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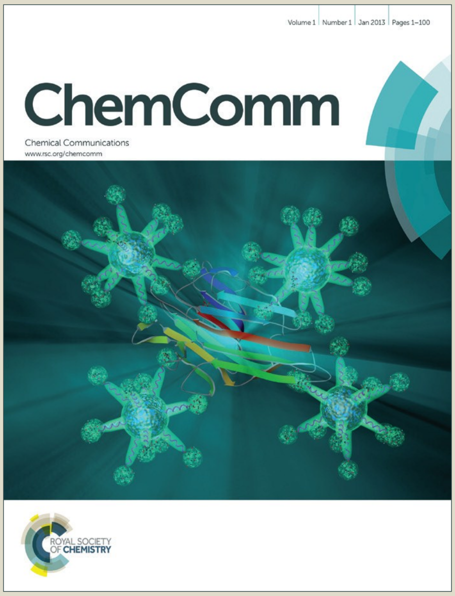

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Chemical Communications

COMMUNICATION

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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An Unusual Chemoselective Oxidation Strategy by an Unprecedented Exploration of Electrophilic Center of DMSO: A New Facet to Classical DMSO Oxidation

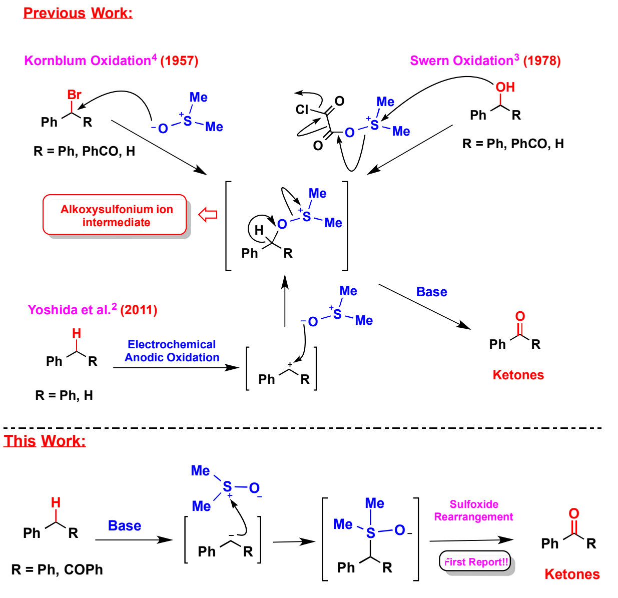
Rajesh Chebolu,[a] Ashish Bahuguna,[a] Reena Sharma,[a] Vivek Kumar Mishra[a] and P. C. Ravikumar*[a]

A conceptually new dimethyl sulfoxide (DMSO) based oxidation process without the use of any activator has been demonstrated for the oxidation of active methylenes and benzhydrols. The developed protocol utilizes electrophilic center of simple DMSO for oxidation, which was unexplored before. Mechanistic investigation has confirmed that the source of oxygen is from DMSO.

Selective oxidation of C-H bond is an area of profound interest in recent years. One of the critical challenges associated with the selective oxidation process is to keep other C-H bonds intact.[1] In 2011, Yoshida's group successfully trapped electrochemically generated carbocations from activated hydrocarbons using dimethyl sulfoxide (DMSO) at low temperature to produce alkoxysulfonium intermediates, which further underwent oxidation[2a] in the presence of a base. Two years later same group reported hydrolysis of alkoxysulfonium intermediate to generate corresponding alcohols.[2b]

The general key intermediate in oxidation reactions using DMSO is an alkoxysulfonium intermediate (Scheme 1), which can be formed through conventional activation of sulfoxide i.e. Swern oxidation,[3] Kornblum oxidation,[4] or by activation of substrate i.e. electrochemical oxidation[2] of the substrate. Prompted by Yoshida's results, we envisioned exploring DMSO as an oxidant for selective oxidation of activated C-H bonds under reverse polarized conditions, as effective tweaking of reactive intermediates i.e. carbo-cations/anions could lead to new synthetic strategies.

