



COPPER-CATALYZED GREEN SYNTHESIS OF AROMATIC CARBOXYLIC ACIDS

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ABSTRACT

A green, simple, practical and efficient copper-catalyzed method for synthesis of aromatic carboxylic acids has been developed. The protocol uses inexpensive $\text{CuCl}_2/\text{DMSO}$ as the catalyst/solvent and readily available acetophenone derivative as the starting materials, and the corresponding aromatic carboxylic acids were obtained in moderate to good yields. The method is tolerant towards functional groups in the substrates.

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INTRODUCTION

Aromatic carboxylic acids and their derivatives are ubiquitous in the world.^[1] Cost, scale long reaction time, ecological issues and the desire to avoid toxic, explosive or expensive reagent; excess reagent, equilibrium reaction condition and/or activation to unstable intermediates are all parameters of varying importance depending on application. Hence, a wide range of methods has been developed for the synthesis of aromatic carboxylic acids. Oxidation of various substituted arenes is a common strategy for synthesis of aromatic carboxylic acids. The traditional methods include oxidation of alkyl arenes,^[2] arylalcohols^[3] and aldehydes,^[4] oxidative cleavage of aromatic alkenes,^[5] alkynes,^[5a,b,6] diols,^[7a] aryl malononitrile^[7c] diketones^[8] and these oxidative protocols are often incompatible with many functional groups because of the participation of special oxidants. The reactions of arylmetallic reagents with carbon dioxide that lead to aromatic carboxylic acids have attracted much attention. Grignard^[9] and organolithium reagents^[10] are strong nucleophiles that react with CO_2 directly to form valuable carboxylic acids and their derivatives

However, their poor functional group compatibility ultimately limits their use. Recently, transition metal-catalyzed carboxylation of arylzinc^[11] and arylboron compounds^[12] with CO_2 has made great progress, and these methods provided a new access to various functionalized aromatic carboxylic acids. However, the expensive arylzinc and arylboron reagents need previous preparation or are purchased. Unfortunately, these methods often require one or more equivalents of these relatively expensive oxidizing agents. Some of these processes

also generate equal amounts of metal waste. Furthermore, oxidation reactions are usually carried out in halogenated organic solvents, typically chlorinated hydrocarbons, which are environmentally undesirable. However it is still a challenge and paramount importance for both economic and environmental reasons to improve known methods and develop green, selective and efficient catalysts for the oxidation of acids that will ensure the production of good yield, operational simplicity, provide mild conditions will allow the use of sensitive substrates. Considering the ready availability and low toxicity of copper catalyzed system enabling easy oxidation of acetophenone has become an important goal to us. In continuation of our endeavour to develop copper catalyzed synthesis of aryl glyoxal^[13] here in we report a green, simple, practical and efficient copper catalyzed one pot synthesis of aromatic carboxylic acids from readily available acetophenone and $\text{CuCl}_2/\text{DMSO}$ as a solvent via oxidative method in 2-3 hrs at 155°C .

RESULT AND DISCUSSION

During the study of copper catalyzed synthesis of aryl glyoxal^[13] from acetophenone at $70-80^\circ\text{C}$ surprising we have observed the formation of aromatic acid in low yield. This result promoted us to observe the effect of copper catalyzed for synthesis of aromatic carboxylic acids. For this we have selected acetophenone as a model substrate to study the oxidation with effect of temperature on the oxidation under neutral condition in presence of dimethyl sulphoxide as a solvent and 2 moles of copper chloride. It was observed that when reaction carried out at $25-60^\circ\text{C}$ there were no change on TLC, indicating no conversion of reactant to product. However, if the temperature was elevated to 70°C slight change observed on TLC indicating reaction is proceeding.

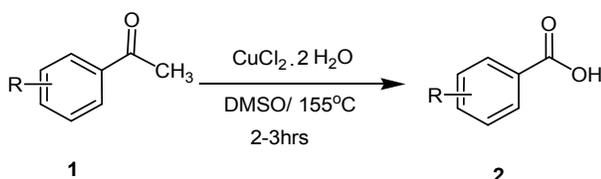
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Table I: Temperature Dependence in the CuCl₂ catalyzed oxidation of acetophenone to Aromatic acid & Arylglyoxal

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

After workup a neutral solid product of arylglyoxal obtained in 25%, (Table I) It was further observed that as the temperature increases from 70- 80°C the yield of arylglyoxal (Table I) increases with slight appearance of benzoic acid this result encourage us to study effect of temperature for synthesis of aromatic carboxylic acid. It was observed that as the temperature increases from 120-160°C the yield of aromatic carboxylic acid increases satisfactorily results of product obtained summarized in Table II

Scheme I: General Oxidation reaction of acetophenone derivative



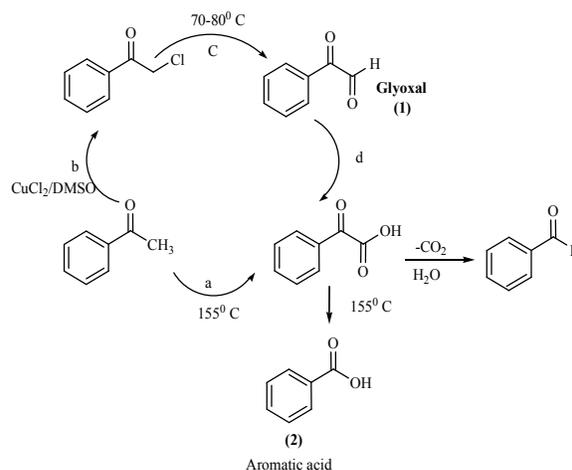
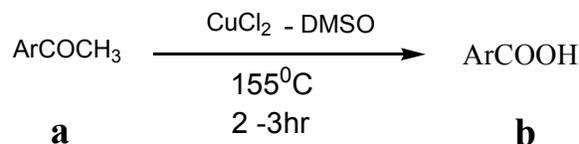
An interesting electronic effect seems to exist for acetophenone oxidation. We observed that long reaction time required for *o*-hydroxyacetophenone which may be attributed to co-ordination of the phenolic on group with copper chloride. The substrate containing electron withdrawing groups showed higher reactivity than one containing electron donating groups. Alkyl groups on aromatic rings were not oxidized of acetophenone could tolerate various functional groups including ether, C-Cl bond, C-Br bond, carboxyl and heterocycle.

