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Note

Oxidation of aryl and heteroaryl methyl ketone to aryl and heteroarylglyoxals by using $CuCl_2$-DMSO

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The oxidation of aryl methyl ketone and heteroaryl methyl ketone to arylglyoxals and heteroaryl glyoxal respectively has been carried out by using the cheap and easily available, non toxic, Lewis acid $CuCl_2$ in DMSO solvent at 70-80°C within 1-2 hr. The reaction can be performed in air without loss of variety of oxidisable fuctional group like phenolic OH, hetroaryl ring, aryl substituted methyl, halo, nitro group, *etc*.

Keywords: Aryl, heteroaryl, ketone, arylglyoxal, heteroarylglyoxal, $CuCl_2$, DMSO

Glyoxal exerts tumor promoting activity on rat glandular stomach carcinogensis[1]. Aryl glyoxal plays important role in the synthesis of 1-aryl substituted hydatoins[2], in synthesis of hetrocycles like 1,2,4-oxadiazine[3], 2-imidazoles[4] and synthesis of large rings like [1.1] (2,3) thiopheno (1,1) ferrocenophane-1,7-dione[5].

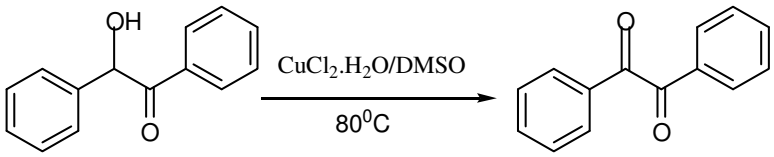
A variety of methods have been reported for the oxidative conversion of aryl methyl ketones to arylglyoxal, for example, selenium dioxide (selenious acid)[6], aq. HBr in DMSO[7] and DMSO-I_2/CuO (Ref 8). Similarly, a variety of methods have been reported for the oxidative conversion of aryl methyl ketones to aromatic acids by subsequent oxidation of arylglyoxal using bromine or iodine[9] in a basic media, sodium nitrite-pyridium polyhydrogen fluoride[10], KOH/DMF[11], sodium bromite[12] in strong basic conditions, $C_6H_5(OCOCF_3)_2$ (Ref 13), disodium nitrosyl penta-cynoferrate[14] and HDNIB-Bu_4NIO_4 (Ref 15). These procedures however, suffer from the following drawbacks: methods need to use either strongly acidic or basic reaction conditions, high cost of the reagents, lengthy procedures, non-compatibility of the other functional groups and low yields, *etc*.

α-Chloroacetophenone was required for some heterocyclic synthesis. It was thought that chloro-acetophenones can be synthesized by using $CuCl_2$ in DMSO. This reagent had been used earlier by this group to bring about oxidative chlorination of 2′-hydroychalcones, isoxazoles, naphthalenes and anthracenes[16]. Copper chloride is a mild, cheap and easily available oxidizing reagent. Moreover, it is useful because it is non toxic. Copper chloride has been used in the dehydrogenation of dihydro pyrimidine[17], for the oxidation of alcohols to the corresponding carbonyl compounds[18], for the cyclization in Biginelli reaction[19], for the oxidative cyclization of 2-aminobenzyl alcohol[20] and cyclization of *o*-hydroxy-β-diketones[21], nitroaldehyde to aryl glyoxal and aryl glyoxalic acids[22]. Henry and co-workers have performed the Pd catalyzed enatioselective intermolecular chlorohydration of olefins[23].

After consideration of several possibilities[24], an alternative preparation of arylglyoxal was sought to avoid some of the drawbacks of the above methods. The conversion of aryl methyl ketones to arylglyoxals through the agency of dimethyl sulfoxide (Me_2SO) and $CuCl_2$ was found attractive.

Results and Discussion

Earlier, the oxidation of benzoin to benzil could be achieved by using copper chloride in dimethyl sulphoxide **(Scheme I)**. Very surprisingly, the formation of product **2 (Scheme I)** could be observed within 20 min with 92% yield. This prompted the study of the effect of copper chloride on active methyl or methylene. To achieve this, acetophenone was selected as a model substrate to study the effect of temperature on the oxidation under neutral conditions in presence of dimethyl sulphoxide as a solvent and 2 moles of copper chloride. It was observed that when the reaction was carried out at 25-60°C there was no change on TLC, indicating no conversion of reactant to product. However, if the temperature was elevated to 70°C a slight change could be observed on TLC indicating the progress of reaction. After workup, a neutral solid product of arylglyoxal was obtained in 25% yield (entry 1 **Table I** and **II**). It was further observed that as the temperature increased from 70-80°C the yield of arylglyoxal (entry1 **Table I** and **II**) also increases.