In contrast to alkoxysulfonium intermediate, the electrophilic nature of sulphur in DMSO towards carbanions for the oxidation process remains unexplored. We planned to explore the reactivity of highly stabilized carbanions towards soft electrophilic center of sulfoxide. We hypothesized that the carbanion formed would react with sulfoxide to form an intermediate which would then undergo sigmatropic rearrangement to give ketones.



Scheme 1 Oxidation methods using DMSO

To evaluate our hypothesis, 1-(4-methoxyphenyl)-2-phenylethanone[5] (pK_a~17) **1a** was taken as the model substrate, as it could generate stabilized enolate anion under mild basic conditions. A test reaction was performed with **1a** and potassium carbonate (K_2CO_3) in DMSO with wide temperature range (rt-150 °C). As expected oxygen was successfully incorporated into the reactant, α-diketone was obtained. With the advent of the initial results, a systematic optimization study has been done to screen various reaction parameters.[6] After extensive optimization studies with solvent, base, temperature and reaction concentration, we were delighted to obtain consistently very good yield of diketone with the catalytic quantity (25 mol%) of milder base, potassium bicarbonate ($KHCO_3$) at lower temperature (80 °C).

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† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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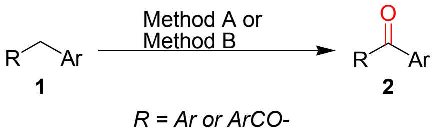
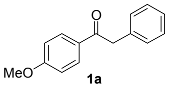
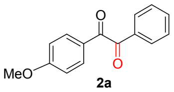
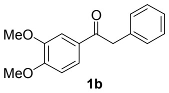
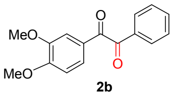
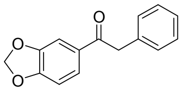
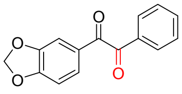
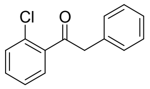
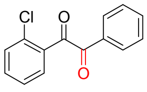
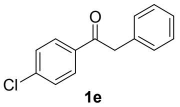
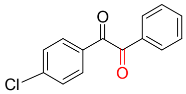
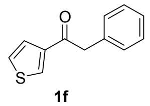
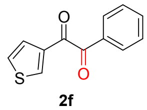
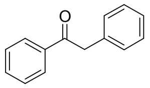
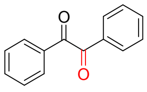
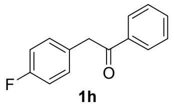
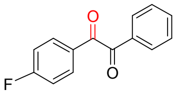
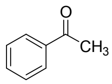
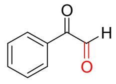
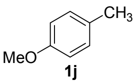
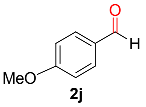
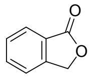
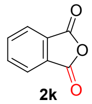
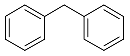
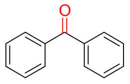
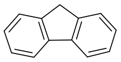
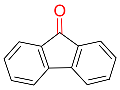
The optimized conditions were tested with various active methylene substrates (Table 1, entries 1-8), all of them underwent smooth oxidation to afford diketones (**2a-h**) in high yields (86-97%) in shorter time periods (0.5-3 h). Further, the reaction scope was examined with mono activated methylene groups i.e. acetophenone and *p*-methoxytoluene (Table 1, entries 9 and 10), but the starting material remained intact even with more basic cesium carbonate (Cs$_2$CO$_3$). Even, the compound with methylene group flanked by phenyl & heteroatom (Table 1, entry 11) also showed resistance to oxidation. Nonetheless, we were pleased with the results, as it provided room for developing this reaction as a chemoselective oxidation protocol. Delightfully, the diactivated methylene C-H bonds (Table 1, entries 12 and 13) were also successfully oxidized under the developed conditions. It signifies that this new procedure could effectively differentiate the oxidation sites of C-H bonds in a given substrate.

