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$DMSO/N_2H_4{\cdot}H_2O/I_2/H_2O/CH_3CN$: A New System for Selective Oxidation of Alcohols in Hydrated Media

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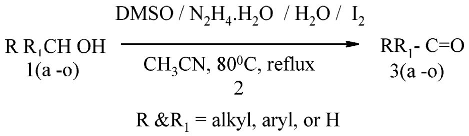
Abstract: A new alternative system for the oxidation of secondary alcohols to ketones with $DMSO/N_2H_4{\cdot}H_2O/I_2/H_2O/CH_3CN$ in hydrated media has been developed. The system also selectively oxidizes the secondary alcoholic groups to the corresponding ketones in the presence of primary alcoholic groups present within the same molecule in moderate to very good yields at reflux temperature.

Oxidation of alcohols to carbonyl compounds is one of the most important transformations in organic syntheses.[1] The selective oxidation of alcohols is still a challenging task to organic chemists particularly when both secondary and primary groups within the same molecule are present. Many selective reagents for the oxidation of secondary alcohols to ketones have been reported, including halogen-based oxidants,[2a] e.g., *N*-chloroacetamide, *N*-chloro/bromosuccinaamide, Cl_2/pyridine, $Br_2/HMPT/NaHCO_3$, $(Bu_3Sn)_2O/Br_2$, $NaOCl/CH_3COOH$, $NaBrO_3/NaHSO_3$, and $CeSO_4/NaBrO_3$. Other important selective oxidizing agents viz. Mo/Zr/W/Ru compounds, peroxides, dioxiranes, and enzymatic methods are also efficient reagents for the selective oxidation of secondary alcohols.[2b] Oxidation by DMSO and related methods[3] is widely used in organic syntheses, although few examples of primary−secondary selectivity have been reported.[4] Aliphatic primary and secondary alcohols were oxidized in the presence of allylic or benzylic alcohols using the $DMSO/(CF_3CO)_2/Et_3N$[5] system. The competitive oxidation of alcohols with $Me_2SO/(COCl)_2/Et_3N$ at −60 °C has demonstrated that alcohols bearing electron-deficient groups are generally less reactive and secondary alcohols were oxidized at faster rates than primary.[6] However, the methods of oxidation by DMSO have disadvantages because of their involvement under anhydrous[3] and low-temperature conditions,[6] use of moisture-sensitive[3c−f,5,6] and toxic reagents[3e] and bases,[5,6] and in some cases, occurrence of Pummerer rearrangements[3a] (up to 50%). Therefore, development of a better selective reagent is desirable.

SCHEME 1



In our previous communications, we reported deoxygenation of nitrones and azoxy compounds to the corresponding imines and azo compounds catalyzed by HI[7] (generated from $AlCl_3{\cdot}6H_2O/NaI/H_2O/CH_3CN$). The same system was used in the dehydration of oximes and amides to nitriles and the Beckmann rearrangements and the Bischler−Napieralski reactions[8] in hydrated media. We now report here the selective oxidation of secondary alcohols to ketones using DMSO catalyzed by HI (generated insitu from $N_2H_4{\cdot}H_2O$ and I_2)[9] in hydrated media at reflux temperature (Scheme 1).

A 1 M quantity of $N_2H_4{\cdot}H_2O$ and a 2 M quantity of I_2 were stirred in aqueous acetonitrile (5:1) for a period of 15 min at room temperature under a nitrogen atmosphere followed by addition of secondary alcohols, and the reaction mixture was stirred for 5 min. To this mixture, was added a 5 M quantity of DMSO and the mixture refluxed at 80 °C, which produced the corresponding ketones in 46−95% yields (Table 1).

The aliphatic secondary alcohols (Table 1, entries **1a**−**1c**) reacted faster than the phenyl-substituted aromatic secondary alcohols (Table 1, entries **1d**−**1f**). The rate as well as the yield of the reactions is dependent on the substituents present in the substrates. Electron-donating groups such as $(CH_3)_2CHCH_2$ or OH (Table 1, entries **1e**−**1g**) on the aromatic ring accelerated the rate of the reaction. But aromatic primary alcohols (Table 2, entries **1j** and **1k**) formed the corresponding aldehydes (only 3.7 and 7%, respectively) after heating for 30 h at 80 °C. The reagent selectively oxidized only the secondary alcohol groups to the corresponding ketones when both the primary and the secondary groups were present within the same molecules (Table 2, entries **1l**−**1o**). The reagent did not reduce alcohols to the corresponding saturated compounds[10] or form any Pummerer rearrangement[3a] type of products. Moreover, oxidations of the secondary alcohols **1a**−**i** with DMSO catalyzed by HI (57 wt %) under the same reaction conditions produced 30−45% yields of ketones. Acetonitrile was the best solvent for

