Neutral, Metal-free Hydration of Alkynes Using Microwave Irradiation in Superheated Water

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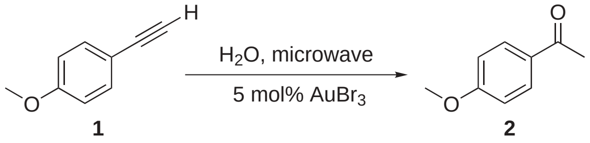
Abstract: A novel methodology for the hydration of alkynes in superheated water using microwave irradiation is reported. Extension of this methodology to hydroamination of alkynes is also described.

Key words: microwave, alkynes, hydration, superheated water

Hydration of alkynes is one of the most useful and convenient transformations to form ketones, and a variety of catalysts have been extensively investigated for this process.[1] Typically, mercury salts are utilized, which sometimes also require the use of strongly acidic conditions.[2] The use of Pd(II), Pt(II) and Cu(II) salts in conjunction with non-coordinating solvents represents an attractive alternative.[3] Recently, the use of Au(I) has been reported to be very effective in the hydration of alkynes and impressive turnover frequency numbers have been reported.[4] Furthermore, metal-free conversion of alkynes to ketones catalyzed by trifluoromethyl sulfonic acid or trifluoromethylsulfonimide have also been reported, though the reaction times tend to be quite long.[5] Recently, a report on the use of Pt(II) complexes in the conversion of alkynes to ketones in water has been reported.[6]

Since the early work of Gedye and Giguere[7] citing the significant improvements in reaction rate using microwave irradiation, there has been a great interest in the application of this technique to a range of synthetic transformations. The technology has evolved in the past decade to allow for safe, rapid and reproducible heating of aqueous and organic solvents to temperatures significantly higher than their boiling point in a controlled manner with suitable safety features in place, followed by rapid quenching using compressed air or nitrogen.[8] Applications to transition metal-catalyzed reactions, heterocycle synthesis and a range of other transformations have been reported.[9] The significant improvements in time, yield and substrate scope of these reactions have been attributed primarily to a thermal effect.[10] Reactions performed using microwave-assisted synthesis in water afford a unique combination of the beneficial effects of significant enhancement in reaction rate along with the use of an environmentally benign solvent.[11] Additionally, water at elevated temperatures possesses remarkably different properties than at ambient temperature.[12] At 200 °C, its dielectric constant is similar to that of acetonitrile, and at temperatures approaching its critical point, water behaves as a pseudo-organic solvent, allowing for the dissolution of many organic substrates.[13] Advantageously, once cooled, the organic products are no longer soluble in ambient temperature water, and this allows for easy post-synthesis product separation.

We wish to report on our studies involving the conversion of alkynes to ketones using microwave irradiation in water. Our studies commenced with attempting to convert 4-ethynyl anisole to 4′-methoxy acetophenone in water using Au(III) as the catalyst, in the absence of acid. Heating a reaction mixture containing **1** and 5 mol% $AuBr_3$ in water at various reaction temperatures using microwave irradiation afforded interesting results (Table 1). There was a strong effect of increasing temperature on this transformation, and treating **1** with $AuBr_3$ in superheated (175 °C or 200 °C) water afforded quantitative conversion to the acetophenone **2**. The pH of the reaction mixture was found to be 6.1 at the end of the reaction, which is significant, given recent results[4] indicating that the hydration



Equation 1

Table 1 Effect of Temperature on Conversion of 4-Ethynyl Anisole to 4′-Methoxyacetophenone

Temperature	Catalyst	Conversion to **2** (%)[a]
125 °C	5 mol%	79
150 °C	5 mol%	99
175 °C	5 mol%	Quantitative
200 °C	5 mol%	Quantitative
200 °C	2 mol%	Quantitative
200 °C	0.5 mol%	Quantitative
200 °C	None	Quantitative[b]

[a] Reactions were irradiated for 20 min and conversion determined by ^1H NMR.
[b] See Figure 1.

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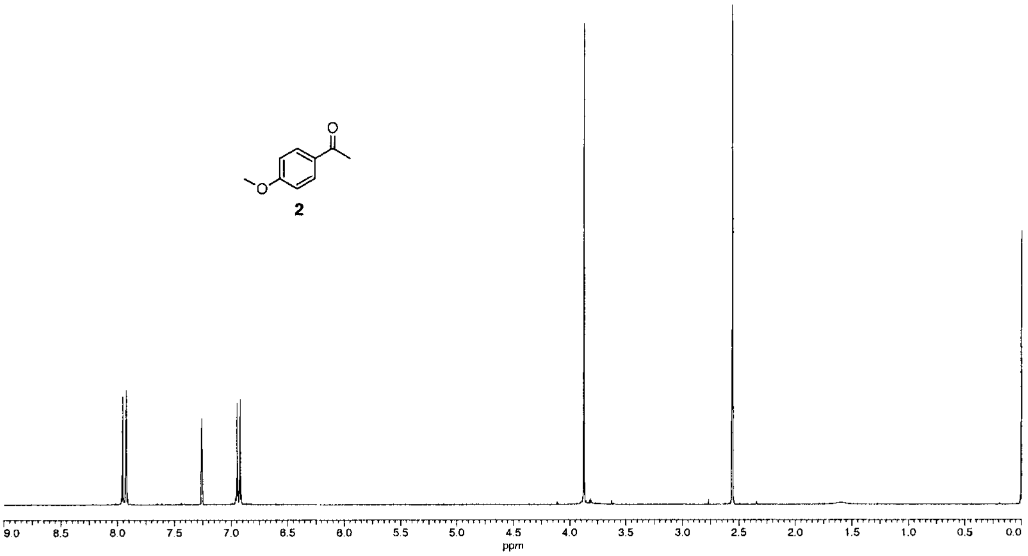


