reaction achieved 100% conversion and, after usual work-up and a single chromatography, gave the disulfide with satisfactory purity (> 99%). Disulfides thus obtained were known compounds, physical properties of which were consistent with literature data. A multigram scale experiment was performed with **1a** (3.3 g, 30 mmol), dry hydrotalcite (15 g) and hexane (150 ml) at 30 °C for 1.5 h, giving **2a** in 94% isolated yield (Table 1, entry 3).

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[‡] A simple, small electric air pump (100 V, 4.5 W) for tropical fish breeding coupled with drying tubes (H_2SO_4 and NaOH tablets) can conveniently be used for this purpose.