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Metal/Catalyst/Reagent free hydration of alkynes up to gram scale under temperature and pressure controlled condition

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## **Graphical Abstract**





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## Metal/Catalyst/Reagent free hydration of alkynes up to gram scale under temperature and pressure controlled condition

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## ARTICLE INFO

## ABSTRACT

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Keywords: Metal-free Autoclave Alkynes Hydration Ketone A new green water-mediated metal/catalyst/reagent-free methodology for hydration of alkyne is devised. The remarkable yields of various ketones were achieved when alkynes were heated at 150 °C under 11 bar pressure in an autoclave for 14 hr in water-methanol solution. Outstanding functional group compatibility for both the terminal and internal alkynes was established. This methodology produces excellent yields up to gram scale under optimised reaction condition.

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### Introduction

Increasing the amount of product with minimising the role of catalyst and raw material is one of the critical aspects among the 12 principles of green chemistry.<sup>1</sup> There were many reports available that demonstrate the applications of green and sustainable methodologies for laboratory and industrial productions. Practising various inexpensive and environmentally benign reaction methodologies have unveiled a new era in the field of chemistry.<sup>2</sup> Optimizing reaction conditions to accomplish without any chemical activation, i.e. without using chemical reagents or catalyst to perform chemical changes; this phenomenon is interesting as well as significantly crucial from commercial and economic perspective. Reordering the physical parameters (temperature and pressure) associated with the reaction may lead to new insights in catalyst-free organic transformation. The use of autoclave technique for hydrogenation<sup>3</sup>, hydration<sup>4</sup> and various other reactions is quite common. Moreover, these methodologies outstandingly reduce the cost and formation of undesired by-products and chemical waste in the reaction.

The Wacker oxidation of alkenes and metal mediated carbonylation of alkynes is extensively used to generate the carbonyl compounds including the ketones, esters, lactone, and melamide.<sup>4,5</sup> The hydration of alkynes had developed a paramount interest worldwide among various research groups, and it is a well-established and more advanced method for the production of ketones. Due to their diversified applications, ketones are the linchpins for various organic syntheses. Moreover, they also serve as versatile intermediates in a wide range of chemical syntheses such as natural products, drugs and other valuable industrial products.<sup>6</sup> The vast diversity of alkyne

substrates are a precursor for hydration reactions, and the applications of obtained carbonyls in organic syntheses<sup>7</sup> is an essential aspect of traditional synthetic chemistry. Transition metals and other metal complexes are extensively used for hydration reactions. Before 1980's mercury compounds such as  $Hg(OTf)_{2,}^{8a}$  HgSO<sub>4</sub>, <sup>8b</sup> and Hg(OAc)<sub>2</sub><sup>8c</sup> were utilised for hydration reactions. While due to the toxicity and hazards to the environment; search for the green, and the economic catalyst is undergoing from many years. There is surplus literature congregated in last two decades representing alkyne hydrations from a variety of transition metals such as Pd<sup>9</sup>, Pt<sup>10</sup>, Rh<sup>11</sup>, Ru<sup>12</sup>,  $Au^{13}$ . However, these metal catalysts are rare and not economically viable. Although some economical alternatives of metal catalyst such as Ag<sup>14</sup>, Fe<sup>15</sup>, Co<sup>16</sup>, Sn and W mix-oxides<sup>17</sup> also been reported in recent past. In some recent reports, acid catalyzed<sup>18</sup> and *para*-methoxybenzenetellurinic acid anhydride<sup>19</sup> indicates that alkyne hydration can be done by metal-free conditions. However, most of the reactions have suffered from at least one or more following drawbacks: (i) Use expensive transition metals (Ru, Rh, Pd, Pt, Au, Ir, Ag) predominantly the recovery and reusability of catalysts and the indispensable use of acid co-catalysts, additives, and promoter; (ii) High price and the light sensitivity of silver salts; (iii) Narrow functional group compatibility; (iv) Large excess of acidic additive besides the metal complexes if any.

In the year 2004, Vasudevan and co-workers<sup>20</sup> reported a catalyst-free methodology which exclusively works for terminal alkynes. The alkynes in superheated water were heated at 200 °C in a microwave reactor for 20 minutes to produces the ketones. Although the catalyst-free alkyne hydration was reported for the first time, but, due to the harsh reaction conditions, the high

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#### Tetrahedron

temperature, unknown pressure, cannot be implemented for large scale synthesis etc. Moreover, this method was not worked for internal alkynes. All these shortfalls made this method inappropriate for the metal-free bulk synthesis of ketones.

### Earlier Methodologies



Metal Catalyst or Acid Catalyst: Au, Pd, Pt, Rh, Ru or CF<sub>3</sub>SO<sub>3</sub>H

#### In Recent Past



The Present Work

$$R$$
 +  $H_2O$  Temperature, Pressure  $O$ 

#### Reaction carried out in Autoclave, without any catalyst

Herein, we investigated a catalyst-free methodology for hydration of terminal and internal alkyne without using any metal or acid catalyst. The present reaction is carried out in an autoclave at high temperature and pressure. Apart from the reactants, the present methodology needs only water/methanol mixture as solvent. The present method has excellent functional group compatibility and also works for both the terminal and internal alkynes and do not produce any unwanted by-product.

