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Simple, economical and environmentally friendly sulfone synthesis

Diego A. Alonso, Carmen Nájera* and Montserrat Varea

Departamento de Química Orgánica, Universidad de Alicante, Apartado 99, 03080 Alicante, Spain

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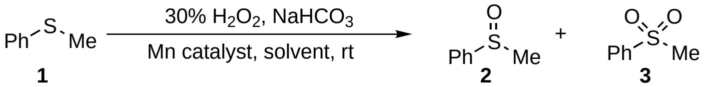
Abstract—Chemoselective sulfur oxidation of functionalized sulfides was developed using catalytic amounts of $MnSO_4 \cdot H_2O$ (1 mol%) and 30% H_2O_2 in the presence of a buffer solution of $NaHCO_3$. Aromatic and aliphatic sulfides were oxidized to sulfones in quantitative yields in 15 min. Different functional groups including double bonds, alcohols, ethers of THP and TBDMS groups were tolerated under these mild and green reaction conditions. © 2002 Elsevier Science Ltd. All rights reserved.

The use of sulfones in organic synthesis has become a classic strategy in the synthesis of many of the most demanding and sophisticated complex molecules.[1] From the methodological point of view, sulfones have been employed in the preparation and functionalization of a wide variety of products by stabilizing α-radicals,[2] α-anions[3] and acting as cationic synthons.[4] Among the different protocols to prepare sulfones, the oxidation of sulfides has become the most popular and straightforward method in organic synthesis.[5] During the last years, very useful procedures involving aqueous hydrogen peroxide (H_2O_2) as terminal oxidant and a catalytic activator have been developed to promote this transformation, due to the effective oxygen-content, low cost, safety in storage and operation and environmentally friendly character of H_2O_2.[6] The activator is essential for the success of the reaction because H_2O_2 is a rather slow oxidizing agent. A novel method for activating hydrogen peroxide by using bicarbonate ion, was described by Drago and co-workers[7] and studied in detail by Richardson et al.[8] Very recently, and based on the peroxymonocarbonate ion chemistry (HCO_4^-), Burgess et al. have described a novel and successful protocol for the epoxidation of olefins using catalytic amounts of $MnSO_4$.[9] Herein, we report our studies in the chemoselective oxidation of aromatic and aliphatic sulfides using a mixture of 30% H_2O_2 and a buffer solution of $NaHCO_3$ in the presence of catalytic amounts of $MnSO_4 \cdot H_2O$.

From initial studies carried out with methyl phenyl sulfide **1**, we found the best reaction conditions by using the sulfide (1 mmol), a 0.2 M buffer solution of $NaHCO_3$ (17 mL), 30% H_2O_2 (5 equiv.) and a catalytic amount of $MnSO_4 \cdot H_2O$ (1 mol%) in the presence of different solvents (23 mL) (Scheme 1). The results are summarized in Table 1. We initially chose DMF as solvent as it was previously reported for this oxidation system in olefin epoxidation processes.[9] The oxidation was efficiently achieved under these conditions in only 15 min, and the presence of the catalyst was crucial to obtain full conversion of the sulfide to the sulfone (Table 1, entries 1 and 2). The same catalytic activity of the promoter, was also observed when using CH_3CN as solvent (Table 1, entry 3). However, when lower amounts of oxidant (3 equiv.) were employed, a significant increase in the reaction time was observed (Table 1, entries 4 and 5). In the absence of $NaHCO_3$ (Table 1,



Scheme 1.

Keywords: green chemistry; hydrogen peroxide; oxidation; sulfides; sulfones.