1 **2**

Scheme I

Table I — Temperature dependence in the $CuCl_2$ catalyzed oxidation of aryl/heteroaryl methyl ketones to aromatic acid and arylglyoxal

Entry	Temp (°C)	Oxidation Product yield (%)	
		Arylglyoxal	Aromatic acid
1	30	00	-
2	60	00	-
3	70	25	-
4	80	90	-
5	120	75	25
6	150	12	88
7	160	10	90

This encouraging result led to the study of a series of other aryl methyl ketones. Gratifyingly, all the reactions proceeded smoothly and afforded the expected products in good yield. An interesting electronic effect seems to exist for aryl methyl ketones oxidation. It was observed that reaction time for electron releasing arens were significantly shorter. The reaction time required for the *o*-hydroxybenzaldehyde requires longer reaction time which might be attributed to co-ordination of the phenolic OH group with copper chlorides. The substrates with electron withdrawing groups also required longer reaction time and gave higher yield. Increasing the temperature decreases the yield of aryl glyoxal. Addition of base did not improve the yields. It was observed that arylglyoxals were the major product at 80°C (**Scheme II**) and aromatic acid were the major product at 155°C.

Further, the effect of copper chloride oxidation on acyl substituted hetroaryl derivatives (entry 18,19,20) was studied and it was found that hetroaryl acyl derivatives were smoothly oxidized to hetroaryl glyoxal without loss of the hetrocyclic ring.

Active methylene containg derivatives (entry 11, 22) also afforded 1,2-diketone product with moderated yield without loss of any substituent present on the aryl ring.

Most interestingly, the reaction appears to be compatible with oxidizing substituents like aryl substituted methyl, nitro, halo and hydroxyl.

The results of the oxidation of several aryl/heteroaryl methyl ketones derivatives to form aryl/heteroaryl glyoxal under atmospheric conditions with $CuCl_2$ in dimethyl sulphoxide are summarised in **Table II**.

Mechanism

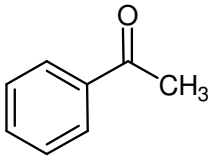
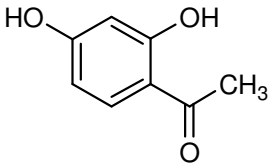
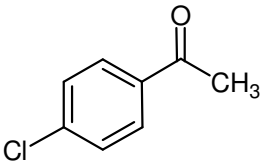
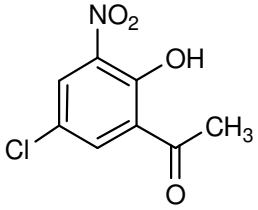
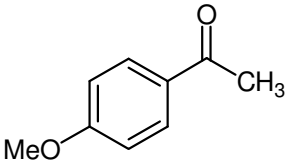
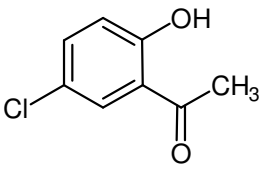
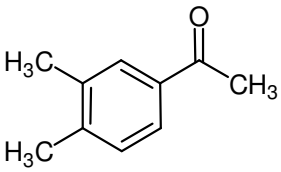
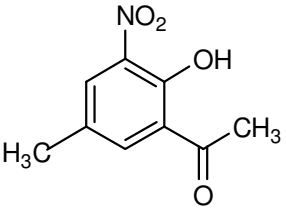
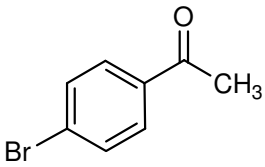
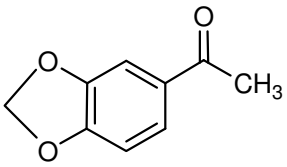
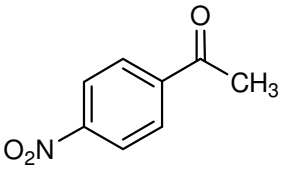
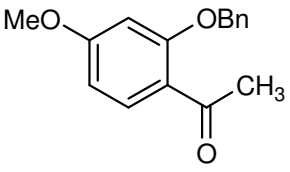
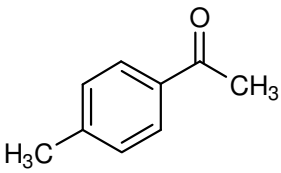
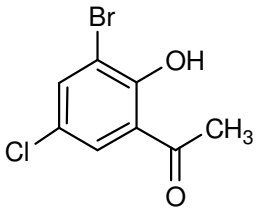
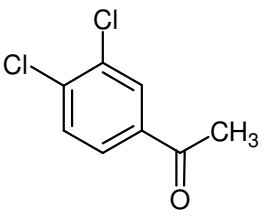
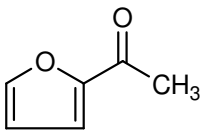
The phenacyl chloride obtained by chlorination of aryl/heteroaryl methyl ketone under neutral conditions can be sequentially oxidized by dimethylsulphoxide to phenyl glyoxal[25-27], which can occur *via* path 'b' shown in **Scheme III**. The mechanism of the oxidation of acetophenone to arylglyoxals may involve chlorination followed by solvolysis of α-chloroacetophenone to α-hydroxyacetophenone[28]. The water required for solvolysis is available in the reaction medium from $CuCl_2.2H_2O$. The mechanism of oxidation of α-hydroxyacetophenone with cupric (II) acetate in aqueous pyridine has been investigated. This reaction is base dependent and involves the removal of a proton from α-methylene group of copper-ketol complex. Since base was not used in the reaction, the possible mechanism for the oxidation of 2′-hydroxyacetophenone to aryl glyoxal may be excluded. The formation of aryl glyoxal is likely by the pathway suggested by Floyd[7].

