

Efficient and One-pot Synthesis of Tetrahydro[b]Pyran Derivatives Catalyzed by Copper Doped Iron Tartarate

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Abstract: The multicomponent environment benign synthesis of tetrahydro[b]pyran derivatives has been prepared by using aldehydes, malanonitrile and dimedone. The reaction is catalyzed by metal tartarate i.e. $\text{CuFe}_2(\text{C}_4\text{H}_4\text{O}_6)_3 \cdot 6\text{H}_2\text{O}$, the synthesized catalyst was characterized by XRD and TEM analytical techniques which reveal the crystalline nature, size and shape of the catalyst particles. The used metal tartarate for synthesis was water soluble and reusable hence even after frequent use it did not lost its activity. The products of given three component synthesis was obtained in very short period of time and has moderate to excellent yield. The synthesis includes green approach due to solvent free condition and easy work-up.

Index Terms: $\text{CuFe}_2(\text{C}_4\text{H}_4\text{O}_6)_3 \cdot 6\text{H}_2\text{O}$, tetrahydro[b]pyran, aldehydes, malanonitrile and dimedone.

I. INTRODUCTION

The tetrahydro[b]pyran derivatives attracted researcher widely as they have various pharmacological properties like diuretics, anticancer, spasmolytic, anti-anaphylactin agent and cognitive enhancer for treatment of neurodegenerative diseases such as Alzheimer, amyotrophic lateral sclerosis, parkinson's disease, Huntington's disease, Down's syndrome and Schizophrenia.¹

The copper doped tartarates has been grown in silica gel and many of tartarate compound find application in medical, Pharmaceutical and industrial fields due to their special properties. For example, injections of Na-Cr tartarate increase the susceptibility of the transplanted sarcoma to the effect of X-rays, calciphylactic responses of various ferrous tartarate compounds prevents anemia of champagne, ferrous tartarate is used to tan skin and manganese tartarate crystals are used as chemical temperature indicator.²

The synthesis of heterocyclic compounds containing oxygen atom like 3,3-arylidene bis(4-hydroxycoumarin) and 1,8-dioxooctahydroxanthene derivative has been reported recently by using ferrite as catalyst³, where as some compounds containing nitrogen atom was synthesized like quinoline and dihydropyrimidines by using tartarate as catalyst.⁴

Literature survey finds use of different catalyst for the preparation of studied tetrahydro[b]pyran derivatives such as ammonium chloride⁵, Fructose⁶, hexadecyldimethylbenzyl ammonium bromide⁷, phthalimide-N-Oxyl⁸, tetramethyl ammonium hydroxide⁹, palladium nanoparticles¹⁰ etc. Some 2-amino-tetrahydrobenzo[b]pyrans can be used as photoactive materials¹¹. Synthesis of tetrahydrobenzo[b]pyrans was traditionally promoted by strong bases. Strong acids or high temperature in the presence of volatile organic compounds.¹²⁻²⁰ All of these have cons and pros but now a day's researcher would like to go for more eco-friendly method which can minimize the hazardous byproducts.

II. EXPERIMENTAL

A. Materials

All the used chemical reagents were of AR grade and all the chemicals were purchased from spectrochem private limited in high purity.

B. Apparatus

Melting points were determine in open capillaries using a digital melting point apparatus, The NMR spectra were recorded by using Bruker ARX-300 spectrometer sample solution were prepared in Chloroform-d containing tetramethylsilane as

internal reference and recorded on 400 MHz and chemical shift value recorded in δ ppm. The IR spectra in KBr were recorded using Perkin-Elmer 1700 spectrophotometer. The progress of reaction was carried out by using TLC.

C. General procedure for preparation of catalyst $\text{CuFe}_2(\text{C}_4\text{H}_4\text{O}_6)_3 \cdot 6\text{H}_2\text{O}$

The co-precipitation method was used to prepare complex. The two metal salts aqueous solution that is $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ were mixed homogeneously in a fixed molar ratio of approximately 2:1. The pH of solution adjusted to slightly acidic condition by dilute H_2SO_4 to hydroxide formation of cation. In this mixture of metal salt the 10% aqueous solution of tartarate is added slowly with constant stirring to get complete precipitation. The stirring is continued for next 30 minutes by adding acetone in equal amount to the ligand solution. A coloured product appeared on standing and cooling the above solution. The precipitate complex was filtered washed with acetone and dried under normal atmospheric conditions and then stored in desiccators to dry.

D. General Procedure for synthesis of tetrahydrobenzo[b] pyran using $\text{CuFe}_2(\text{C}_4\text{H}_4\text{O}_6)_3 \cdot 6\text{H}_2\text{O}$

The mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol), water (10 ml) and $\text{CuFe}_2(\text{C}_4\text{H}_4\text{O}_6)_3 \cdot 6\text{H}_2\text{O}$ (0.01gm) was prepared properly by using glass rod and refluxed, the progress of reaction was monitored by TLC by using solvent system Ethyl acetate and n-hexane (20:80). After completion of reaction the mixture was cooled and poured on 20 ml crushed ice. The solid product was filtered, washed with water, dried and recrystallized by using ethanol to get corresponding tetrahydrobenzo[b] pyran. The products were confirmed by melting point, IR and ^1H NMR spectrum.

E. Selected spectral data:

2-Amino-(4-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-Chromene-3-carbonitrile (Entry 4, Table 3): ^1H NMR (400 MHz, DMSO- d_6): δ =0.93 (s,3H), 1.02(s,3H), 2.10 (d,1H) 2.21 (d,1H), 2.50 (s,2H), 4.19 (s,1H), 7.05 (s,2H), 7.18 (d,2H), 7.33 (d,2H) ppm. IR(KBr) : 3381, 3184, 2959, 2188, 1674, 1635, 1604, 1365, 1216 cm^{-1} .

