

## Clean and fast oxidative transformation of thiols to disulfides under solvent-free conditions

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**Abstract**—We present here a fast, solvent-free synthesis of symmetrical disulfides using solid supported catalyst ( $\text{Al}_2\text{O}_3/\text{KF}$ ). The reaction was performed at room temperature, by gentle heating or under MW irradiation. This efficient and improved method is general for liquid thiols, affording the disulfides in good to excellent yields. The catalytic system can be re-used two times without previous treatment and with comparable activity.

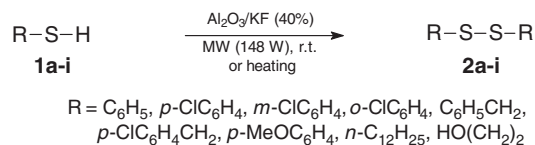
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Selective oxidative conversion of thiols is the most exploited method for the synthesis of symmetric disulfides, mainly because of the large number of commercially available thiols. Besides, thiols and disulfides play important roles in the biological process.<sup>1</sup> Most of the described methods for oxidation of thiols to disulfides make use of volatile organic solvents<sup>2</sup> and are promoted by anhydrous potassium phosphate,<sup>2a</sup> potassium permanganate,<sup>2b</sup> molecular bromine supported on silica gel,<sup>2c</sup> *N*-phenyltriazolinedione,<sup>2d</sup>  $\text{VO}(\text{acac})_2$ ,<sup>2e</sup> trichloroisocyanuric acid,<sup>2f</sup> nitric acid,<sup>2g</sup> 1,3-dibromo-5,5-dimethylhydantoin,<sup>2h</sup> basic alumina,<sup>2i</sup>  $\text{CsF}$ -Celite,<sup>2j</sup> and montmorillonite K10.<sup>2k</sup> More recently, cleaner protocols have been described under solvent-free conditions.<sup>2d,3</sup> These methods use *N*-phenyltriazolinedione,<sup>2d</sup> pyridinium chlorochromate,<sup>3a</sup> 1,3-dibromo-5,5-dimethylhydantoin,<sup>3b</sup>  $\text{SO}_2\text{Cl}_2$ ,<sup>3c</sup> trichloronitromethane,<sup>3d</sup>  $\text{KMnO}_4/\text{MnO}_2$ ,<sup>3e</sup> and  $\text{KMnO}_4$  supported on montmorillonite K10<sup>3f</sup> as catalysts. However, most of these protocols use expensive and toxic reagents and/or long reaction times. On the other hand, the use of potassium fluoride supported on alumina ( $\text{Al}_2\text{O}_3/\text{KF}$ ) as a greener catalytic system for a number of transformations has been described.<sup>4</sup> By using  $\text{Al}_2\text{O}_3/\text{KF}$ , the products can be easily isolated by filtration and the generation of large amounts of salts at the end of the synthesis, as well

as the use of stoichiometric strong bases, can be avoided.

Our major research goal has been the development of new and cleaner protocols for the preparation and synthetic applications of organochalcogenium compounds.<sup>5</sup> In continuation to these studies, we describe here the results of the oxidation of thiols **1** to disulfides **2** using  $\text{Al}_2\text{O}_3/\text{KF}$ , under solvent-free conditions at room temperature, or under microwave irradiation (MW) (Scheme 1).<sup>6,7</sup>

Initially we examined the reaction time and the amount of  $\text{Al}_2\text{O}_3/\text{KF}$  (40%) effects on the oxidation of phenylthiol (**1a**) to diphenyldisulfide (**2a**).<sup>7</sup> It was found that when **1a** (2 mmol) was stirred at room temperature in the presence of 0.1 g (64 mol %) of  $\text{Al}_2\text{O}_3/\text{KF}$  (40%), the reaction proceeded slowly to afford **2a** in 52% yield after 4 h. However, by using 0.2 g (128 mol %) of  $\text{Al}_2\text{O}_3/\text{KF}$  (40%), **2a** was obtained in 73% yield after 3 h (Table 1, entry 1, Method A). The stirring at room temperature for further prolonged time (24 h) afforded **2a** in comparable yield (71%). When 0.3 g (192 mol %) of the catalytic system was used, the yield of disulfide



Scheme 1.

**Keywords:** Microwave irradiation; Solid-supported catalysis; Solvent-free reaction; Disulfides.

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**Table 1.** Solvent-free synthesis of symmetrical disulfides **2a–i**

