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## Copper-catalyzed Markovnikov hydration of alkynes

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#### ARTICLE INFO

#### ABSTRACT

hydration reaction have also been studied.

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#### 1. Introduction

The application of water in organic transformation as an economical and environmental friendly reagent is remarkable in pharmaceutical industry.<sup>1</sup> Hydration of alkynes is one of the important reactions for the introduction of valuable carbonyl functionality. In the earlier days, mercury salts<sup>2</sup> were used for the hydration of alkynes; however, they are not preferred choice for industrial application due to their environmental hazardous nature. Several groups have been working on the development of mercury free alternative methodology toward hydration of alkynes. In contrast, many research groups have reported regioselective iron catalyzed hydration of alkyne, which requires additives and long reaction time.<sup>3</sup> Wang and co-workers have performed the synthesis of ketone from alkyne using In(OTf)<sub>3</sub> as a catalyst and TsOH as an additive.<sup>4</sup> Naka and co-workers have reported water-soluble cobalt(III) porphyrin complexes mediated hydration of terminal alkyne to methyl ketone.<sup>5</sup> Zhao et al. have developed Pd(II)catalyzed hydration of alkynylphosphonates to the corresponding β-ketophosphonates.<sup>6</sup> N-heterocyclic carbene-gold complexes have also been used for the conversion of alkyne to carbonyl.<sup>7</sup> Different silver salts have been developed for hydration of terminal alkyne to corresponding keto-product.<sup>8</sup> Alami and co-workers have reported regioselective hydration of internal alkynes using TsOH in EtOH.<sup>9</sup> Ogo et al. have synthesized iridium complexes for the hydration of tetrolic acid ethyl ester.<sup>10</sup> Wass and co-workers have developed

platinum(II) diphosphinamine complexes for the conversion of alkyne to carbonyl.<sup>11a</sup> Li et al. have reported Cul catalyzed hydration of alkynes and subsequent cyclization to benzofuran using additives.<sup>1b</sup> All these catalytic hydration of alkyne exclusively gave Markovnikov product, however Ru-based catalyzed hydration of alkyne gave exclusively *anti*-Markovnikov product.<sup>12</sup> Some of these catalyst are expensive, not suitable for commercial purposes, and offered long reaction time for completion of reaction. Recently, copper triflate catalyzed hydration of aryl alkyne under microwave conditions have been reported using acetic acid as a solvent.<sup>13</sup> Herein, we report a highly efficient, inexpensive conventional method of copper triflate catalyzed Markovnikov hydration of alkyne using ethyl acetate as solvent, without addition of any additives with shorter reaction time compared to other conventional methods (Scheme 1).

Conventional, highly efficient, inexpensive copper triflate catalyzed regioselective Markovnikov hydra-

tion of terminal and internal alkynes have been reported. Significant shorter reaction time and excellent

yield without addition of additive make the method attractive. Effects of catalyst and solvent on the

$$- H \qquad \xrightarrow{Cu(OTf)_2, H_2O,} R \xrightarrow{Cu(OTf)_2, H$$

Scheme 1. Copper-catalyzed Markovnikov hydration of alkynes.

#### 2. Results and discussion

R-

Phenyl acetylene was used as a model to explore the scope of reaction. Initially, we have investigated different copper salt as a catalyst for the hydration of alkyne and among them  $Cu(OTf)_2$  emerged out the most effective for hydration of phenyl acetylene (Table 1, entry 8). Only 10% of product was formed with CuBr<sub>2</sub> (Table 1, entry 5) and rest of the copper catalysts are not able to





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#### Table 1

Screening of different reaction condition for hydration of phenyl acetylene<sup>a</sup>



4	CuCl <sub>2</sub>	EtOAc	12	n.r.	
5	CuBr <sub>2</sub>	EtOAc	12	10	
6	CuCl	EtOAc	12	n.r.	
7 <sup>c</sup>	Cu(OTf) <sub>2</sub>	EtOAc	6	85	
8 <sup>e</sup>	Cu(OTf) <sub>2</sub>	EtOAc	2	88	
9 <sup>d</sup>	Cu(OTf) <sub>2</sub>	EtOAc	1	66	
10	—	EtOAc	12	n.r	
11	Cu(OTf) <sub>2</sub>	1,2-DCE	3	56	
12	Cu(OTf) <sub>2</sub>	EtOH	12	15	
13	Cu(OTf) <sub>2</sub>	Toluene	12	n.r.	
14	Cu(OTf) <sub>2</sub>	MeCN	12	n.r.	
15	Cu(OTf) <sub>2</sub>	DMF	12	n.r.	
16	$Cu(OTf)_2$	THF	12	n.r.	

n.r. no reaction.

