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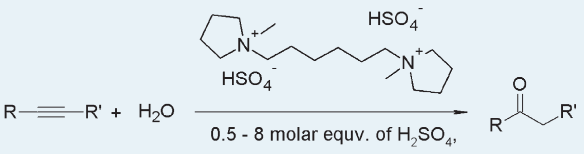
Sulfuric Acid-Catalyzed Conversion of Alkynes to Ketones in an Ionic Liquid Medium under Mild Reaction Conditions

Wing-Leung Wong, Kam-Piu Ho, Lawrence Yoon Suk Lee, Kin-Ming Lam, Zhong-Yuan Zhou,
Tak Hang Chan, and Kwok-Yin Wong*

Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon,
Hong Kong SAR, China

S Supporting Information

ABSTRACT: An efficient and recyclable ionic liquid system containing a small amount of sulfuric acid as the catalyst (0.5−8.0 mol equiv to substrate) has been successfully developed for hydration of various alkynes under mild reaction conditions (40 °C, 0.5 h) to give high yields of ketones (88−100%) as products. The system does not involve heavy metal catalysts or concentrated acids and is simple and easy to prepare and exhibits excellent catalytic activity and isolated yield toward the hydration of alkynes to ketones. The efficiency of the system is attributed to the high chemical activity of protons in the ionic liquid medium.



Rapid hydration of terminal and internal alkynes to ketones with 88 - 100 % yields

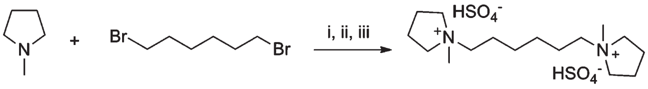
KEYWORDS: ionic liquids, homogeneous catalysis, hydration, alkynes, ketones

Hydration of alkynes to carbonyl compounds is one of the most important and fundamental functional group transformations.[1−3] The reaction involves the simple addition of a water molecule to the alkyne with 100% atom efficiency and is regarded as a convenient and efficient method for the production of ketones and aldehydes.[2,3] The traditional method (Berthelot's alkyne hydration) employs a stoichiometric amount of mercury salt as the catalyst under acidic conditions.[4−9] Although this process allows very good yields, pollution problems associated with the handling and disposal of toxic mercury compounds limited its use for wide applications and large scale synthesis.

Research on alkyne hydration is still growing because there are great demands for a more effective, practical, and environmentally friendly methodology.[10−13] Over the past several decades, alternative metal complexes, such as those of Ru(III),[14,15] Ru(II),[16−19] Os(II),[20] Rh(III),[21,22] Ir(III),[23,24] Pd(II),[25] Pt(II),[26,27] Au(III),[28−34] and Fe(III),[35,36] have proved to be useful in alkyne hydration catalysis. In addition, concentrated sulfuric acid is known to promote the alkyne hydration process. However, a large excess amount of sulfuric acid (>1500 equivalents to the alkyne substrate) is required.[37] Other organic acids, such as trifluoromethanesulfonic acid[38] (10−20 mol %) and *p*-toluenesulfonic acid[39] (20 mol %) are also active for alkyne hydration in organic solvents under high temperature (100 °C) and long reaction time (18−48 h) conditions.

In recent years, sustainable chemistry, particularly its applications in organic synthesis and catalysis, has become an important research topic. We are interested in the development of simple and robust ionic liquids as both the reaction medium and catalyst/cocatalyst for organic transformations under mild processing conditions.[40−42] There are a lot of advantages of using ionic liquids for organic synthesis.[43] For example, ionic liquids are nonvolatile and recyclable and possess tunable polarity and miscibility with various organic and inorganic compounds. Most interestingly, ionic liquids can be made task-specific (e.g., as catalysts) through molecular design.[44] Although it has been reported that some Brønsted acids behave as superacids in ionic liquids,[45,46] reports on the application of this high chemical activity of protons in organic transformations are limited.[47,48] Herein, we report a new ionic liquid catalytic system containing a small amount of H_2SO_4 for the rapid hydration of alkynes to ketones under metal-free and very mild reaction conditions.