The formation of α-bromoketone from 2-hydroxyacetophenone by using $CuBr_2$ has been reported[7]. However, the oxidation with DMSO in presence of K_2CO_3 at 120°C was observed as a slow process[29]. Shinara has reported that the peroxide-sulphate Cu^{++} system yields benzyl alcohol, benzaldehyde, benzoic acid and phenyglyoxalic acid as an intermediate in the oxidation of mandelic acid[30].

Thus, acetophenone can be oxidized to the corresponding α-keto acid *via* path 'a' and further decarboxylation to aldehydes or oxidative decarboxylation to benzoic acids.

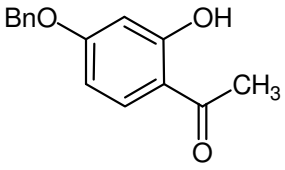
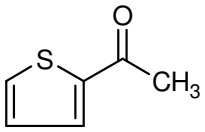
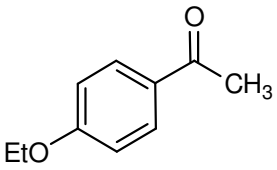
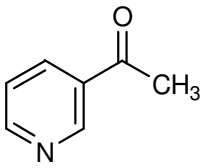
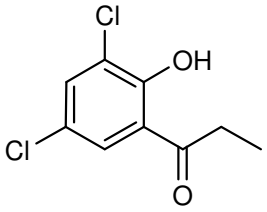
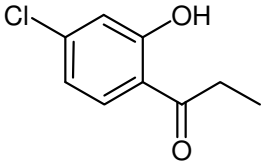
2-Hydroxyacetophenone with $CuCl_2$/DMSO gave 2-hydroxyphenylglyoxal. This is similar to the earlier reported result by Fodor and Kovacs[31]. The other

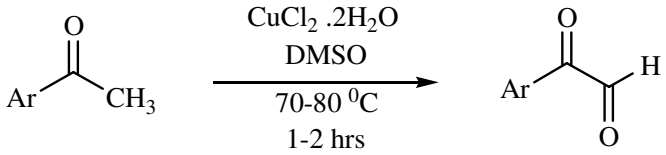
Table II — Oxidation of aryl/hetroaryl methyl ketones to aryl/hetroaryl glyoxal by copper chloride in DMSO

Entry	Substrate	Yield (%)	Entry	Substrate	Yield (%)
1		86	12		38
2		85	13		89
3		81	14		88
4		78	15		92
5		90	16		80
6		71	17		52
7		92	18		95
8		80	19		72

—Contd

Table II — Oxidation of aryl/hetroaryl methyl ketones to aryl/hetroaryl glyoxal by copper chloride in DMSO—*Contd*

Entry	Substrate	Yield (%)	Entry	Substrate	Yield (%)
9		52	20		75
10		80	21		62
11		85	22		68



