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Alumina: an Efficient and Reusable Catalyst for the Oxidative Coupling of Thiols with DMSO†

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An inexpensive combination of common laboratory reagents, dimethyl sulfoxide (DMSO) and chromatographic neutral alumina, gives an efficient, selective, and high-yielding oxidation of aromatic, aliphatic and alicyclic thiols to the corresponding disulfides in excellent yields under relatively mild conditions.

In recent attempts to develop new synthetic reactions using reagents insoluble in aprotic solvents, we have been fascinated with a remarkable catalysis of chromatographic alumina enabling selective oxidations of a number of functional groups[1] and electrophilic chlorination of aromatic ethers[2] to occur under mild conditions. This finding together with our continued interest in the chemistry of sulfur compounds[1,3] prompted us to investigate the oxidation of thiols to disulfides[4] with DMSO in combination with alumina as the solid catalyst. Conventional DMSO‡ oxidations of thiols are in general slow and, in certain cases, gave the disulfides only in moderate yields.[6] Consequently, it is desirable to provide an effective, but simple method of accelerating the reaction and/or enhancing disulfide yields in order to make the DMSO oxidation practically attractive.

Oxidation of thiols **1** was carried out simply by efficiently stirring a heterogeneous mixture of **1** and chromatographic neutral alumina in DMSO at 40–70 °C. An unpleasant odour of concomitantly formed dimethyl sulfide (DMS) at the work-up stage is observed, however, this indicates successful oxidation. DMSO is not an easy solvent to remove by distillation because of its high boiling point (189 °C), but its reasonable solubility in water allowed its easy removal by aqueous washing of the reaction mixture. Accordingly, disulfides **2** can be readily worked-up without difficulty. Benzenethiol **1a**, for example, cleanly afforded 94% of diphenyl disulfide **2a** after 30 min reaction at 40 °C if alumina was added (entry 1); otherwise, the reaction gave only 11% of **2a** and 89% of **1a** remained unreacted even after 1 h, clearly indicating that the alumina catalysed the reaction. A multigram scale reaction of **1a** resulted in successful formation of **2a** (see Experimental). Oxidations of aromatic thiols **1b**–**j** can also be easily achieved, irrespective of the electronic properties of substituents and their positions on the benzene ring. It is well known that the ease with which thiols are oxidised with DMSO is strongly dependent on their acidity (pK_a) and, since aliphatic thiols are less acidic, they are much less reactive than aryl thiols.[6b,c] In fact, comparative studies using typical aryl and aliphatic thiols (**1a**, **k**, **o**: p$K_a = 6–7$, 10.5 and 14, respectively)[6b] showed that their conversions under the conditions given in entry 1 are 100, 56, and 18%, respectively. Aliphatic and alicyclic thiols, however, can be favorably oxidised under selected conditions, affording disulfides in excellent yields.

$$\underset{\mathbf{1}}{2\,\text{R-SH}} + \text{DMSO} \xrightarrow{\text{i}} \underset{\mathbf{2}}{\text{R-S-S-R}} + \text{DMS} + \text{H}_2\text{O}$$

	R		R		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 i, Alumina, 40–70 °C

Earlier work closely related to the present oxidation, *viz.* air oxidation using basic alumina as solid catalyst[7] and oxidation with DMSO,[6] have elegantly postulated the roles of alumina and DMSO in those reactions. These methods, however, inconveniently required long periods of time and/or high temperature to effect the reactions. Thus, there have been a number of kinetic[6e,8a] and preparative[8b] investigations into promoted DMSO oxidations using acids and bases,[6e] or halogen compounds[8a,b] as catalysts. For example, Oae and coworkers have reported that I$_2$-catalysed DMSO oxidation at ambient temperature for 5 h gives aliphatic and aromatic disulfides in essentially quantitative yield.[8b] Although elevated temperature (40–70 °C) was required to effect the present reaction, reaction periods were shorter than those of Oae's procedure.[8b] Moreover, it can be emphasized that the alumina is convenient, safe to handle and, after calcination, the recovered alumina can be used