Scheme 1. Synthetic Route to Ionic Liquid $\mathbf{1\cdot(HSO_4)_2}$[a]



$\mathbf{1\cdot(HSO_4)_2}$

[a] (i) Reflux in acetonitrile to give $\mathbf{1\cdot(Br)_2}$; (ii) removal of the bromide anions by Ag_2O in water at room temperature to give $\mathbf{1\cdot(OH)_2}$; (iii) neutralization of $\mathbf{1\cdot(OH)_2}$ with H_2SO_4 in water to give $\mathbf{1\cdot(HSO_4)_2}$.

The ionic liquid shown in Scheme 1 was prepared in 10-g quantity via simple synthetic procedures from inexpensive and commercially available starting materials (for detailed synthetic procedures and characterizations, see the Supporting Information). The ionic liquid $\mathbf{1\cdot(HSO_4)_2}$ is a hygroscopic solid at room temperature and readily jellifies upon the absorption of moisture from air. The X-ray structure of $\mathbf{1\cdot(HSO_4)_2}$ further

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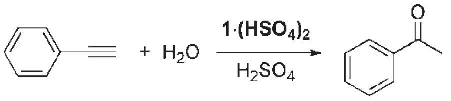
Table 1. Hydration of Phenylacetylene in Ionic Liquid[a]



entry	PhCCH (mmol)	H_2SO_4 (mmol)	time (h)	temp (°C)	yield (%)[b]
1	6.0	3.0	5.0	60	94
2	6.0	3.0	2.0	80	99
3	1.0	3.5	0.5	40	15
4	1.0	5.0	0.5	40	64
5	1.0	7.0	0.5	40	92
6	1.0	8.0	0.5	40	100
7	3.0	8.0	1.0	40	100
8	6.0	8.0	2.0	40	98[c]
9[d]	25	32	1.0	40	98[c]
10[d]	70	32	2.0	40	89[e]

[a] Reaction conditions: 7 mmol of **1·$(HSO_4)_2$**, 2 mol equiv of DI water with respect to PhCCH. [b] Conversion of PhCCH determined by gas chromatography with tetradecane as internal standard. [c] Isolated yield. [d] Larger-scale process: 28 mmol of **1·$(HSO_4)_2$** was used. [e] Isolated yield by vacuum distillation after complete conversion.

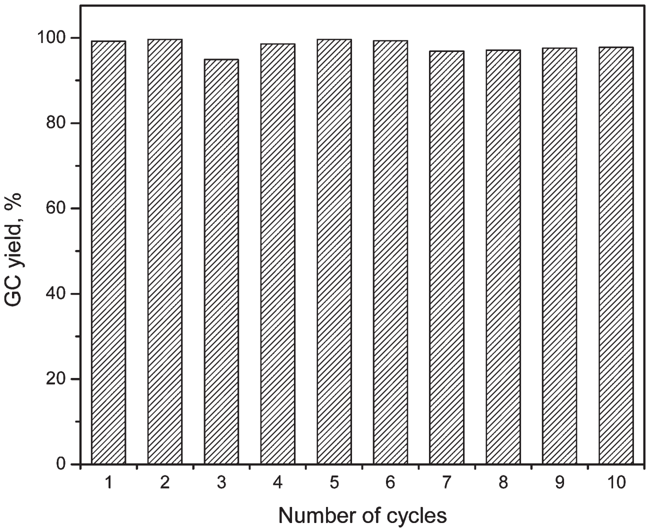


Figure 1. Recycling study of the **1·$(HSO_4)_2$**−H_2SO_4 system for hydration of phenylacetylene. Reaction conditions: 7 mmol of **1·$(HSO_4)_2$**, 3.5 mmol of H_2SO_4, 1 mmol of PhCCH, 2 mmol of D.I. water, 40 °C, 0.5 h. To the recycled **1·$(HSO_4)_2$**−H_2SO_4, only phenylacetylene (1 mmol) and H_2O (2 mmol) were added, and the next cycle was carried out under the same conditions.

confirms that the positively charged pyrrolidinium units are balanced with two hydrogen sulfate (**HSO_4^-**) counterions.[49]