Ar=aryl/hetroaryl

38-95%

3 **4**

Scheme II

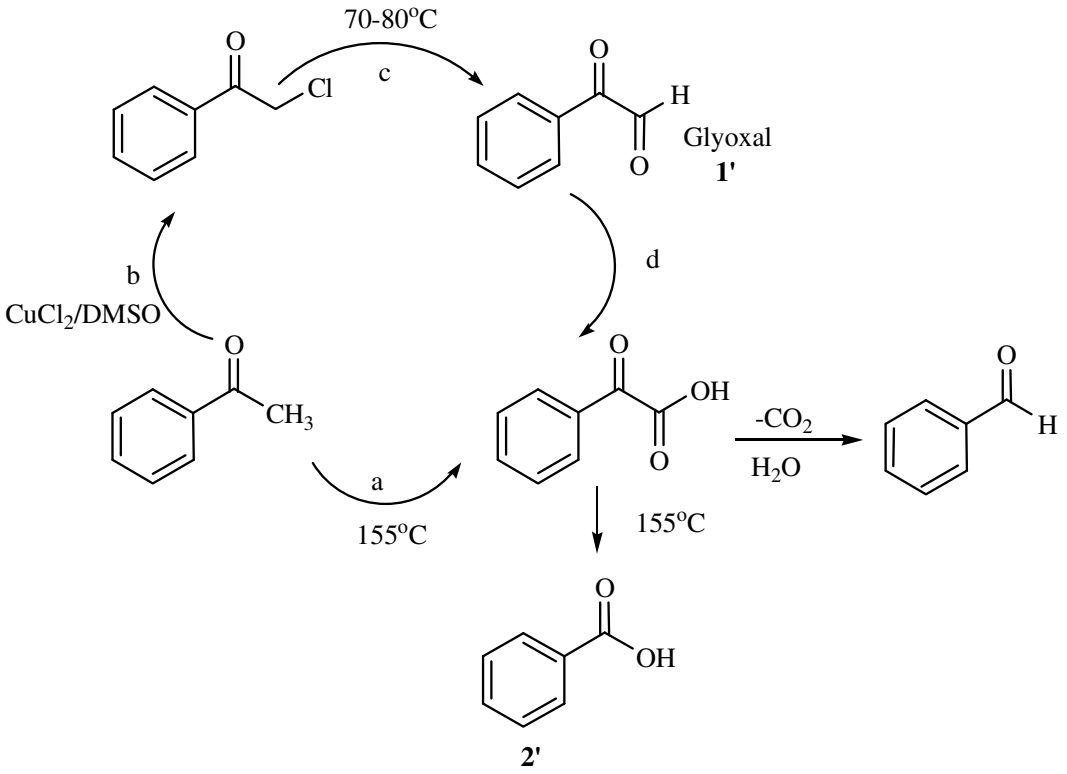
oxidation products like 2-hydroxyphenylglyoxalic acid and hemiacetal were not isolated, since, under the reaction conditions aldehyde group could not be oxidized to acid[32].

Experimental results showed that in the proposed mechanism, step b and step c might have comparable reactive rates when the reaction temperature was in the range of 70-80°C. However, if the temperature was elevated to 155°C the oxidation step from a to d might be the fastest reaction in the whole system and the corresponding aromatic acid was the major product.

Experimental Section

Typical experimental procedure: A mixture of aryl/heteroaryl methyl ketone **A (Scheme II)** (1 eq) and $CuCl_2$ (2 eq) in freshly distilled dimethyl sulphoxide was stirred at 80°C for 1-2 hr. Then it was diluted with water, acidified with dil HCl and extracted with ether. The product was purified by recrystallization from ethanol or hexane.

All oxidation products are known compounds and the melting points and spectroscopic data (NMR, IR and MS) of all those compounds matched the physical and spectral data reported in the literature[33]. All melting points were determined by open capillary method and are uncorrected. ^{1}H NMR spectra were recorded on Varian 300 spectrometer with TMS as internal standard. All solvents were distilled directly prior to use. Alcohols, DMSO and $CuCl_2$ were purchased from Fluka and Merck. The homogeneity of the products and reaction monitoring were accomplished by TLC with silica gel GF_{254}.



Scheme III

2-oxo-2 phenylacetaldehyde, 1. Yield 86%; m.p.76-79°C; IR($CHCl_3$):1690,1723, 2720, 2825 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.45-7.80 (5H, m, Ar-H), 9.52(s, -CHO); ^{13}C NMR($CDCl_3$): δ 190.0, 187.8, 137.9, 134.6, 130.9, 130.8,129.9, 129.4. Anal. Found: C, 71.64; H, 4.47. Calcd for $C_8H_6O_2$: C, 71.58; H, 4.80%.