#### **Result and discussion**

To follow the principles of green chemistry, we were interested in developing a metal-free reaction method for hydration of alkynes. Phenylacetylene was chosen as a model substrate for all the optimisation. After some reactions under different conditions with no results, our series of the trail is interrupted by a trace product obtained in a reaction carried out in an autoclave. Desired product acetophenone was obtained through a reaction of phenylacetylene in an autoclave at 150 °C and 11 bar of argon gas pressure in 14 hr. Here, methanol was used as a solvent in the reaction. Scheme 1 represents the parameters where the desired alkyne hydration product was obtained. (Table 1, entry 9)



Scheme 1: Temperature and pressure controlled the formation of ketones

In the reaction, the inert gas pressure plays an important role. During the pressure optimisation, it was found that product yield was proportionally increased with continuously increasing pressure from 0 to 11 bar (table 1, entry 1-6). Pressure below 9 bar does not initiate the reaction, while a small quantity of product was obtained at 9 bar pressure of inert gas. Increasing the pressure up to 11 bar increases the product yield. However, the further increase in pressure does not produce any change in the yield (Table 1, entry 7-9). We investigated argon, nitrogen and  $CO_2$  gas for to generate the desired pressure but irrespective of the nature of gas the product formation was consistent and hardly brings any changes in the yield of transformed product. Since, the

phenylacetylene is a volatile and low boiling liquid, at low pressure and high temperature; it vaporizes, and in the gaseous phase, it is quite rare to react with the liquid water present in the solvent mixture. While in present reaction conditions, the moderate pressure and high temperature restricted the vaporization of alkynes which make unable to convert it in its vapor form, hence, it can undergo a hydration reaction. In our opinion, it could be the best possible effect of pressure on to the reaction. The optimised value of pressure for to get the highest yield of desired product is 11 bar, while the higher pressure of inert gas does not affect the product yield and supports our proposed hypothesis. Another reason for this reaction may be the higher ionisation of water molecules at higher pressure. In the earlier reports related to the studies of ionisation of water at various pressure and temperatures<sup>21</sup> suggested that ionisation of water molecules increases at higher pressure and the ionization of water increases with the increasing temperature. Here, both the facts again support the present hypothesis of the high yield of hydrated product at a relatively high temperature and moderate to high pressure.

Using water as a solvent reaction does not undergo any transformation. (Table 1, entry 10). Hence, a mixture of water and methanol was used as a solvent. Gratifyingly, the 1:1 ratio of water and methanol as solvent enormously increases the yield of desired product (table 1, entry 11). The presence of methanol in reaction mixture enhances the solubility of the acetylenes in water. Moreover, it also help in the ionisation of water which directly favours the hydration reactions.<sup>22a,22b</sup> As it is reported earlier that ionisation in water can be increased by increasing temperature, pressure or both and by adding alcohols.<sup>22c</sup> Also by increasing these parameters viscosity and surface tension of water decreases and dielectric constant increases which improves the solubility of organic compounds in water.<sup>22d</sup> Decreasing the amount of water in solvent mixture produces the moderate product yield (Table 1, entry 12). Inversely, the increasing the amount of water in the solvent mixture improves the product yield and the maximum recorded yield of 79% was obtained with 1:2 ratio of methanol and water (Table 1, entry 13). Use of other alcohols, ethanol, isopropyl alcohol and tert-butanol showed a substantial decrease in the yield.

Further optimisation of temperature and time was carried out. Temperature up to 110 °C does not produce even a trace of desired product. Increasing the temperature to 120 °C a low yield of the phenylacetylene obtained. Amount of product was consistently increased with increasing the temperature up to 150 °C (Table 1, entry 14-17), furthermore increase of temperature up to 180 °C does not show any changes in the yield of product (Table 1, entry 18-20). Duration of reaction up to 14 hr or more produces a consistent yield (Table 1, entry 21-25), while the least 4-8 hr reaction produces below to average yield. However, it further increases up to 14 hr and then become consistent (Table 1, entry 26-28).

Present methodology was also found compatible with wide variety functionalities. The substrate scope of this reaction is represented in Table 2. Phenyl acetylenes substituted with electron-donating or withdrawing groups produces excellent yield of their corresponding methyl ketones. Besides the phenyl acetylene, other aromatic alkynes (both terminal and internal), including the functional groups like fluoro, chloro, bromo, amino, alkyl, alkoxy also proceed hydration and affords excellent yields. The ferrocenyl acetylene yield acetylferrocene in 83% (Table 2, entries 2). *ortho-, meta-* and *para-* methyl-phenyl acetylene reacted smoothly, forming the corresponding methyl ketones in 84 %, 82 % and 83 % respectively (Table 2, entries 3-5). Halo-substituted phenyl acetylenes such as 4-fluoro-, 4-

chloro-, 4-bromo and 2-chlorophenyl acetylene yielded 78 %, 76 %, 73 % and 72 % respectively (Table 2, entries 6-9). ortho- and para- methoxyphenylacetylene gave the corresponding products in 84 % and 83 % yield (Table 2, entries 10, 11). 4ethylphenylacetylene reacted easily and formed the corresponding ketones in 85% yields (Table 2, entries 12). The 4tert-butylphenylacetylene gave the corresponding ketones in 89 % (Table 2, entries 13); while the 3-aminophenylacetylene yielded 80 % of the hydrated product (Table 2, entries 14).