With the initial observations, a plausible mechanism (Scheme 2) was proposed for the oxidation of C-H bond using DMSO as an oxidant. Initially, the soft carbanion formed interacts with the soft electrophilic sulphur of dimethyl sulfoxide to form an intermediate **I**, which undergoes subsequent 1, 2 – sigmatropic rearrangement to give an alkoxide ion intermediate **II**. The generated alkoxide ion intermediate would then couple with electrophilic sulphur of DMSO to form an adduct **III**, which finally undergoes proton transfer followed by E1cb elimination to produce the oxidation product. It is interesting to note the results obtained with the toluene (pK_a = 43), diphenyl methane (pK_a = 32.2), and acetophenone (pK_a = 24.7).[7] Even though, α C-H bond of acetophenone is more acidic than the methylene C-H bond of diphenyl methane, acetophenone (Table 1, entry 9) did not undergo oxidation. Even phthalide (Table 1, entry 11) could not be influenced to undergo oxidation. This indicates that the developed protocol is not solely a base catalyzed reaction, but it majorly relies on the soft nature of the carbanion to interact with the soft electrophile of DMSO. It is the critical factor for the developed protocol in enabling oxidation products with high chemoselectivities.

Table 1. Scope of DMSO oxidation of active methylene compounds[a, b]



Entry	Substrate	Product	Yield (%)[c]
1[a]	 **1a**	 **2a**	96
2[a]	 **1b**	 **2b**	90
3[a]	 **1c**	 **2c**	95
4[a]	 **1d**	 **2d**	86
5[a]	 **1e**	 **2e**	91
6[a]	 **1f**	 **2f**	85
7[a]	 **1g**	 **2g**	96
8[a]	 **1h**	 **2h**	96
9[a, b]	 **1i**	 **2i**	0[d]
10[a, b]	 **1j**	 **2j**	0[d]
11[a, b]	 **1k**	 **2k**	0[d]
12[b]	 **1l**	 **2l**	95
13[b]	 **1m**	 **2m**	94

[a] Method A: **1** (0.25 mmol), KHCO$_3$ (0.0625 mmol) in DMSO (0.05M) at 80 °C for 0.5-3 h. [b] Method B: **1** (0.25 mmol), Cs$_2$CO$_3$ (0.0625 mmol) in DMSO (0.05M) at 125 °C for 12-24 h. [c] Yield of isolated pure product. [d] Reactant was intact even after 48 h.

In the proposed mechanistic path, the oxygen atom in the product is obtained from the sulfoxide and not from atmospheric oxygen. To support this assumption, a set of three reactions (Scheme 3) was performed with same substrate and base for 1.5 h under different reaction environments i.e. a) under nitrogen atmosphere b) under oxygen atmosphere and c) under vacuum (0.01 mm of Hg).

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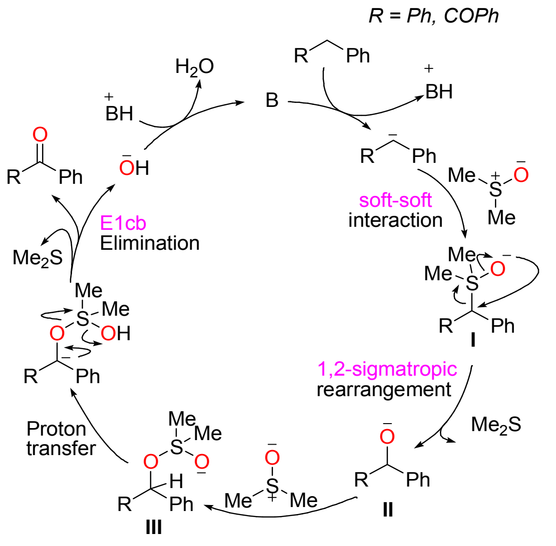
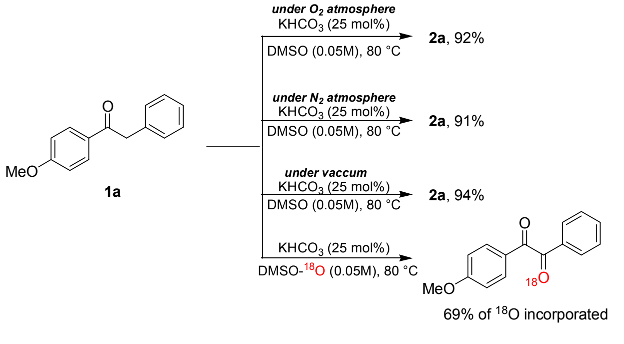


