

## Synthesis of Substituted Phenyl Acetic Acid Using benzylicorganozinc Reagents and Carbon Dioxide

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### ABSTRACT

*The benzylic iodide is undergoes fast zinc insertion reaction compare to chloride and bromide. The most important method for preparation of substituted phenyl acetic acid is passing carbon dioxide gas through the solution of benzylicorganozinc compound in the presence of tetrakis acetonitrile copper (I) tetrafluoroborate as catalyst. The LiCl assist zinc insertion reaction, solubilize the catalyst and activate electrophile.*

**Keywords:** benzylicorganozinc reagent, carbon dioxide, copper (i) complex. phenyl acetic acid.

### Introduction

The carboxylic acid has vast array of medicinally important compounds as well as synthon in many organic transformation<sup>[1]</sup>. There are many valuable compound bearing carboxylic acid exhibit remarkable therapeutic activities such as aspirin, ibuprofen etc<sup>[2-3]</sup>. The well established method for preparation of carboxylic acid includes hydrolysis of nitriles or the oxidation of alcohol or aldehyde<sup>[1]</sup>. Carbon dioxide is an ideal carbon source because of its abundant, cheap, nontoxic and renewable source<sup>[4]</sup>. The carbon-carbon bond forming reactions of carbon dioxide with alkenes, alkynes, dienes, organometallic compound aryl boronic esters, aryl halides and arenes using transition metal catalyst<sup>[5]</sup>.

The benzylic organometallic compounds are often difficult to prepare due to formation of cross-coupling product<sup>[6]</sup> Direct metallation using strong base lead to ring metalated product<sup>[7]</sup>. Knochel et. al. reported mild and general synthesis of functionalized benzylic zinc bromide. The reaction of benzylic bromide with activated zinc using 1,2-dibromoethane in THF furnishes the benzylic zinc bromide in high yield<sup>[8]</sup>. Recently, polyfunctional benzylic zinc reagents are prepared by direct insertion of zinc dust into benzyl chlorides in presence of LiCl<sup>[9]</sup>. Reactivity of benzylic zinc halide is enhanced by transmetalation it react with variety of electrophile. The present protocol involve use of carbon dioxide in the carbon-carbon bond forming reaction. The carboxylation of benzylicorganozinc reagent catalyzed by  $(\text{CH}_3\text{CN})_4\text{CuBF}_4$ <sup>[10]</sup>.  $\text{Cu}(\text{MeCN})_4\text{BF}_4$  known as Kuba catalyst and catalyzed addition of 2-pyridylzinc bromide to acid chlorides<sup>[11]</sup>.

### Experimental section

While conducting this experiment two important precautions are taken where strictly anhydrous condition was maintained and All glassware dried overnight 150<sup>0</sup>C before use. All analytical grade chemicals were purchased and used without further purification. All solvents were dried as per Vogel's

practical book procedure. The  $^1\text{H}$ NMR spectra were obtained on Bruker DRX – 400 advance instrument using  $\text{CDCl}_3$  as solvent and TMS as internal standard at 400MHz.

### Typical procedure for preparation of copper (I) catalyst

4g (0.028 mole) cuprous oxide mixed with 80 ml acetonitrile in RBF suspension was observed. 113 mmole acid was added slowly with constant stirring at room temp. exotherm observed. The reaction mixture was kept at  $50^\circ\text{C}$  for 30 min then filtered removing any unreacted copper (I) oxide. The colorless clear solution was then cooled at  $-10^\circ\text{C}$  in a freezer and left overnight. A white colored crystal settle at the bottom of RBF which was separated by filtration washed with diethyl ether under nitrogen atmosphere. Then the copper salt was recrystallised and store in acetonitrile. All the copper salts were confirmed by melting point.<sup>[9]</sup>

### Typical procedure for preparation of rieke zinc metal

One 50 ml two neck RBF was equipped with rubber septa, stopper and magnetic bar flush by nitrogen. A small amount freshly cut of lithium 0.05g ( 7.204 mmole), naphthalene 0.1 g ( 0.7813 mmole) and 5 ml dry THF was charged by syringe clear solution was observed. The mixture was stirred at room temp. Colorless solution changes to dark green.

Second 50 ml two neck RBF was equipped with rubber septa, stopper and magnetic bar flush by nitrogen. Anhydrous Zinc chloride 0.5g ( 3.724mmole) was charged and 5ml dry THF added by syringe clear solution obtained. The zinc chloride solution was added to above dark green solution by syringe through septum. The mixture was stirred for 1 hr black-grey colored zinc metal observed in RBF. The weight of zinc metal generated after reduction was 0.210 gram i.e.0.003211 mole.

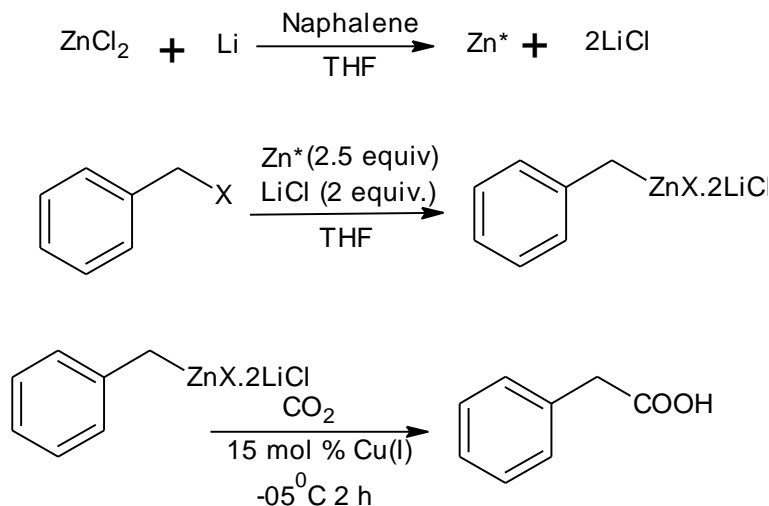
### Typical procedure for preparation of benzylic zinc halide and addition to Carbondioxide.