2-(4-Chlorophenyl)2-oxoacetaldehyd, 2. Yield 85%; m.p.233-35°C; IR(KBr):1692,1725, 2721, 2824 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.46 (2H, d, *J*=8.0 Hz, Ar-H),7.75(2H, d, *J*=8.0 Hz, Ar-H) 9.53 (s, -CHO); ^{13}C NMR($CDCl_3$): δ 191.0, 188.8, 138.2, 134.9, 131.9, 130.1,130.0, 129.8. Anal. Found: C, 57.14; H, 2.97; Cl, 20.84. Calcd for $C_8H_5O_2Cl$: C, 57.60; H, 3.0; Cl, 20.10%.

2(3,4-dimethylphenyl)-2-oxoacetaldehyde, 4. Yield 78%; m.p.145-48°C; IR ($CHCl_3$):1689, 1721, 2720, 2820, 2940 cm^{-1}; ^1H NMR($CDCl_3$): δ 2.32 (3H, s, $–CH_3$), 2.35 (3H, s, $–CH_3$) 7.10 (1H, d, *J*= 8.2 Hz, Ar-H), 7.43(1H, dd, *J*=3.2Hz Ar-H), 7.56(1H, dd, *J*=8.2;3.2Hz Ar-H), 9.53(s, -CHO); ^{13}C NMR($CDCl_3$): δ 190.0, 187.0, 139.2, 137.4, 133.9, 131.4,130.8,129.4, 17.8,17.7. Anal. Found: C, 74.07; H, 6.27. Calcd for $C_{10}H_{10}O_2$: C, 74.07; H, 6.17%.

2-(4-Bromophenyl)2-oxoacetaldehyde, 5. Yield 90%; m.p.125-26.5°C; IR($CHCl_3$):1695,1728, 2721, 2824 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.62 (2H, d, *J*=8.1 Hz, Ar-H), 7.70(2H, d, *J*=8.1 Hz, Ar-H) 9.54(s,-CHO); ^{13}C NMR($CDCl_3$): δ 190.9, 188.7, 138.1, 134.8, 131.7, 130.6,130.1, 129.8. Anal. Found: C, 51.61; H, 2.69; Br, 28.49. Calcd for $C_8H_5O_2Br$: C, 51.51; H, 2.79; Br, 28.19%.

2-(4-Nitrophenyl)2-oxoacetaldehyde, 6. Yield 71%; m.p.55-70°C; IR($CHCl_3$): 1344, 1522, 1698, 1730, 2727, 2825 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.46 (2H, d, *J*=8.8 Hz, Ar-H),7.75(2H, d, *J*=8.8 Hz, Ar-H) 9.53(s.-CHO); ^{13}C NMR($CDCl_3$): δ 192.3, 189.8, 139.2, 135.9, 132.9, 131.1,131.0, 129.8. Anal. Found: C, 53.62; H, 2.99; N, 7.80. Calcd for $C_8H_5O_4N$: C, 53.63; H, 2.79; N, 7.82%.

2-(2,4-dihydroxyphenyl)-2-oxoacetaldehyde, 11. Yield 38%; m.p.175-78°C; IR(KBr): 1224, 1360, 1690, 1723, 2721, 2825, 3372 cm^{-1}; ^1H NMR($CDCl_3$): δ 5.1 (1H,s,D2O exchangeable,-OH), 5.14 (1H,s,D_2O

exchangeable,-OH), 6.40-7.47 (3H, m, Ar-H), 9.53(s, -CHO); ^{13}C NMR($CDCl_3$): δ 191.1, 188.2, 138.1, 134.7, 131.5, 130.1, 130.0, 128.8. Anal. Found: C, 57.83; H, 4.69. Calcd for $C_8H_6O_4$: C, 57.73; H, 3.61%.

Conclusion

The present investigations are an attempt to point out some of the salient features of the reaction of aromatic ketones with dimethyl sulphoxide in presence of $CuCl_2$. This method is compatible with a variety of functional groups. It can tolerate moisture and oxygen from the reaction system. Thus, the present work provides an efficient and inexpensive oxidation procedure for a variety of aryl methyl ketones and heteroaryl methyl ketones. The ease of handling, ready availability, cheapness and non toxicity of the reagent and short reaction duration added to the advantages of this procedure. The conversion of aryl methyl ketones to aryl methyl described here will find wide synthetic applications.

Acknowledgment

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