Scheme 2. Catalytic cycle for the oxidation of C-H bond using DMSO

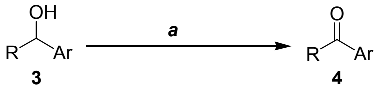
If the oxygen atom has been transferred into the molecule from atmospheric oxygen, the other two conditions (under nitrogen & vacuum conditions) should have shown inferior results, but the three different conditions were showing similar results. This preliminary result supports that the incorporated oxygen in the product is indeed coming from DMSO. We would like to further confirm this by isotopic labelling study. Therefore, a reaction was performed in ^{18}O labelled DMSO with the substrate **1a** under the standard reaction condition. As anticipated, the ^{18}O incorporated product was obtained in high yield confirming that the oxygen atom in the product was derived from DMSO itself.[6a,8] It is worth mentioning here that during the reaction process, we also observed the foul smell of dimethyl sulfide (DMS), which again reconfirms the proposed mechanism wherein DMS is a byproduct. The reaction of **1a** with radical scavenger has no influence in the reaction rate and yield, which signifies that the reaction proceed *via* ionic path way.



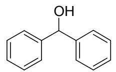
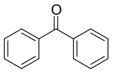
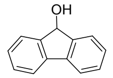
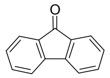
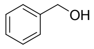
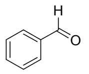
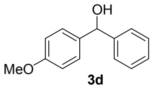
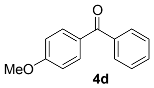
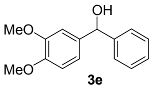
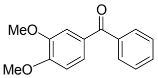
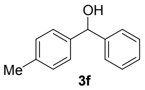
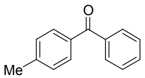
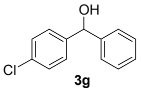
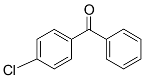
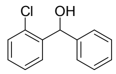
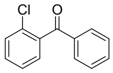
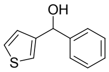
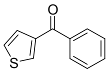
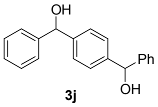
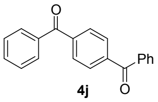
Scheme 3. Experiments for mechanistic investigation

Further, we tried to trace out the reactive intermediates using mass spectrometry with the oxidation of **1a** using $KHCO_3$ in DMSO. The alkoxide ion intermediate **II** (*m/z* = 241) was detected in negative mode of electron spray ionization mass spectrometry (ESI-MS) technique.

Table 2. Scope of DMSO oxidation of benzhydrols[a]



R = Ar or Het-Ar

Entry	Substrate	Product	Yield (%)[b]
1	 **3a**	 **4a**	96[c]
2	 **3b**	 **4b**	94
3	 **3c**	 **4c**	0[d]
4	 **3d**	 **4d**	92
5	 **3e**	 **4e**	91
6	 **3f**	 **4f**	96
7	 **3g**	 **4g**	95
8	 **3h**	 **4h**	92
9	 **3i**	 **4i**	94
10	 **3j**	 **4j**	90

[a] **3** (0.25 mmol), Cs_2CO_3 (0.0625 mmol) in DMSO (0.05M) at 125 °C for 12-24 h. [b] Yield of isolated pure product. [c] **3a** (0.25 mmol), K_2CO_3 (0.0625 mmol) in DMSO (0.05M) at 125°C for 24 h yielded 94% of **4a**. [d] Reactant was intact even after 48h.

To further justify the involvement of alkoxide ion intermediate **II**, an NMR experiment was performed with diphenyl methane **1l** as its alkoxide ion would be more stable and hence could be easily detected in NMR. During the course of reaction of **1l** in DMSO-d_6 under the standard conditions, the peak at **δ**=3.88 due to methylene protons of the reactant slowly disappeared and the diagnostic peak of the alkoxide ion intermediate **II** of diphenyl methane appeared at **δ**=5.64 gradually increasing its intensity upto a certain time interval, and completely disintegrates at the final stage. This particular experiment not only evidenced the involvement of alkoxide ion intermediate