Table 1	Optimization of react	ion	parameters	with
	phenylacetyl	ene		

$\bigwedge$	//	Autoclave		► (			
	140°C, 14hr, Argon 11 bar						
	1	Vethanol : water (	1:2)		$\checkmark$		
	٨٣						
Entry	Pressure	Solvent Ratio	Temp	Time	Yield <sup>a</sup>		
-	(Bar)	(MeOH: Water)	(C)	(h)	(%)		
1.	00	1:2	150	14	nd		
2.	9.0	1:2	150	14	23		
3.	9.5	1:2	150	14	34		
4.	10.0	1:2	150	14	45		
5.	10.5	1:2	150	14	60		
6.	11.0	1:2	150	14	79		
7.	11.5	1:2	150	14	79		
8.	12.0	1:2	150	14	79		
9.	11.0	1:0	150	14	Trace		
10.	11.5	0:1	150	14	nd		
11.	12.0	1:1	150	14	69		
12.	11.0	2:1	150	14	45		
13.	11.0	1:2	150	14	79		
14.	11.0	1:2	120	14	20		
15.	11.0	1:2	130	14	50		
16.	11.0	1:2	140	14	60		
17.	11.0	1:2	150	14	79		
18.	11.0	1:2	160	14	79		
19.	11.0	1:2	170	14	79		
20.	11.0	1:2	180	14	79		
21.	11.0	1:2	150	4	nd		
22.	11.0	1:2	150	8	23		
23.	11.0	1:2	150	10	43		
24.	11.0	1:2	150	12	67		
25.	11.0	1:2	150	14	79		
26.	11.0	1:2	150	16	79		
27.	11.0	1:2	150	18	79		
28.	11.0	1:2	150	20	79		

Condition: Solvent MeOH: Water (1:2), Temperature 150 °C, 11.0 bar argon, 14 hr, <sup>a</sup>Isolated yield, nd = not detected

The reaction was further extended to the internal alkynes with maintaining the similar reaction parameters, a significant transformation of 78 % was obtained with the symmetrical diphenyl acetylene while 80 % yield of the hydrated product was recorded with the unsymmetrical 1-methvl-4-(phenylethynyl)benzene respectively (Table 2, entries 15 and 16). Here, hydration of both the symmetrical and unsymmetrical diarylacetylene regioselectively forms only one product and the formation of carbonyl group is preferred at the position where carbonyl is conjugated with a substituted phenyl group.<sup>23</sup>

Table 2 Substrate scope of hydration reaction in an autoclave





Condition: Solvent MeOH: Water (1:2), Temperature 150 °C, 11.0 bar argon, 14 hr, <sup>a</sup> isolated yield

To address the issue of scalability of the method which was the limitation of the previous approach,<sup>20</sup> in the present method 1 gm of phenyl acetylene was considered for the reaction with adopting the optimised reaction parameters after the completion of the reaction, a 70% of acetophenone was isolated. This indicates the present method can be utilized for the bulk production in relevant industries.

#### Conclusion

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In this note, we had devised a new metal/catalyst/reagent-free methodology for hydration of alkynes at possible reaction conditions. Transformation of acetylene to ketone was entirely controlled by tuning the temperature and pressure of the reaction. The reaction shows excellent functional group compatibility and works smoothly for aryl containing either electron donating or withdrawing functional groups. Moreover, significant yield of the product was also obtained irrespective the position of functional group attached with benzene. Hence, reaction indicates the robustness nature towards all possible alkynes. Apart from alkynes present method need the only mixture of water and methanol as solvent and does not form any by-product. This method offers high atom economy and successfully implemented for the bulk synthesis of ketone in fine chemical industries.

### The general procedure of the reaction

In a 100 mL capacity of autoclave vessel a 60 mL solution of methanol and water (1:2) was added, further 1mmol alkynes were added to this solution. The autoclave was three times purged with the gas and then finally pressurized up to the 11 bar pressure. The reaction mixture was vigorously stirred at 150 °C for continuous 14 hr. After the completion of the reaction, the reactor was cooled to room temperature, and then the argon pressure was carefully released to the atmospheric pressure. Methanol from the reaction mixture is removed using rotatory evaporator. After that, the reaction mixture was transferred in a separating funnel, and it was worked up with ethyl acetate. The organic layer was separated and dried over Na<sub>2</sub>SO<sub>4</sub>. Afterwards, it was filtered and concentrated under reduced pressure. The resulted crude mixture was purified by silica gel column chromatography using ethyl acetate/n-hexane as eluent, and pure keto product was isolated.

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### **IUSCRIPT** ACCEPTED

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## Highlights

- Autoclave assisted metal/reagent/catalyst ٠ free hydration of terminal and internal alkynes.
- Acctiontic

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