In the initial investigation, phenylacetylene (PhCCH) was selected as a model substrate for alkyne hydration catalysis with **1·$(HSO_4)_2$** as the reaction medium in the absence of Brønsted acid at 40 °C. No hydration of PhCCH was observed, and the substrate was recovered 100% by extraction after 30 min. Adding a small amount of H_2SO_4 (0.5 mol equiv to substrate) to the ionic liquid medium, however, led to the slow conversion of PhCCH to acetophenone at 60 °C (94% yield after 5 h, Table 1, entry 1). Increasing the reaction temperature from 60 to 80 °C would shorten the reaction time to 2 h and further improve the yield of acetophenone to 99% (Table 1, entry 2). To allow the system to work under milder reaction conditions (such as lower temperature and shorter reaction time), the amount of H_2SO_4 added to the medium was adjusted gradually. Table 1 summarizes the results of PhCCH hydration in **1·$(HSO_4)_2$** with various amounts of sulfuric acid added to the system. In general, the conversion of PhCCH to acetophenone was enhanced dramatically (entries 3−6) as the concentration of sulfuric acid was increased. The complete conversion of PhCCH to acetophenone with 100% selectivity was achieved within 30 min at 40 °C when 8 mol equiv of sulfuric acid was used (Table 1, entry 6). These results are one of the best among the reported systems for hydration of PhCCH without a transition metal catalyst under such mild reaction conditions.

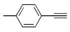
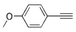
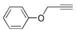
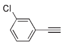
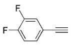
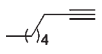
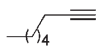
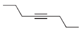
The reactivity of the ionic liquid system for larger-scale synthesis was also explored. The reactions with 3 and 6 mmol of PhCCH produced excellent isolated yields (>98%) within 2 h (Table 1, entries 7 and 8). In the case of 25 mmol scale reaction, the conversion was completed within 1 h, and 98% of isolated yield was obtained. Even with a further increased amount of substrate (70 mmol, 7.2 g), the hydration process proceeded smoothly, and complete conversion was achieved: the product acetophenone was isolated in 89% yield (7.5 g) by vacuum distillation (Table 1, entry 10). These excellent results show the promise of the **1·$(HSO_4)_2$** system for large scale synthesis under mild reaction conditions and its potential practical application in the process of terminal alkyne hydration.

To demonstrate the robustness and durability of the **1·$(HSO_4)_2$** system, both the ionic liquid medium and H_2SO_4 were recycled 10 times for the catalysis. At the end of each cycle, the reaction product was extracted for the determination of yield by gas chromatography. Only PhCCH (1 mmol) and H_2O (2 mmol) were freshly added for the next cycle. Throughout all the reaction cycles, comparable yields (on average 96%) were observed, as shown in Figure 1. These results strongly suggest that the **1·$(HSO_4)_2$**−H_2SO_4 system is a robust and recyclable system that can constantly promote the transformation of terminal alkyne to ketone without losing its catalytic reactivity.

The hydration of other alkynes by **1·$(HSO_4)_2$**−H_2SO_4 was also investigated, and the results are summarized in Table 2. The ionic liquid system shows excellent reactivity toward the electron-rich alkynes. The alkynes (Table 2, entries 1−4) were completely transformed into their corresponding ketones within 0.5 h at 40 °C. With a relatively electron-deficient terminal alkynes, such as 3,4-difluorophenylacetylene, however, only 88% conversion was obtained under the same reaction conditions (Table 2, entry 5). The hydration of a long-chain aliphatic terminal alkyne, 1-octyne, was also investigated. It seems that the poor solubility of the nonpolar alkyne in ionic liquid medium significantly reduced the productivity, affording only 66% yield of hydrated product. The solubility was improved by raising the reaction temperature from 40 to 60 °C, which led to complete conversion within 1 h. Similar results were also observed in the hydration of aliphatic internal alkynes, such as 4-octyne. The production of 4-octanone from 4-octyne was improved from 72% to 100% by raising the reaction temperature to 60 °C under the same conditions (Table 2, entry 8). These results reveal that both aliphatic terminal and internal alkynes can be transformed into ketones effectively in the **1·$(HSO_4)_2$**−H_2SO_4 system.

The reaction mechanism of acid-catalyzed alkyne hydration is generally believed to proceed via the rate-limiting protonation of

Table 2. Rapid Hydration of Other Alkynes in Ionic Liquid Medium[a]

Entry	Alkynes	Temp (°C)	Time (h)	Yield[b] (%)
1		40	0.5	100
2		40	0.5	100
3		40	0.5	100
4		40	0.5	100
5		40	0.5	88
6		40	0.5	66
7		60	1.0	100
8		60	1.0	100

[a] Reaction conditions: 7 mmol of **1**·**(HSO$_4$)$_2$**, 8 mmol of H_2SO_4, 2 mmol of DI water and 1 mmol of alkyne; after extraction of product, the reaction medium of **1**·**(HSO$_4$)$_2$**—H_2SO_4 was recycled for the next experiment. [b] Conversion was determined by gas chromatography with tetradecane as internal standard.