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DOI: 10.1039/C5CC05713B

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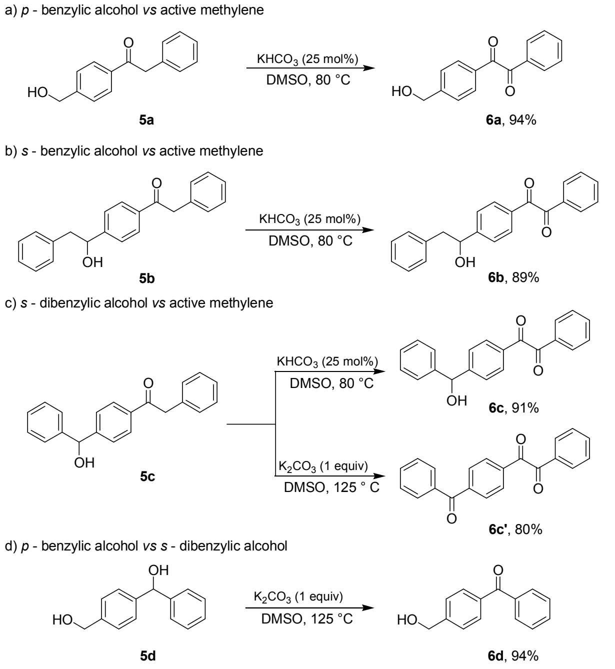
II, but also opened an opportunity to extend the present protocol on alcohol oxidation.

A number of activated alcohols (Table 2) were subjected to this oxidation protocol with Cs_2CO_3 as a base instead of $KHCO_3$, as the reaction rate was very slow with $KHCO_3$.[6a] Contrary to our expectation benzyl alcohol (Table 2, entry 3) was intact under the same reaction conditions even after 24 h. It is worth mentioning that the present reaction works equally well with K_2CO_3, but at a slower rate. In contrast to the other known oxidation protocols,[9] the developed protocol has the potential to evolve as an efficient, transition metal free, green chemoselective oxidation method.

To highlight the chemoselective application of the developed protocol, we designed and synthesized model substrates with competitive oxidizable functional groups. At first, we tested the developed protocol with a substrate **5a** containing *p*-benzyl alcohol and carbonyl activated benzylic methylene groups.



Scheme 4. Evaluation of present DMSO oxidation protocol on chemoselective substrates

To our delight the active methylene position got oxidized selectively in high yields **6a** with the primary benzylic alcohol group intact (Scheme 4a). Next, the optimized conditions were evaluated with the substrate **5b** containing *sec*-benzylic alcohol and carbonyl activated benzylic methylene groups, as expected we got excellent chemoselective oxidation product **6b** (Scheme 4b). Encouraged by these results, we further designed a substrate **5c** (Scheme 4c) with highly activated benzhydrol unit and carbonyl activated benzylic methylene unit. Even the highly activated benzhydrol remained intact and selectively produced the diketone **6c** in excellent yield. To the best of our knowledge, this is the first report which specifically oxidizes the active methylene group in presence of benzylic alcohol and benzhydrol.[10] We futher examined with the substrate **5d** containing mono & diactivated benzylic alcohols and afforded siginificant yield of **6d** with excellent selecitivity. These results have shown the importance and robustness of the present chemoselective oxidation strategy using DMSO as an oxidant.

In summary, to best of our knowledge, this is the first report to utilize the electrophilic centre of DMSO without using any activator for the oxidation of active methylene compounds and benzhydrols. This procedure also shows unusual chemoselectivities in excellent yields. The role of DMSO in the present oxidation strategy was successfully demonstrated with the help of analytical, experimental and ^{18}O-isotopic labelling studies. The developed protocol neither utilizes the DMSO activators nor metal oxidant, which is highly desirable owing to their practical applicability and environmentally benign nature. Further studies are in progress to explore and utilize the electrophilic sulphur of sulfoxide for achieving various selective oxidations.

This work was supported by SERB, DST New Delhi (SR/FT/CS-92/2011) and SEED Grant of IIT Mandi. RS, AB and VKM & RC thank DST, CSIR and IIT Mandi respectively, for financial assistance. AMRC sophisticated instrumental facilities are gratefully acknowledged.

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