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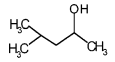
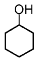
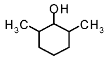
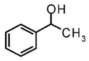
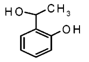
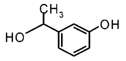
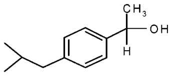
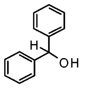
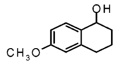
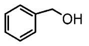
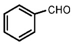
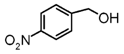
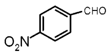
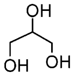
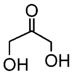
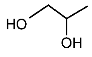
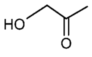
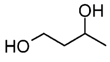
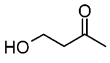
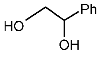
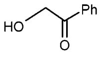
TABLE 1. Oxidation of Secondary Alcohols

Entry	Secondary Alcohols 1(a-i)	Time (hr)^b	Yields%^{a} Ketones 3(a-i)^c
1a		2.5	95
1b		3.5	69
1c		6.5	74
1d		7.5	65
1e		7.5	63
1f		7.5	64.7
1g		6	85
1h		18	46
1i		6	65

^{a} Isolated yield. ^{b} Reflux temperature (80 °C). ^{c} The structures of the compounds were determined by using ^{1} H NMR, FTIR, and ^{13}C NMR analyses and comparison with authentic samples.[14]

TABLE 2. Selective Oxidation of Secondary Alcohols

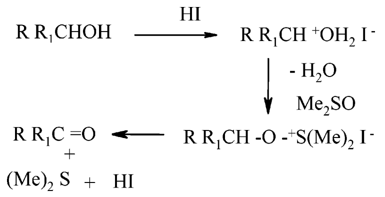
Entry	Substrates 1(j-o)	Time (hr)^b	Carbonyl Compounds 3(j-o)	Yields%^{a,c}
1j		30		3.7
1k		30		7
1l		5.5		44
1m		4		46
1n		4.5		50
1o		6		45

^{a} Isolated yield. ^{b} Reflux temperature (80 °C). ^{c} The structures of the compounds were determined by using ^{1} H NMR, FTIR, and ^{13}C NMR analyses and comparison with authentic samples.[14]

both yields and rates of the reaction, in contrast to $CHCl_3$ and CH_2Cl_2.

While the exact mechanism of selective oxidation is not clear at present and we propose that hydrazine reduces I_2 to HI,[9] HI reacts with the hydroxyl group of secondary alcohols to generate carbocations to produce ketones in the presence of DMSO. The secondary carbocation is more stable than primary carbocation in the transition state,[11] which may facilitate the faster oxidation of secondary alcohol to ketones under the reaction conditions. It has been found that the system oxidized benzyl alcohol to benzaldehyde (3.7%) [2,4-dinitrophenyl hydrazone derivative, mp 236 °C (lit·^{12} mp 237 °C)] when refluxed for 30 h. DMSO is the oxidizing agent, which was confirmed by carrying out the oxidation under a nitrogen atmosphere, and it was found that air[11] did not affect the acid-catalyzed oxidation. Also, the dimethyl sulfide formed in the reaction mixture reacted with mercuric chloride to give the mercuric chloride derivativ,e mp.147−49 °C (lit.$^{1313-14}$ mp150−51 °C). On the basis of these results, a plausible mechanism is proposed (Scheme 2).

SCHEME 2



In conclusion, a new, selective, and efficient alternate method has been developed for the oxidation of secondary alcohols to ketones in moderate to very good yields in hydrated media. It does not involve moisture-sensitive and toxic reagents and bases in the reaction mixture. In addition, it can selectively oxidize only the secondary alcoholic groups in the presence of primary alcohols present within the same molecule and it does not reduce the alcohols to the corresponding saturated compounds.

Experimental Section:

General Procedure for the Oxidation of Secondary Alcohols. Hydrazine monohydrate (51 mg, 1 mmol) and iodine (506 mg, 2 mmol) were stirred in aqueous acetonitrile (10 mL) [CH_3CN/H_2O 5:1] for 15 min under a nitrogen atmosphere, and secondary alcohol (1 mmol) was added to it. The reaction mixture was stirred for another 5 min at room temperature. DMSO (390 mg, 5 mmol) was added to the reaction mixture and refluxed at 80 °C under nitrogen. The solvent was distilled off to half of its volume under reduced pressure, poured into water (100 mL), and extracted with diethyl ether (2 × 25 mL). The organic layer was washed with 5% sodium thiosulfate solution (20 mL) and then with water (2 × 50 mL) and dried over Na_2SO_4. The residue was purified by preparative TLC and gave the analytically pure ketones. All of the products were commercially available and identified by comparison of the isolated products with authentic samples.

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Supporting Information Available: Characterization data including ^{1}H and ^{13}C NMR and FTIR of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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