* Corresponding author. Fax: +34-96-5903549; e-mail: cnajera@ua.es

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Table 1. Reaction conditions study

Entry	$MnSO_4 \cdot H_2O$ (mol%)	H_2O_2 (equiv.)	Solvent	*t* (h)	**2**:**3**[a]
1	0	5	DMF	0.25	52:48
2	1	5	DMF	0.25	0:100 (85)
3	1	5	CH_3CN	0.25	0:100 (93)
4	0	3	CH_3CN	24	43:57
5	1	3	CH_3CN	24	6:94
6	1	5[b]	CH_3CN	24	100:0
7	1	5	EtOH	24	62:38
8	1	5	NMP	24	75:25
9	1	5	Acetone	24	100[c]
10	1[d]	5	CH_3CN	24	77:17
11	1[e]	5	CH_3CN	0.25	31:69[f]
12	1	5		0.25	0:100 (70)

[a] Conversion and ratio determined by ^1H NMR analysis (300 MHz) based on starting material. In brackets isolated yield after work-up.

[b] The reaction was carried out in the absence of $NaHCO_3$.

[c] A mixture of **2**/**3** = 78:22 was obtained after 24 h in the absence of catalyst.

[d] $MnCO_3$ (1 mol%) was used as catalyst.

[e] $MnCl_2$ (1 mol%) was used as catalyst.

[f] Full conversion was observed after 2 h by ^1H NMR analysis.

entry 6), only sulfoxide **2**[10] was obtained, which clearly indicated the existence of a ternary catalytic system (H_2O_2–$NaHCO_3$–$MnSO_4$). Lower catalytic activities were observed with other solvents such as EtOH, NMP and acetone (Table 1, entries 7–9). Other Mn(II) salts such as $MnCO_3$ and $MnCl_2$ proved to be less effective promoters than $MnSO_4$ (Table 1, entries 10 and 11). We were also delighted to see that the reaction could be run under organic solvent-free conditions[6] affording the corresponding methyl phenyl sulfone in a good yield (Table 1, entry 12).

In order to establish the general applicability of the method, various functionalized sulfides were subjected to the oxidation protocol (Scheme 2, Table 2). In the case of diphenyl sulfide **4**, both in DMF and CH_3CN full oxidation of the starting material to the sulfone was obtained even in the absence of catalyst (Table 2, entries 1–3). Yields were always very high and acetonitrile showed to be the best solvent again as demonstrated in the oxidation of benzyl phenyl sulfide (Table 2, entries 4 and 5).[11] In the oxidation of *p*-anisyl methyl sulfide **6**, a substrate with a high nucleophilic character, the reaction was much faster in DMF than in CH_3CN where the absence of the catalyst had a beneficial effect in the reaction scope (Table 2, entries 6–9). However, in other examples CH_3CN was better solvent than DMF to get full oxidation to the sulfone (Table 2, entries 10–18).

The chemoselectivity of the procedure was noteworthy. Under these conditions, various functional groups including alcohols, tetrahydropyranyl (THP) and *tert*-butyldimethylsilyl (TBDMS) ethers were tolerated (Table 2, entries 10–15). Aryl alkyl sulfide **10**, bearing electron withdrawing groups such us CF_3 in the aromatic ring did not affect the synthetic efficiency of the method and afforded the corresponding π-deficient sulfone with an excellent yield (entry 16).[12] Ester **11** was converted to the sulfone as major reaction product only in CH_3CN (Table 2, entries 17–18). Very deactivated substrates such as ester **12** was converted to the sulfoxide (Table 1, entry 19). With respect to the selectivity towards double bonds, both vinylic and allylic sulfides were cleanly transformed to the corresponding sulfones with no traces of epoxidation byproducts (Table 2, entries 20–23). Surprisingly, even normally reactive trisubstituted olefinic moieties in sulfides **17** and **18** were inert as well under these oxidation conditions (Table 2, entries 24 and 25).

As conclusion, $MnSO_4$ is an excellent catalyst promoting the highly chemoselective and fast oxidation of functionalized sulfides with 30% H_2O_2 and $NaHCO_3$ under very mild conditions. Different functional groups including double bonds, alcohols, ethers of THP and TBDMS groups and esters were tolerated under this environmentally friendly sulfone synthesis protocol.[13]

Typical experimental procedure: To a stirred solution of sulfide (1 mmol) and $MnSO_4$ monohydrate (2 mg, 1 mol%) in the corresponding solvent (23 mL), was added at room temperature an aqueous mixture comprised by 30% H_2O_2 (5 mmol, 515 μL) and a 0.2 M buffer solution of $NaHCO_3$ (17 mL) previously prepared at 0°C. After 15 min the reaction was quenched with a saturated NaCl solution, extracted with ethyl acetate and dried with anhydrous $MgSO_4$. Filtration and evaporation afforded the corresponding pure crude sulfones.

$$\mathrm{RSR'} \xrightarrow[\mathrm{MnSO_4.\ H_2O,\ solvent,\ rt}]{\mathrm{30\%\ H_2O_2,\ NaHCO_3}} \mathrm{RSO_2R'}$$

Scheme 2.