2-Amino-(4-nitrophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-Chromene-3-carbonitrile (Entry 6, Table 3): ^1H NMR (400 MHz, DMSO- d_6): δ =0.94 (s,3H), 1.02(s,3H), 2.07 (d,1H) 2.21 (d,1H), 2.52 (s,2H), 4.35 (s,1H), 7.17 (s,2H), 7.44

(d,2H), 8.14(d,2H) ppm. IR(KBr) : 3407, 3317, 3176, 2183, 1671, 1630, 1594, 1521, 1350, 1216, 1031 cm^{-1} .

III. RESULT AND DISCUSSION

Initially, the catalyst was prepared and reported elemental analysis was compared with observed data of weight % of Cu-Fe tartarate complex which was quite similar. The synthesized metal complexes are powdered solid, colored and stable towards air and moisture at room temperature. As shown in table I. The XRD and TEM data of tartarate complex were compared with standard data and found to be very similar which confirmed the formation of complex.

Table I. Observed Weight % of Cu-Fe tartarate complex

| Element | Weight % | Atomic % | Uncert % | Correction | K-factor |
|---------|----------|----------|----------|------------|----------|
| C(K) | 9.76 | 26.42 | 0.23 | 0.26 | 3.940 |
| O(K) | 16.38 | 33.28 | 0.21 | 0.49 | 1.974 |
| Fe(K) | 35.87 | 20.87 | 0.22 | 0.99 | 1.403 |
| Cu(K) | 37.96 | 19.41 | 0.26 | 0.99 | 1.667 |

The synthesis of tetrahydrobenzo[b] pyran was carried out by using 4-nitro benzaldehyde as trial reaction in different condition to determine the best method to optimize reaction conditions like temperature, reaction time, solvent etc. as shown in table II. When reaction carried out in catalyst free condition by only stirring at room temperature no product was formed after 45 minutes, where as by reflux at 60°C in ethanol formed product after 2.5 hours and eventually in presence of $\text{CuFe}_2(\text{C}_4\text{H}_4\text{O}_6)_3 \cdot 6\text{H}_2\text{O}$ commendable product formed within 30 minutes. It was observed 0.01 gm of the catalyst was sufficient to promote the reaction. The catalyst has benefit rather than water solubility is reusability as well, it can be recovered after completion of reaction without losing its activity and could be reuse for frequent cycles.

Table II. Optimization of reaction condition

| Entry | Catalyst | Reaction condition | Time (Min.) | Yield (%) |
|-------|---|---|-------------|------------|
| 1 | No catalyst | Ethanol/ RT/Stirring | 45 | No product |
| 2 | No catalyst | Ethanol/60°C/ Reflux | 130 | 80 |
| 3 | $\text{CuFe}_2(\text{C}_4\text{H}_4\text{O}_6)_3 \cdot 6\text{H}_2\text{O}$ | $\text{H}_2\text{O}/60^\circ\text{C}/$ Reflux | 30 | 90 |

To check the generality scope of this new methodology, we performed reactions of various substituted aromatic aldehydes shown in table III. The nature of substituent like electron donating and electron withdrawing has played no significant role in reaction time and yield of corresponding products. The

reaction was carried out in water hence has attractive feature as carried out neatly and solvent free. This would provide us very easy work up and no complicated isolation method was required. The metal tartarate acts similar to Lewis acid which can provide plausible product of given reaction in Scheme 1.

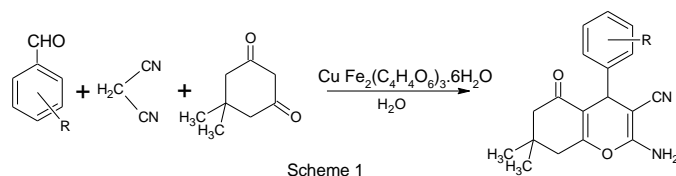


Table III. Tetrahydrobenzo[b] pyran derivatives catalyzed by $\text{CuFe}_2(\text{C}_4\text{H}_4\text{O}_6)_3 \cdot 6\text{H}_2\text{O}$

| Entry | Aldehydes | Time (Min.) | Product | Yield % | M.P °C | | References |
|-------|----------------------------|-------------|---------|---------|---------|----------|------------|
| | | | | | Found | Reported | |
| 1 | Benzaldehyde | 30 | 1a | 90 | 232-234 | 234-235 | 21 |
| 2 | 4-methoxy benzaldehyde | 30 | 5a | 90 | 202-204 | 201-202 | 21 |
| 3 | 2-hydroxy benzaldehyde | 30 | 7a | 92 | 226-228 | 224-226 | 21 |
| 4 | 4-chloro benzaldehyde | 30 | 4a | 95 | 212-214 | 215-217 | 22 |
| 5 | 3-nitro benzaldehyde | 30 | 3a | 92 | 210-212 | 214-216 | 22 |
| 6 | 4-nitro benzaldehyde | 30 | 2a | 95 | 178-180 | 179-180 | 23 |
| 7 | 4-flouro benzaldehyde | 30 | 6a | 90 | 222-224 | - | - |
| 8 | 3,4-dimethoxy Benzaldehyde | 30 | 8a | 90 | 210-212 | - | - |

CONCLUSION

In conclusion we have developed mild, efficient, environment benign method for the synthesis of pharmacodynamically active tetrahydrobenzo[b] pyran derivatives by using water soluble and reusable catalyst that is $\text{CuFe}_2(\text{C}_4\text{H}_4\text{O}_6)_3 \cdot 6\text{H}_2\text{O}$. The present method has simple procedure, easy work-up and lesser time, high yield compared

to many reported methods and performed under solvent free condition.

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