Anhydrous  $\text{LiCl}$  ( 2 equivalent) was dissolved in 2 ml dry THF and charged to  $-05^\circ\text{C}$  cooled zinc metal (2.5 equivalent) solution by syringe. Benzyl halide (1 equivalent) was dissolved in 2ml dry THF add to zinc metal solution and slowly allow to raise room temperature in 2-3 hr zinc insertion takes place. The organozinc reagent formation was confirm by TLC i.e. consumption of benzylic halide. Again organozinc reagent containing solution cool to  $-05^\circ\text{C}$  then carbon dioxide gas was continues pass through reaction mixture and add solid catalyst 15 mol %. The temperature of reaction mixture was allow to rise slowly stir 3 hr. Add 25 ml saturated ammonium chloride solution stir reaction mixture for 1 hr at rt and heat the reaction mixture to evaporate THF completely. The product was extracted in ethyl acetate wash by water dried organic layer over sodium sulphate. The product was purified by recrystallisation in ethanol. The yield was reported.

### Result and discussion

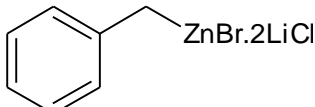
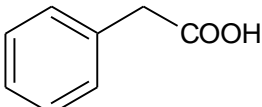
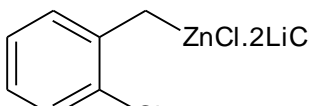
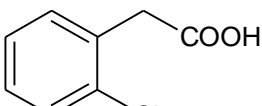
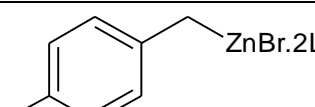
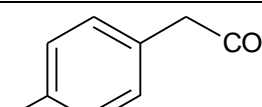
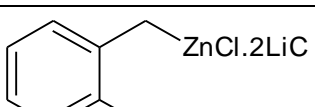
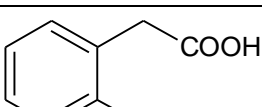
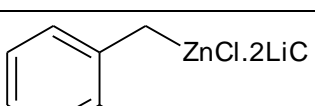
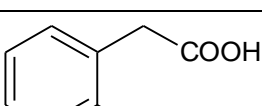
We have prepared active zinc metal by reduction of zinc chloride using lithium naphthalenide known as rieke zinc. This is the highest active form of zinc used for oxidative insertion in benzyl halide i.e. preparation of benzylic zinc halide.  $\text{LiCl}$  in THF not only solubilize the benzylic zinc halide but also assist the zinc insertion into benzylic halide. We have analyzed the zinc insertion reaction in different benzylic halide. We found that benzyl iodide undergoes fast, benzylic bromide moderate and benzylic chloride very slow zinc insertion reaction. We have report above observed by iodometric titration<sup>[12]</sup>. and TLC after 30 min.

The carbon dioxide gas was pass through the benzylic zinc halides solution at  $-05^{\circ}\text{C}$  in presence of  $\text{Cu}(\text{MeCN})_4\text{BF}_4$  copper complex as catalyst. The progress of reaction was monitored by TLC reaction mixture was allow to raise room temperature. Quench the reaction mixture by saturated ammonium chloride solution and evaporate THF completely, extract the product in ethyl acetate.



Scheme 1:- Synthesis of phenyl acetic acid

**Table 1 Substituted phenyl acetic acid derivatives.**

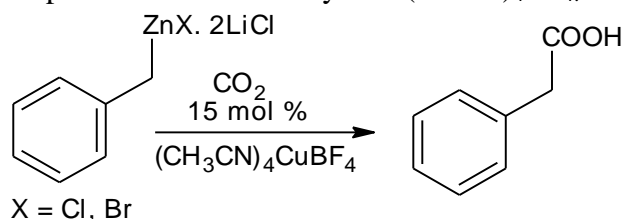
Entry	Benzylicorganozinc reagent	Product	Yield	Colour	M. Point
a			78%	White	$77^{\circ}\text{C}$
b			82%	Light Yellow	$92^{\circ}\text{C}$
c			84%	Light Yellow	$116^{\circ}\text{C}$
d			74%	White	$106^{\circ}\text{C}$
e			80%	Cream	$120^{\circ}\text{C}$

All the products are purified by recrystallisation in ethanol and yield was reported. The products were confirmed by melting point comparism with standard data, analyzed by IR,  $^1\text{H}$ NMR and  $^{13}\text{C}$ NMR.

The carboxylic group compound has tremendous potential in organic transformation i.e. versatile precursor in organic synthesis.

### Conclusion

We have prepared substituted phenyl acetic acid by most straightforward method for accessing carboxylic acid is the direct carboxylation of benzylic organozinc reagent, using carbon dioxide in the presence of new catalyst  $(\text{CH}_3\text{CN})_4\text{CuBF}_4$ , as shown below.



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