Figure 1 Crude ^1H NMR in $CDCl_3$ of the conversion of **1** to **2** in superheated water

of alkynes using Au(I) did not proceed in the absence of a strong acid such as H_2SO_4 or CF_3SO_3H. We next proceeded to study the effect of lower catalyst loadings on this transformation.

While catalyst loadings as low as 0.5 mol% were efficient in catalyzing the hydration, we were surprised to note that heating compound **1** in neat water in the absence of any Au(III) catalyst afforded a quantitative conversion to the corresponding acetophenone (Figure 1).

This represents a unique method for the hydration of alkynes in which neither the use of Hg(II), other metal salts nor strong acid is essential.[14] Further, the reaction is completed within 20 minutes, making it a rapid and practical manner to synthesize ketones from alkynes.

We then proceeded to explore the scope of the reaction by varying the position and substituents on the phenyl ring (Table 2). In general, electron-donating substituents on the phenyl ring promoted the hydration of the alkyne, even in the absence of $AuBr_3$. Electron-withdrawing substituents tend to hydrate sluggishly in the 20 minute reaction time, but addition of 2 mol% $AuBr_3$ results in >30% conversion. The improved hydration of alkynes in the presence of Au salts follows the trend observed by Tanaka et al.[4] However, it must be noted that no acid was required for the microwave-promoted hydrations reported in this study. In order to discount the possible catalytic role of trace metals in the water being used as the solvent, **1** was heated in triply pure water (<0.1 ppm metal content) at 200 °C for 20 minutes to afford 94% conversion to **2**.

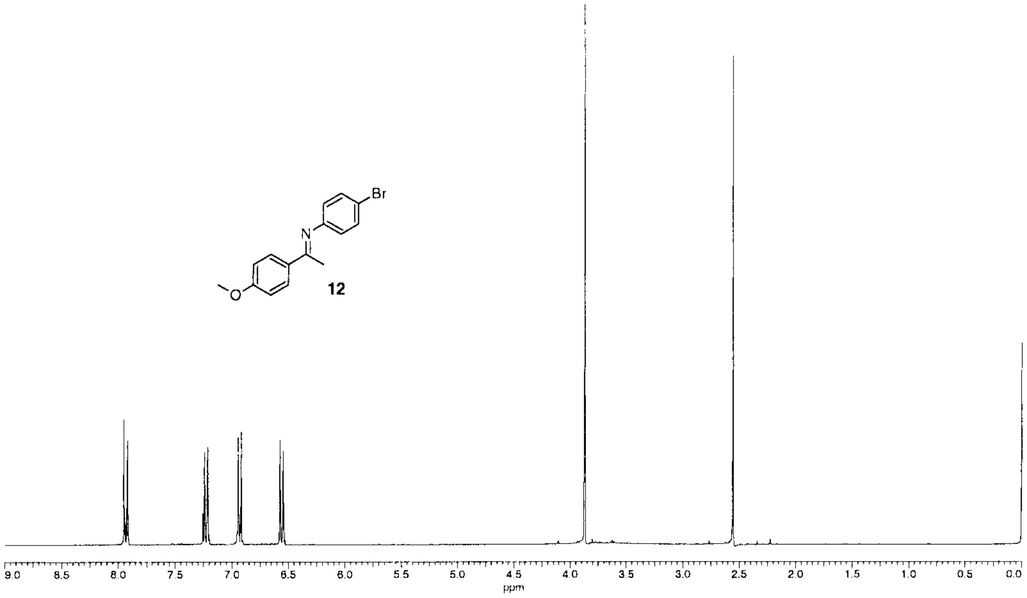


Figure 2 Crude ^1H NMR in $CDCl_3$ of the conversion of **1** to **12** in superheated water, containing 4-bromoaniline

Aliphatic alkynes did not afford any of the desired products either in the absence or presence of $AuBr_3$, possibly due to decomposition at the elevated temperature required for this transformation.

Katritzky and Siskin[15] have reported the formation of acetophenone by heating phenyl acetylene in water at 250 °C for 5 days, although significant amounts of napthalenes and biphenyl compounds were obtained. No other side products were observed in the current study, indicating that the use of microwave-assisted synthesis not only results in significantly shorter reaction times, but higher yields and cleaner products as well.