<sup>a</sup> Reaction condition: phenylacetylene (1 equiv), solvent (1.0 mL), water (2 equiv), and catalyst (20 mol %) at 100 °C.

<sup>b</sup> Isolated yield.

<sup>c</sup> 10 mol % Cu(OTf)<sub>2</sub>

d 40 mol % Cu(OTf)2.

<sup>e</sup> Bold indicated the optimal reaction condition.

provide any significant hydration on phenyl acetylene. Then, we optimized different equivalent of Cu(OTf)<sub>2</sub> for catalytic activity and find out that the 10 mol% of Cu(OTf)<sub>2</sub> requires longer time for completion of reaction while 40 mol% requires shorter reaction time with comparatively low yield. 20 mol % was found to be best optimal conditions with excellent yield. Moreover, hydration reaction did not take place in the absence of catalyst, which showed the presence of some catalyst is essential to move the reaction in forward direction. We have screened different solvents on feasibility of the reaction with this catalyst and find out that EtOAc is the most appropriate for catalysis, which gave 88% yield (Table 1, entry 8). 1,2-Dichloroethane is the next good solvent, which gave the product in 56% yield (Table 1, entry 11) while in EtOH reaction is slow and product was isolated in 15% even after 12 h, (Table 1, entry 12). Use of other common solvents such as toluene, MeCN, DMF, THF did not bring about any significant hydration product.

We have also explored the scope of reaction with electron donating or withdrawing group on aromatic alkyne to insight the effect on catalytic activity. To our delight, we find out that electron rich aromatic alkyne accelerated the reaction and gave the corresponding aryl ketone in excellent yield with shorter reaction time (Table 2, entry 2-4) while presence of electron withdrawing groups on aromatic alkyne requires longer reaction time for the conversion to corresponding ketone in good yield (Table 2, entry 5). 3-Ethynylaniline (1f) as unprotected amine was hydrated in good yield while protected aniline (1g) took comparatively longer time for hydration (Table 2, entry 6-7). It should be noted halogenated aromatic alkynes were well tolerated under this catalytic system and took comparatively less time than ethyl 4-ethynylbenzoate (Table 2, entry 8–9). Additionally, polycyclic aromatic alkynes worked well and afforded the corresponding methyl ketone in excellent yields (Table 2, entry 10–13). Besides, heterocyclic aromatic alkyne (1n) performed hydration smoothly and corresponding product was isolated in good yield (Table 2, entry 14). Moreover, aliphatic alkyne underwent hydration smoothly and yielded the corresponding product in good yield (Table 2, entry 15).

We have also explored the scope of this catalytic system on internal alkyne, 1,2-diphenylacetylene (**1p**) requires longer time for

#### Table 2

Regioselective hydration on different alkyne with Cu(OTf)2<sup>a</sup>

	Cu(OTf) <sub>2</sub> , H <sub>2</sub> O, EtOAc				
		$R_1 R_2 - R_2$	► 100 °C	R1 2 R2	
-	Entry	Alkyne	Product	Time (h)	Yield (%) <sup>b</sup>
-	1	√H la		2	88
	2	—————————————————————————————————————		1	91
	3	MeO-	MeO-	0 	90
	4	H Id	2d		96
	5	EtOOC-	EtOOC	→O 12	84
	6	H <sub>2</sub> N If	H <sub>2</sub> N 2f	0 / 3	89
	7	NHCOOEt	NHCOO O 2g	Et 8	80
	8	CI Ih		5	86
	9	FH	F-2i	0 ⁄ 5 \	82
	10	H		2	94
	11	MeO Ik	MeO 2k		95
	12			2	93
	13	⟨н н	2m	<sup>O</sup> 2	96
	14		S 2n	2	84

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