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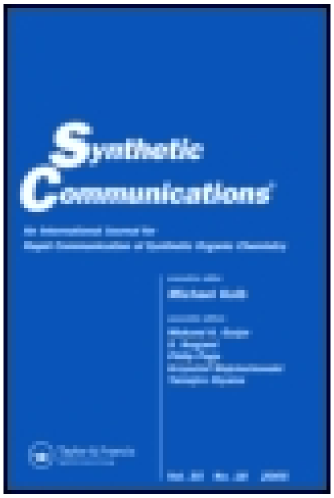

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Development of a Metal-Free Oxidation of Alcohols with Dimethyl Sulfoxide (DMSO) Activated by Tosyl Chloride

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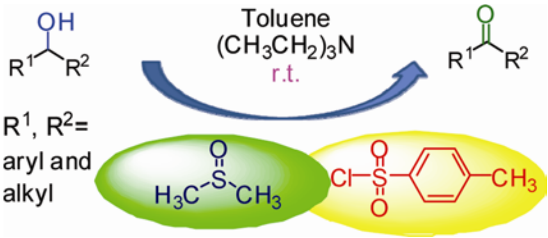
Abstract

This paper proposes an efficient metal-free method for the mild oxidation of alcohols using dimethyl sulfoxide/tosyl chloride at ambient temperature. The procedure described here is an easy and practical method for the oxidation of primary, secondary, allylic, and benzylic alcohols into their corresponding aldehydes and ketones. The notable advantages of this protocol are mild reaction conditions, high yields, high selectivity, and the simple work-up with minimal waste containing no metallic components. The mechanism of the transformation is also investigated.



KEYWORDS: Metal-free; oxidation; Alcohol; Dimethyl sulfoxide; Tosyl chloride; Aldehyde; Ketone.

INTRODUCTION

The green chemistry revolution has recently resulted in much attention being directed toward establishing green chemical processes for the synthesis of aldehydes and ketones which are versatile intermediates of valuable compounds in organic chemistry from both academic and industrial perspectives.

Oxidation is a very appropriate transformation for preparing carbonyl derivatives as makes it unnecessary to introduce any new group to the substrate.[1]

There are numerous oxidation methods, such as using transition metal derivatives involving homogeneous [2]and heterogeneous catalysts,[3] organic compounds itself arguably an even more important backbone such as Dess–Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodo-3(1H)-one),[4] IBX (1-hydroxy-1,2-benziodoxol-3(1H)-one),[5] Bis-IBX,[6] tetrapropylammonium perruthenate (TPAP),[7] 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO),[8] and N-tert-Butylbenzenesulfenamide.[9]

A useful environmentally benign and metal-free method for oxidation of hydroxyl groups in aliphatic and aromatic compounds is using a combination of dimethyl sulfoxide (DMSO) and an electrophilic species at low temperature (-60 to -10 °C).[10] Following the discovery of transformation of an alcohol dissolved in dry DMSO with *N,N′*-dicyclohexylcarbodiimide (DCC) to a corresponding aldehyde or ketone,[11] the intermediacy of "activated" sulfoxide derivatives has been substantiated by scientists.[12] This type of oxidation of alcohols can be carried out under very mild conditions, avoids the use of toxic metals, and no further oxidation to give carboxylic acids.

On this basis, various agents have been reported to be effective in the oxidation of alcohols. A few examples are acetic anhydride,[13]phosphorus pentoxide,[14] sulfur trioxide in the form of its pyridine complex,[15] trifluoroacetic anhydride,[16] oxalyl chloride (Swern oxidation),[17] thionyl chloride,[18] HBr[19], *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate (TBTU) [20] in combination with DMSO, and heterogenous Swern oxidation by DMSO/SiO_2-Cl system.[21]

During the investigations, Albright briefly mentioned cyanuric chloride, *p*-toluenesulfonyl chloride, *p*-toluenesulfonic anhydride, and methanesulfonic anhydride with dimethyl sulfoxide as mild oxidative reagents for oxidizing alcohols to carbonyl derivatives in hexamethylphosphoramide (HMPA) at -20°C. [22]

However, some of presented methods restricted by poor yields, result in undesired products (i.e., methylthiomethyl ethers and Pummerer rearrangement), cryogenic temperatures (-60 to -10°C) for successful activation, and the use of expensive oxidizing agents. It should be noted that some activators react violently and exothermically with DMSO at room temperature and the excess of the activator necessary for efficient conversion. Also, there are solubility problems at low temperature.

In continuation of this study, it was considered that the more efficient methods are needed for the oxidation of alcohols under ambient conditions with high yield.

The *p*-toluenesulfonyl chloride (Tosyl chloride, TsCl) is a commercially available and inexpensive reagent that exhibits a variety of interesting and useful properties. The *p*-toluenesulfonate (tosylate) group has been successfully used as a good leaving group in nucleophilic substitution (SN) reactions.[23] The formation of an O–S bond by replacing chlorine in sulfonyl chloride makes this group a practical intermediate.

The present research is a report on a general method for effective oxidation of hydroxyl group under mild reaction conditions using DMSO/TsCl as a highly selective and efficient oxidant.