Table 2. Oxidation of sulfides to sulfones catalyzed by $MnSO_4 \cdot H_2O$

Entry	Sulfide	H_2O_2 (equiv.)	Solvent	*t* (h)	Yield (%)[a]
1	PhSPh (**4**)	3	CH_3CN	0.25	100 (94)
2	PhSPh (**4**)	3	DMF	0.25	100 (94)
3	PhSPh (**4**)	2[b]	CH_3CN	0.25	100
4	$PhSCH_2Ph$ (**5**)	5	DMF	24	55
5	$PhSCH_2Ph$ (**5**)	5	CH_3CN	0.25	100 (99)
6	4-$MeOC_6H_4SMe$ (**6**)	5	DMF	0.25	100 (70)
7	4-$MeOC_6H_4SMe$ (**6**)	5[b]	DMF	0.25	100
8	4-$MeOC_6H_4SMe$ (**6**)	3.5	CH_3CN	24	63
9	4-$MeOC_6H_4SMe$ (**6**)	3.5[b]	CH_3CN	24	98
10	$PhSCH_2CH_2OH$ (**7**)	5	DMF	0.25	72
11	$PhSCH_2CH_2OH$ (**7**)	5	CH_3CN	0.25	100 (88)
12	$PhSCH_2CH_2OTHP$ (**8**)	5	DMF	0.25	80
13	$PhSCH_2CH_2OTHP$ (**8**)	5	CH_3CN	0.25	100 (85)
14	$PhSCH_2CH_2OTBDMS$ (**9**)	5	DMF	0.25	72[c]
15	$PhSCH_2CH_2OTBDMS$ (**9**)	5	CH_3CN	0.25	100 (86)
16	3,5-$(CF_3)_2C_6H_3SCH_2CH_2OH$ (**10**)	5	CH_3CN	0.25	100
17	$PhSCH_2CO_2CH_2Ph$ (**11**)	5	DMF	0.25	100[d]
18	$PhSCH_2CO_2CH_2Ph$ (**11**)	5	CH_3CN	0.25	80[e]
19	3-$CF_3C_6H_4SCO_2CH_2Ph$ (**12**)	5	CH_3CN	24	100[d]
20	$PhSCH{=}CH_2$ (**13**)	5	CH_3CN	0.25	100 (93)
21	$PhSCH_2CH{=}CH_2$ (**14**)	5	CH_3CN	0.25	100 (80)
22	$(CH_2{=}CHCH_2)_2S$ (**15**)	5	CH_3CN	0.25	95
23	$PhCH_2SCH_2CH{=}CH_2$ (**16**)	5	CH_3CN	0.25	100 (94)
24	$PhSCH_2CH{=}C(Me)_2$ (**17**)	5	DMF	0.25	100 (90)
25	$PhSCH_2CH{=}C(Me)CH{=}C(Me)_2$ (**18**)	5	CH_3CN	0.25	100 (87)

[a] Conversion determined by ^{1}H NMR analysis based on initial methyl phenyl sulfide. In brackets isolated yield after work-up. All products were pure by ^{1}H NMR analysis (300 MHz).

[b] The reaction was run in the absence of catalyst.

[c] Yield of sulfoxide. Only traces of sulfone (6%) were detected by ^{1}H NMR analysis.

[d] Yield of sulfoxide. No sulfone was detected in the crude reaction mixture by ^{1}H NMR analysis.

[e] 20% of the corresponding sulfoxide was obtained as by-product.

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