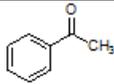
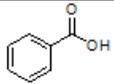
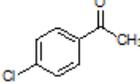
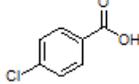
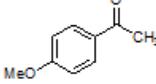
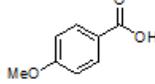
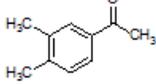
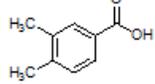
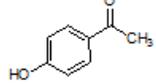
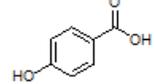
Mechanism

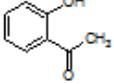
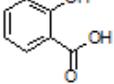
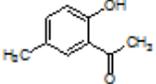
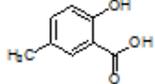
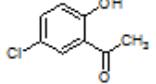
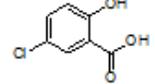
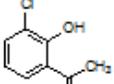
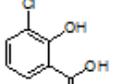
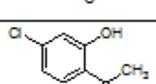
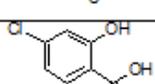
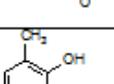
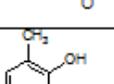
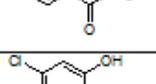
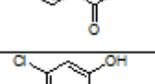
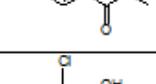
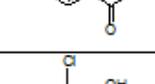
In this phenacyl chloride obtained by chlorination of aryl/heteroaryl methyl ketone under neutral condition can be sequentially oxidized by dimethylsulphoxide to phenyl glyoxal,^[14-16] which can occur via path 'b' shown in (Scheme II). The mechanism of the oxidation of acetophenone to arylglyoxals may involve chlorination followed by solvolysis of α -chloroacetophenone to α -hydroxyacetophenone.^[17] The water required for solvolysis is available in reaction medium from CuCl₂·2H₂O. The mechanism of oxidation of α -hydroxyacetophenone with cupric (II) acetate in aqueous pyridine has been investigated. This reaction is base dependent and involved the proton removal 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 then likely to be suggested by Floyd.^[18] The formation of α - bromoketone from 2-hydroxyacetophenone by using CuBr₂ was reported.^[18] However, the oxidation with DMSO in presence of K₂CO₃ at 120°C was

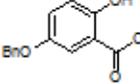
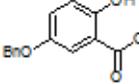
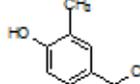
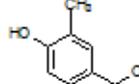
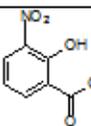
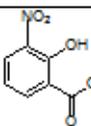
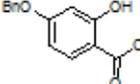
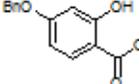
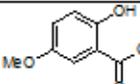
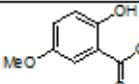
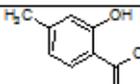
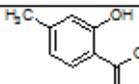
observed as a slow process.^[17] Shinara has reported that peroxodisulphate Cu⁺⁺ system yield benzyl alcohol, benzaldehyde, benzoic acid and phenylglyoxalic acid as an intermediate in the oxidation of mandelic acid.^[20] The oxidation of acetophenone to the corresponding benzoic acid derivative are probably involves an oxidative decarboxylation reaction which can occur via path 'a' or 'b' shown in scheme II. Thus acetophenone can be oxidized to the corresponding α -keto acid via path 'a' with further decarboxylation to aldehydes or oxidative decarboxylation to benzoic acids. This result is similar to the earlier reported by Fodor and Kovacs.^[21] Experimental result showed that in mechanism Step b and Step c might have approximate 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-d might be fast reaction in the whole system and the corresponding aromatic acid was the major product.

Scheme II: Mechanism by CuCl₂/DMSO

**Table 2: Oxidation of acetophenone to benzoic acid derivatives by copper chloride in DMSO at 155°C**

Entry	Reactant a	Product b	Yield (%)
1			89
2			100
3			72
4			74
5			70

6			70
7			74
8			88
9			88
10			86
11			74
12			85
13			87

14			72
15			72
16			88
17			72
18			71
19			72
20			82

Conclusion

In summary, we have developed an efficient copper-catalyzed method for synthesis of aromatic carboxylic acids. The protocol uses inexpensive $\text{CuCl}_2/\text{DMSO}$ as a catalyst/solvent and readily available acetophenone as a starting materials the corresponding aromatic carboxylic acids were obtained in moderate to good yields. The method is of tolerance toward various functional groups in the substrate and the synthesis of the aromatic carboxylic acids will attract much attention in industrial and academic researches because of their wide application in various fields.

Experimental Section

All oxidation products were known compounds and were identified by comparison of their physical and spectral data with those of authentic samples^[22]. Acetophenone derivatives, DMSO and CuCl_2 were purchased from Fluka and Merck. The purity of the products and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates.

General procedure for the oxidation

CuCl_2 (2mole) was added to the stirred solution of acetophenone (1Mole) in DMSO as a solvent. The reaction mixture was heated as required at 155°C for benzoic acid derivative for 0.5 - 2.5 hrs completion of reaction was followed by monitoring TLC then reaction mixture was diluted with water, acidified with HCl and then extracted with ether. The crude mixture was purified by chromatography to afford product.

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