In this procedure, transformation starts at 0° C and then mildly rises to the ambient temperature. To our knowledge, activation of DMSO at ambient temperature has rarely been tried due to the formation of side products, and indeed a large number of previous studies focused on low temperature conditions.

Our methodology is considerably simple and selective. It considers room temperature conditions and produces good yields with minimal waste streams. The reaction was carried out with oxidation of a wide range of alcohols.

DISCUSSION

As discussed elsewhere, temperature control is necessary for activating agents that react exothermically with DMSO at room temperature. A particular drawback from an industrial point of view is that the activated DMSO intermediate is unstable at or above about -20° C. It was reasoned that a revision in reaction conditions may turn the reaction into a mild and efficient procedure.

To study the combination of tosyl chloride and DMSO in alcohol oxidation, the solvent, temperature, and molar ratio were screened as the common factors affecting the reaction.

For this purpose, a model reaction of benzyl alcohol in DMSO and tosyl chloride was initially performed in the presence of triethylamine.

As for the solvent effect, the reaction was carried out using 1.5 equivalents TsCl and 3 equivalents DMSO in tetrahydrofuran (THF), toluene, and dichloromethane (DCM) at ambient temperature and -25°C. In the presence of DCM and THF, at low temperature any product was produced, but the result of oxidation in toluene was trace. Although the solvents, toluene and DCM are satisfactory at ambient temperature, distilled dry toluene is better because it leads to cleaner products. Since dry toluene produced the best conversion and yield at ambient temperature, it was chosen as the preferred solvent for the reaction.

The corresponding benzaldehyd was obtained with the dropwise addition of benzyl alcohol to the stirred mixture of DMSO/TsCl in toluene at 0°C, and the mixed temperature became ambient. After 90 min, triethylamine was added, and the mixture was stirred for 10 min.

Under the same conditions, four variations of the molar ratio of TsCl to DMSO to triethylamine (1: 1: 3; 2: 2: 3; 2: 3: 3; 1.5: 3: 3) were examined. The ratio 1.5: 3: 3 was the best. The excess of base is necessary for the consumption of the acids produced in reaction media and for the efficient conversion of hydroxyl group to carbonyl function.

We further used TsCl (1.5 equivalent) in DMSO (3.0 equivalent) in toluene at ambient temperature under air atmosphere as the optimized reaction condition to probe the scope of oxidation of various types of alcohols (Scheme 1).

Table 1 shows that oxidation of various types of alcohol is completed under desired reaction conditions with good to excellent yields. All the products are pure. An important observation was the generality of the method for the oxidation of a wide range of hydroxyl compounds to carbonyl derivatives.

In addition, this method was successfully applied to the transformation of benzylic derivatives. The slight decrease in the conversion of 2-substituted benzylic alcohols can be ascribed to steric hindrance (Table 1, Entries 1-7).

An attractive feature of this reagent is that it can selectively oxidate allylic alcohol to afford a corresponding α,β-unsaturated carbonyl compound within a few minutes and with excellent yield (Table 1, Entry 8).

In particular, the method showed excellent activity for the oxidation of primary aliphatic alcohols under the same reaction conditions furnished the corresponding product with excellent yields in all cases. As can be seen in Table 1 (Entries 9–13), the yield rises with an increase in the number of carbons (Table 1, Entries 9–13).

On a comparative basis, the oxidation of secondary aliphatic alcohols produced good yields of the corresponding ketones (Table 1, Entries 14-17). Increasing the bulk of the substituents attached to the hydroxyl group reduces yields of carbonyls as compared with benzylic derivatives.

The mechanistic illustration of these reactions prompted us to envision the in situ formation of tosyloxydimethylsulfonium chloride **3** or chlorodimethylsulfonium tosylate **4** from the interaction of DMSO and tosyl chloride. The first intermediate quickly reacts with alcohol **1** to give the key alkoxydimethylsulfonium salt **5**. The additions of triethylamine will deprotonate the alkoxydimethylsulfonium ion to give intermediate **6** [12] which is alternatively converted to dimethyl sulfide (DMS) and the desired ketone or aldehyde (Scheme 2).

The research by Kornblum and colleagues demonstrated that the sulfonates of primary alcohols react with DMSO to yield carbonyl compounds.[24]

So it can be proposed that oxidation proceeds via alkyl tosylate. In this manner, the alcoholic compound was first converted to alkyl tosylate **7** by TsCl. Under these conditions, the alkyl tosylate **7** is consumed by DMSO as a nucleophilic ionizing solvent to form the alkoxydimethylsulfonium tosylate **8**. Then, the alkoxydimethylsulfonium tosylate **8** collapses to carbonyl and dimethylsulfide (DMS) via the formation of the intermediate **6** after the addition of triethylamine (Scheme 3).

To better clarify the role of tosyl chloride in this protocol, another experiment was performed.

First, benzyl tosylate was prepared with *p*-toluenesulfonyl chloride in pyridine using the Tipson's method. [25] The oxidation of benzyl tosylate was then conducted under the same reaction conditions as before. Interestingly, the corresponding benzaldehyde was not observed. Therefore, the formation of aldehyde can be conveniently accommodated by the first pathway.