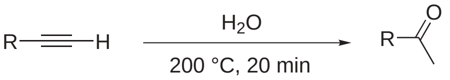
As a control experiment, **1** was heated in water maintained at 200 °C in an oil-bath for up to 30 minutes in a sealed tube, with and without Au(III), the results of which are shown in Table 2. Comparison of the results obtained without Au(III) using microwave irradiation and convection heating are striking; convection heating typically results in the formation of thermal gradients with only part of the sample being heated at the desired temperature despite vigorous stirring, microwave irradiation in a single-mode cavity results in volumetric heating, it is difficult to attribute the superior conversion obtained using microwave irradiation to non-thermal effects.

Given the facile conversion of **1** to ketone **2** at an elevated temperature in the absence of a metal catalyst within 20 minutes, we sought to extend this methodology to effect a one-pot conversion of alkynes to imines, a conversion traditionally achieved via hydroamination. Intermolecular hydroamination of alkynes to form imines has been a much sought after transformation and several catalytic variants of this process have recently been reported. Most of these involve the use of metals such as Zr, Ti, Rh, Pd, etc.[16] Despite these advances, the yield, catalytic efficiency and procedural simplicity are still unsatisfactory for practical implementation, and the development of new catalytic systems continues to be an active area of research.

Heating a mixture of **1** and 4-bromo aniline in water at 200 °C for 20 minutes in a microwave, afforded the ketimine **12** in 87% yield (Figure 2). A similar profile was observed when the reaction was performed in the presence of $AuBr_3$. These results provide a convenient access to products achieved traditionally under harsh hydroamination conditions using convection heating.[17]

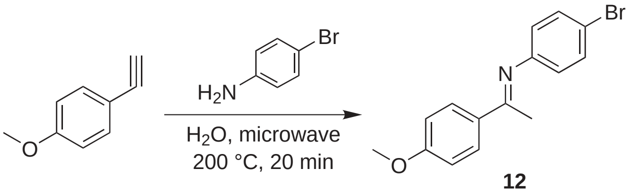
In conclusion, a novel method for the hydration and hydroamination of alkynes using superheated water is reported. Since the metal-catalyzed hydrations and hydroaminations invoke coordination to the alkynes prior to nucleophilic attack, at this time, the mechanism of this observation remains unclear. An increase in the dissociation constant of water by **3** orders of magnitude at temperatures at or greater than 200 °C[18] allows it to act as an acid, base or acid-base bi-catalyst, and sufficiently high H^+ concentrations to catalyze the dehydration of alcohols to alkenes in the absence of acid in supercritical water have been reported.[10] In the current study, pH measure-

Table 2 Hydration of Aryl Ketones in Superheated Water



No.	R	Method[a]	Yield (%)
1	4-OCH_3 phenyl	A	94
	4-OCH_3 phenyl	B	96
3	2-OCH_3 phenyl	A	100
	2-OCH_3 phenyl	B	100
4	4-NH_2 phenyl	A	96
	4-NH_2 phenyl	B	100
5	Phenyl	A	75
	Phenyl	B	91
6	3-OH phenyl	A	12
	3-OH phenyl	B	100
7	4-OCH_2CH_3 phenyl	A	27
	4-OCH_2CH_3 phenyl	B	90
8	3-NH_2 phenyl	A	90
	3-NH_2 phenyl	B	90
9	4-Cl phenyl	A	20
	4-Cl phenyl	B	33
10	4-CH_3 phenyl	A	98
	4-CH_3 phenyl	B	100
11	4-Br phenyl	A	0
	4-Br phenyl	B	30
12	4-OCH_3 phenyl	C	< 5
	4-OCH_3 phenyl	D	60

[a] Method A: substrate + water, microwave heating; Method B: substrate + water + 2 mol% $AuBr_3$, microwave heating; Method C: substrate + water, convection heating; Method D: substrate + water + 2 mol% $AuBr_3$, convection heating.



12

Equation 2

ments before and after the reactions were completed (7.1 and 6.0 respectively) did not indicate a significant increase in acidity at the end of the reaction, though pH measurements during the reaction were precluded due to safety reasons. In the context of results observed in this study, it is also not possible to discount localized acidity at the interface of the glass vessels and the reaction medium. Studies are underway to elucidate the mechanism and expand the scope of hydrations, which can be performed in superheated water.[19]

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(19) (a) **Typical Procedure for the Hydration of Alkynes**: A suspension of the alkyne in a mixture of the alkyne (0.1 mol) and 3 mL water in a sealed reaction vial was heated at 200 °C in an Emrys® synthesizer for 20 min, following which the sample was cooled using compressed air. The product usually separated from the water on standing or could be extracted using 3 mL diethyl ether to afford the desired ketones in yields described in Table 2, which demonstrated purity and analytical data consistent with commercial products. (b) **Typical Procedure for the Hydroamination of Alkynes**: A mixture of the alkyne (0.87 mmol), amine (0.87 mmol) and water (3 mL) in a sealed reaction vial was heated at 200 °C in an Emrys® synthesizer for 20 min, following which the sample was cooled using compressed air. The product was extracted using diethyl ether (3 mL) to afford 0.23 g of **12** (ref. 17).