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Communications

Magtrieve™: A New Reagent for the Oxidation of Thiols to Disulfides under a Neutral and Anhydrous Condition

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The oxidative conversion of thiols to disulfides is a useful transformation in organic synthesis as well as biochemistry.[1] This oxidation has been carried out using a variety of reagents[2] including halogens,[3] periodate,[4] calcium hypochlorite,[5] peroxodisulfate,[6] *N*-hydroxy-*o*-benzenedisulfonimide,[7] sodium chlorite,[8] thallium(III) acetate,[9] enzyme,[10] CCl_4,[11] transition metals such as Fe(III),[12] Cu(II),[12b] active MnO_2,[13] potassium ferrate(VI),[14] rhenium catalyst,[15] and tellurite,[16] trichloronitromethane,[17] and Caros acid (H_2SO_5)[18] among others. However, some reagents mentioned above suffer from disadvantages such as incompatibility with certain functional groups, toxic nature of reagents, strong acidic conditions, or nonavailability of reagents.

Magtrieve™ is Dupont's trademark for its magnetically retrievable oxidant based on chromium dioxide (CrO_2).[19] This reagent was first used for the mild oxidation of alcohols.[20] Since only the surface of Magtrieve™ is reduced during the oxidation process, this oxidant is still ferromagnetic and can be conveniently removed by magnet, after use. Because Magtrieve™ can be recycled by simple heating in air, this reagent can serve as a mild and environment-friendly oxidant.

We recently reported that Magtrieve™ can be used as an oxidant for the aromatization of 1,4-dihydropyridines to pyridines[21] and the generation of diphenyldiazomethane from benzophenone hydrazone.[22] Our experience with Magtrieve™ prompted us to investigate the possibility of using this reagent as a new oxidant for thiols. In this communication, we report that Magtrieve™ can serve as a new oxidant for the heterogeneous oxidation of thiols to disulfides under a neutral and anhydrous condition, as shown in Table 1.

$$2\ \text{R-SH} \xrightarrow[CHCl_3,\ 20\ ^\circ C]{\text{Magtrieve}^{TM}\ (CrO_2)} \text{R-S-S-R}$$

The oxidation was performed by stirring a mixture of thiol and Magtrieve™ in chloroform at 20 °C under nitrogen, except for dodecanethiol and benzyl mercaptan. For the aromatic thiols, the oxidation was complete within a few hours. In contrast, the oxidation of aliphatic long-chain thiol such

Table 1. Oxidation[a] of Thiols to Disulfides with Magtrieve™

$$2\ \text{R-SH} \xrightarrow[CHCl_3,\ 20\ ^\circ C]{\text{Magtrieve}^{TM}\ (CrO_2)} \text{R-S-S-R}$$

Entries	Thiols (R-SH)	Time (h)	Yield (%)[b]	mp (°C)	Lit. mp (°C)
1	2-mercaptobenzothiazole	1	91	180-182	183-184[c]
2	2,6-$(CH_3)_2C_6H_3SH$	6	93	104-105	105-106[d]
3	2,5-$(CH_3)_2C_6H_3SH$	3	92	48-49	46.5-48[e]
4	C_6H_5SH	2	92	58-59	59-60[f]
5	4-BrC_6H_4SH	1	96	91-92	92-94[f]
6	2-mercaptopyridine	1	98	55-57	56-58[g]
7	$HSCH_2CH_2OH$	2	93	oil	26-28[h]
8a	*n*-$C_{11}H_{23}CH_2SH$	120	73[i]	31-32	30-31[j]
8b		48[k]	99		
9a	$PhCH_2SH$	24	50[i]	69-70	71-72[e]
9b		8[l]	91		
10	1,2-$(HSCH_2)_2C_6H_4$	2	87	76-77	77-78[f]
11	8-mercaptomenthone	24	trace[m]		
12	Ph_3CSH	24	trace[m]		

[a]All reactions were conducted at 20 °C, using 1 mmol of thiol and 1.51 g of Magtrieve™ in chloroform (20 mL) under nitrogen, unless noted otherwise. [b]Yield refers to the pure isolated product. [c]*Ref.* 12a. [d]*Beilstein* E IV **6**, 3125. [e]*Beilstein* E IV **6**, 3171. [f]*Dictionary of Organic Compounds*; Chapman and Hall: London, 6th Ed., 1996. [g]*Ref.* 6. [h]*Beilstein* E IV **1**, 2442. [i]The rest is the starting thiol. [j]*Beilstein* E IV **1**, 1853. [k]in refluxing toluene. [l]in refluxing chloroform. [m]Inertness of tertiary thiols to oxidation may be ascribed to the poor absorption on Magtrieve™ surface due to the unfavorable steric strain.[23]

as dodecanethiol required higher reaction temperature and longer time (entry 8). The higher reactivity of aromatic thiols toward Magtrieve™ may be ascribed to the more acidic nature of aromatic thiols.[23] Tertiary thiols (entries 11, 12) were inert to oxidation. Although Magtrieve™ is known to oxidize unactivated alcohols to carbonyl compounds in refluxing toluene,[20] the chemoselective oxidation of thiol containing a primary hydroxyl group was achieved at 20 °C (entry 7).

Oxidation of 2-mercaptopyridine (entry 6) is representative. To a solution of 2-mercaptopyridine (110 mg, 1.0 mmol) in chloroform (20 mL) was added Magtrieve™ (1.51 g) all at once at 20 °C. The mixture was stirred under nitrogen atmosphere for 1 h, until TLC showed the absence of the starting material (R_f of thiol = 0.15, R_f of disulfide = 0.55 in EtOAc : hexanes = 1 : 1). A magnet was placed on one side of the flask and the solution was decanted. The oxidant was rinsed with EtOAc (3 × 20 mL) and this solution was combined with the decantate. The whole solution was dried with Na_2SO_4 and concentrated to give 108 mg (98%) of the pure product (^{1}H NMR and TLC) as a pale yellow solid, mp 55-57 °C (Lit.[6] mp 56-58 °C).

A previous study of the oxidation of thiols by transition metal oxides showed that disulfides are formed by the coupling of thiyl radicals (RS•).[23] Similar mechanism for thiol oxidation on Magtrieve™ can be suggested as follows:[20,24]

$$RSH \cdot Cr^{IV}O_2 \longrightarrow RS^{\bullet} + HOCr^{III}O$$

$$2\,RS^{\bullet} \longrightarrow RS\text{-}SR$$

In conclusion, the easy work-up, the recyclability of the used reagent, the neutral and anhydrous reaction condition, the chemoselectivity, the commercial availability, and high yields make the use of Magtrieve™ attractive for the lab-scale oxidation of thiols to disulfides.

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