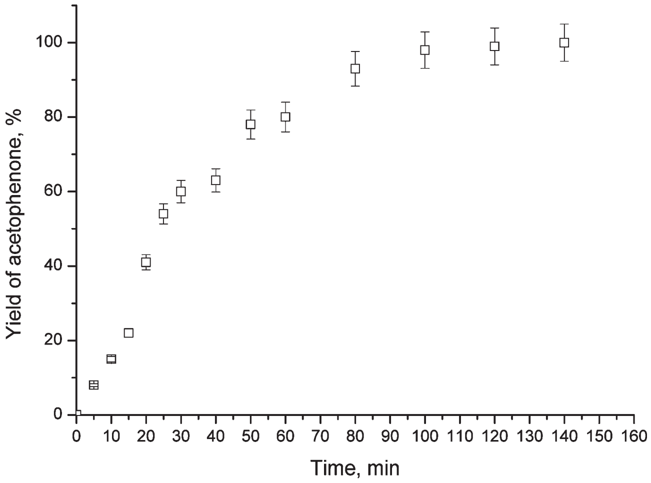


Figure 2. A kinetics study on the transformation of PhCCH to acetophenone at 80 °C (reaction conditions: 6.0 mmol of PhCCH, 3.0 mmol H_2SO_4, 18 mmol D.I. water, 3.1 g **1**·**(HSO$_4$)$_2$**; the yields of acetophenone were monitored by gas chromatography—mass spectrometry).

the carbon—carbon triple bond, followed by rapid addition of water to generate an enol, which gives ketone as the final product via keto—enol tautomerism.[37,50−52] The fact that only a small amount of acid is required in our system (as compared with the use of concentrated H_2SO_4 in aqueous medium[37]) implies high chemical activity of the protons in the ionic liquid. The chemical activity of protons in Brønsted acids is determined by the solvation of the protons and the anions of the acids: the weaker the solvation of protons and the stronger the solvation of anions, the higher the proton activity.[53] Although weak solvation of protons logically leads to their high chemical activity, strong solvation of anions provides a good energetic for proton dissociation.[53]

It has been reported that HCl in chloroaluminate melt[45] and $HNTf_2$ in [BMIM][NTf_2][46] (BMIM = 1-butyl-3-methylimidazolium, NTf_2 = $N(CF_3SO_2)_2$) behave as superacids. The superacidity can be attributed to the weak solvation of protons and strong solvation of anions by the ionic liquids. In our system, a small amount of water (a few molar equivalents to alkyne) is present as cosubstrate. Because water provides good solvation for protons, we expect an increase in the reaction rate as the water is consumed. Indeed, this can be observed in the conversion of PhCCH to acetophenone (Figure 2). The initial rate for the reaction is relatively slow compared with that measured after the first 15 min of the process. The observation can be interpreted as the increase in proton chemical activity caused by poorer solvation as water is consumed during the process.

In summary, an effective and recyclable protocol using a simple ionic liquid with a small amount of sulfuric acid for the transformation of various alkynes to ketones under mild conditions has been successfully developed. The system is easy to prepare and yet exhibits excellent reactivity and stability over multiple cycles. We also demonstrated that larger scale hydration of phenylacetylene could proceed smoothly with good yield and selectivity. The reaction products can be isolated in high yields by vacuum distillation, which makes the protocol more practical for industrial applications.

■ ASSOCIATED CONTENT

S Supporting Information. The X-ray crystal stryucture of **1**·**(HSO$_4$)$_2$**, ^{1}H and ^{13}C NMR, ESI-MS data, detailed synthetic procedures for the ionic liquid, and experimental procedures for catalysis. This material is available free of charge via the Internet at http://pubs.acs.org/.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: +852 2364 9932. E-mail: bckywong@polyu.edu.hk.

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(49) $\mathbf{1}\cdot(\mathbf{HSO_4})_2$ is a very hygroscopic solid at room temperature (mp = 184 °C) and completely liquefies in the presence of a small amount of H_2O. Detailed characterizations are provided in the Supporting Information.

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