CONCLUSIONS

This research found that a very efficient agent in the oxidation of alcohols is dimethyl sulfoxide in the presence of tosyl chloride. The generality of the procedure, mild reaction conditions, selectivity, and good to excellent yields could make this method a useful addition to previously reported methods. In view of exploiting the transformation, metal-free oxidation at ambient temperature was employed.

EXPERIMENTAL

Instrumentation

All chemicals were purchased from commercial suppliers and were distilled or recrystallized before use. NMR spectra (^{1}H NMR and ^{13}C NMR) were obtained using a 250 Bruker Avance instrument with the chemical shifts being reported as δ parts per million and the couplings being expressed in hertz. The IR spectra were recorded using an FT-IR Brucker-Vector in KBr/Nujol mull. The analysis of the organic phases was performed via Gas-liquid chromatography (GLC) using a 6890 network GC system of Agilent on an HP-5 (30.0 m × 0.320 mm × 0.25 µm) column. Merck silica gel 60 F254 plates were used to monitor the reaction progress in thin-layer chromatography (TLC).

General Procedure

The Dimethyl sulfoxide (DMSO) (0.23 gr; 3 mmol) was added dropwise to the stirred mixture of tosyl chloride (0.29 gr; 1.5 mmol) and dry toluene (2.0 ml) at 0°C for 10 min and stirring was continued for another 15 min. A solution of alcohol (1.0 mmol) in dry toluene (1 ml) was then injected into the solution, and the temperature of the resulting mixture was brought to the ambient temperature. The mixture was stirred at ambient temperature for 90 min before triethylamine (0.30 gr; 3.0 mmol) was added dropwise in ca. 10 min. Once the reaction was complete, the complex was treated with water (5 mL), and the mixture was extracted using toluene (2×5 mL). The organic layer was dried over sodium sulfate (Na_2SO_4). Samples of the reaction mixture were monitored by GC. The products of the reaction were determined via comparison with those of authentic samples of carbonyl compounds.[26]

Full experimental data are available in the online supplemental section.

SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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Table 1. Oxidation of alcohols using DMSO /TsCl [a]

Entry	R^1	R^2	Time (min)[b]	Yield (%)[c]
1	C_6H_5	H	10	>99
2	2-BrC_6H_4	H	10	>99
3	2,4-$Cl_2C_6H_3$	H	10	94
4	4- $CH_3OC_6H_4$	H	10	>99
5	4-$CH_3C_6H_4$	H	10	>99
6	4-$(CH_3)_2CHC_6H_4$	H	10	>99
7	4-$NO_2C_6H_4$	H	20	95
8	$C_6H_5CH{=}CHCH_2$	H	20	>99
9	$C_6H_5CH_2$ CH_2	H	25	90
10	$C_6H_5CH_2$ CH_2CH_2	H	20	95
11	$CH_3(CH_2)_5$	H	25	87
12	$CH_3(CH_2)_6$	H	25	95
13	$CH_3(CH_2)_7$	H	25	>99
14	$CH_3(CH_2)_5$	CH_3	25	90
15	$C_6H_5CH_2$	CH_3	25	80

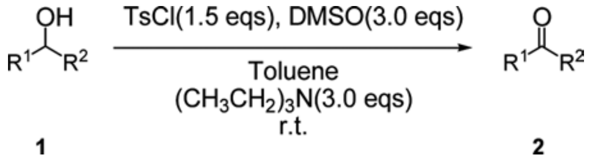
		CH_2		
16	Cyclohexanol		25	85
17	2-Adamantanol		25	87

[a] Conditions: Substrate: DMSO: TsCl 1:3:1.5 (molar ratio); $(CH_3CH_2)_3N$ (3mmol); toluene as solvent; r.t.

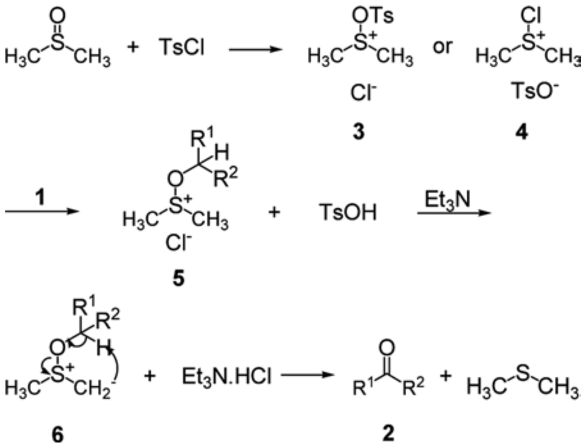
[b] After addition of triethylamine.

[c] GC yield.

Scheme 1. Oxidation of alcohol derivatives



Scheme 2. The proposed mechanism for the oxidation of alcohol derivatives in the presence of DMSO/TsCl



Scheme 3. The proposed mechanism for the oxidation of alcohol derivatives in the presence of DMSO/TsCl via alkyl tosylate formation