Table 1 Oxidative coupling of thiols with DMSO and alumina[a]

Entry	*t*/h	*T*/°C	Disulfide (%)[b]	Entry	*t*/h	*T*/°C	Disulfide (%)[b]
1	0.5	40	**2a** (94)	10	0.5	40	**2j** (92)
2	0.5	40	**2b** (95)	11	0.75	70	**2k** (98)
3[c]	0.5	40	**2c** (96)	12	2.5	70	**21** (97)
4	0.5	40	**2d** (94)	13	2.5	70	**2m** (95)
5	0.5	40	**2e** (94)	14	2.5	70	**2n** (96)
6	0.5	40	**2f** (98)	15	2.5	70	**2o** (quant.)
7	0.5	50	**2g** (92)	16	2.5	70	**2p** (99)
8	0.5	40	**2h** (93)	17	2.5	70	**2q** (91)
9	0.5	40	**2i** (98)	18[d]	2.5	70	**2r** (quant.)

[a]Thiol **1** (1 mmol), predried neutral alumina (1.5 g), DMSO (5 ml). [b]Isolated yield of disulfide **2** based on the starting **1**. [c]Alumina (2 g). [d]Alumina (2.5 g).

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‡Useful information on chemical and physical properties of DMSO is available; ref. 5.

Table 2 Recycling of alumina in the oxidation of benzenethiol **1a** with DMSO[a]

Run	1	2	3	4	5	6	7	8
2a[b] (%)	94	93	94	93	94	89	90	91

[a] At 40 °C, for 0.5 h; **1a** (1 mmol), predried neutral alumina (1.5 g), DMSO (5 ml). [b] Average GLC yield of diphenyl disulfide **2a** from several experiments based on the starting **1a**; biphenyl was used as an internal standard.

for several repeat oxidations without serious decrease in activity (Table 2). These advantages might make the present system a useful modification of conventional DMSO oxidations.

In conclusion, a reusable catalyst, alumina, aided DMSO oxidation of a broad range of thiols, providing a practical (inexpensive, simple, fast, high-yielding) procedure for disulfide synthesis.

Experimental

General.—^{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 FID *via* a 2 mm × 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. Thiols **2a–o** and reagent grade DMSO were used as received from commercial sources; the purities of thiols were checked by GLC prior to use. Chromatographic neutral alumina (ICN Biomedical, Alumina N, Super I) was predried in an oven at 500 °C for 1 h.

Oxidation Procedure.—A representative procedure was as follows: a 30 ml two-necked round bottom flask, equipped with a Teflon-coated stirrer bar and a reflux condenser, the top of which was fitted with a $CaCl_2$ drying tube, was charged with benzenethiol **1a** (0.110 g, 1 mmol), DMSO (5 ml), and predried alumina (1 g) and was then immersed in a thermostatic oil-bath. The resultant heterogeneous mixture was maintained at 40 °C while efficient stirring was continued for 30 min in order to ensure smooth reaction and to attain reproducible results. The reaction mixture was cooled rapidly to room temperature by external cooling and was then filtered through a sintered glass funnel. The filter cake was washed thoroughly with portions of ether (total 50 ml), and the combined solvent was washed with brine (20 ml × 3) to remove DMSO and dried ($MgSO_4$). Filtration, removal of the ether on a rotary evaporator, followed by chromatography on silica gel (hexane–AcOEt), gave pure (^{1}H NMR, GC and TLC) diphenyl disulfide **2a** in 94% yield (0.103 g, mp 60–61 °C; reported mp[9] 62–63 °C). The recovered alumina was calcined at 500 °C for 3 h with shaking at 30 min intervals and was able to be used for repeat runs.

Gram scale synthetic reaction carried out with DMSO (30 ml), **1a** (50 mmol, 5.5 g) and alumina (7 g) in a 100 ml round bottom three necked flask, fitted with the same equipments as those employed in small scale experiments, at 40 °C for 1 h gave 5.18 g of **2a** (95%).

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