Entry	Thiol <b>1</b>	Disulfide <b>2</b>	Time (min)	Method <sup>a</sup> (Yield, %) <sup>b</sup>
1	C <sub>6</sub> H <sub>5</sub> SH <b>1a</b>	(C <sub>6</sub> H <sub>5</sub> S) <sub>2</sub> <b>2a</b>	180	A (73)
2	<b>1a</b>	<b>2a</b>	2	B (93)
3	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> SH <b>1b</b>	( <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> S) <sub>2</sub> <b>2b</b>	300	A (80)
4	<b>1b</b>	<b>2b</b>	3.5	B (95)
5	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub> SH <b>1c</b>	( <i>m</i> -ClC <sub>6</sub> H <sub>4</sub> S) <sub>2</sub> <b>2c</b>	240	A (78)
6	<b>1c</b>	<b>2c</b>	3	B (90)
7	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> SH <b>1d</b>	( <i>o</i> -ClC <sub>6</sub> H <sub>4</sub> S) <sub>2</sub> <b>2d</b>	90	A (84)
8	<b>1d</b>	<b>2d</b>	1.5	B (96)
9	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SH <b>1e</b>	(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> S) <sub>2</sub> <b>2e</b>	330	A (73)
10	<b>1e</b>	<b>2e</b>	4	B (86)
11	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> SH <b>1f</b>	( <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> S) <sub>2</sub> <b>2f</b>	300	A (82)
12	<b>1f</b>	<b>2f</b>	2	B (97)
13	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> SH <b>1g</b>	( <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> S) <sub>2</sub> <b>2g</b>	360	A (55)
14	<b>1g</b>	<b>2g</b>	4	B (72)
15	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> SH <b>1h</b>	[CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> S] <sub>2</sub> <b>2h</b>	600	A (70) <sup>c</sup>
16	HO(CH <sub>2</sub> ) <sub>2</sub> SH <b>1i</b>	[HO(CH <sub>2</sub> ) <sub>2</sub> S] <sub>2</sub> <b>2i</b>	420	A (48) <sup>d</sup>

<sup>a</sup> Method A: The experiments were performed at room temperature. Method B: The experiments were performed under MW irradiation at 148 W.

<sup>b</sup> Yields of pure products isolated by column chromatography; the spectral data and mp were in perfect agreement with those reported in the literature.<sup>2,3</sup>

<sup>c</sup> The reaction mixture was heated at 70 °C.

<sup>d</sup> The reaction mixture was heated at 50 °C.

**2a** was not significantly increased. Similarly, using Al<sub>2</sub>O<sub>3</sub>/KF in the presence of benzene (5 mL), **2a** was obtained in 75% yield after stirring for 4 h at room temperature. By using basic alumina without KF, the desired product **2a** was obtained only in 44% yield after stirring at room temperature for 4.5 h. Aiming to reduce the reaction time, the mixture was irradiated with microwaves (148 W/70 °C, Method B). Complete consumption of thiol **1a** was observed after irradiation for 2 min and **2a** was obtained in 93% yield (Table 1, entry 2). When the same protocol was performed at reduced MW power (125 W/55 °C), the formation of **2a** was observed in 81% yield after a longer reaction time (60 min).

In order to check the possibility of intervention of specific (nonpurely thermal) microwave effects, the reaction was also examined using a pre-heated oil-bath at the same final temperature (70–75 °C), as measured at the end of exposure to the MW-assisted synthesis. However, it was observed that 2 h was required to obtain **2a** in yield (85%) similar to that obtained after 2 min under MW.

Since the best conditions were established, the protocols were extended to the oxidation of other aromatic thiols with good results using Methods A and B (Scheme 1, Table 1, entries 3–14). However, for the aliphatic thiols **1h–i**, the respective products **2h–i** could be obtained only using conventional heating (entries 15 and 16). It was also observed that the catalytic system can be re-used for two cycles, just by washing it with ethyl acetate and drying under vacuum. The recycled catalytic system was successfully employed to both the methods, at room temperature and under microwave irradiation.

In conclusion, several disulfides could be prepared directly under solvent-free conditions in the presence of solid-supported basic catalysis, which can be re-used

twice. This method consists in low consumption of solvent, short reaction time, mild reaction conditions, excellent yields, and simplicity, with non-aqueous work-up. Besides, the reaction time was dramatically reduced and the yields were increased by irradiation with microwaves.

### Acknowledgments

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  - Preparation of alumina supported potassium fluoride:*<sup>8</sup> To a 100 mL beaker was added alumina (6.0 g of  $\text{Al}_2\text{O}_3$  90, 0.063–0.200 mm, Merck),  $\text{KF}\cdot 2\text{H}_2\text{O}$  (5.2 g) and water (10 mL). The suspension was stirred for 1 h at 65 °C, dried at 80 °C for 1 h and for additional 4 h at 300 °C in an oven, and then cooled in a desiccator. The content of KF is about 40% (m/m).
  - General procedure for the oxidation of thiols under solvent-free conditions. Method A:*  $\text{Al}_2\text{O}_3/\text{KF}$  (0.2 g, 128 mol%, obtained as described above) was added to thiol (2 mmol) and the whole mixture was stirred at room temperature and the reaction progress was followed by TLC. After stirring for 1.5–10 h (Table 1), ethyl acetate (10 mL) was added and the organic solution was separated of the aluminum oxide by filtration. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography over silica gel eluting with hexanes (**2a–h**) or a hexanes–AcOEt 8:2 mixture (**2i**) yielding the products. *Method B:* The aforementioned whole mixture was previously stirred for 1 min and then irradiated with microwaves (used a domestic Panasonic model Piccolo NN-S42BK, operating at 2.45 MHz) at 148 W<sup>9</sup> for 1.5–4.0 min (Table 1). The reaction progress was followed by TLC and the product was filtered off the aluminum oxide by washing with ethyl acetate (10 mL). The solvent was evaporated under reduced pressure and the residue was purified according to described above Method A.
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