



Iron-catalyzed indirect hydration of alkynes in presence of methanesulfonic acid [☆]



Jungmin Park ^a, Jihee Yeon ^a, Phil Ho Lee ^b, Kooyeon Lee ^{a,c,*}

^a Department of Bio-Health Technology, Kangwon National University, Chuncheon 200-701, Republic of Korea

^b Department of Chemistry, Kangwon National University, Chuncheon 200-701, Republic of Korea

^c Institute of Bioscience and Biotechnology, Kangwon National University, Chuncheon 200-701, Republic of Korea

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ABSTRACT

We have demonstrated that the $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and methanesulfonic acid systems show high reaction efficiency for the indirect hydration of various alkynes in DCE. The reaction proceeds under mild conditions to produce various ketones from alkynes. A mechanistic study of the reaction intermediates showed that the alkyne was readily converted into vinyl sulfonate corresponding to the addition of MsOH to the C–C triple bonds, which in turn was transformed to the ketone in the presence of MsOH .

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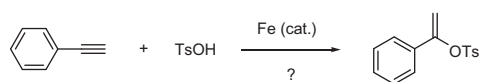
The transition-metal-catalyzed hydration of alkynes is one of the most straightforward methods for the synthesis of carbonyl compounds.¹ The addition of water to an alkyne has long been a well-known chemical transformation. In the last decade, this reaction has specifically attracted renewed interest with the development of atom-economical reactions.² This reaction was first reported by Berthelot in 1862, which was classically catalyzed by mercury(II) salts as a Lewis acid in aqueous sulfuric acid solution.³ However, this reaction has some disadvantages such as the necessity of using highly toxic mercury(II) salts and the strong acidic conditions. Therefore, alternative mercury(II)-free catalysts based on Au,⁴ Ru,⁵ Rh,⁶ Pt,⁷ and other metals⁸ have been developed for the hydration of alkynes. The stoichiometric hydration of an alkyne to methyl ketone is mediated by iron(III) chloride.^{9a} Recently, the first iron-catalyzed hydration of a terminal alkyne has been reported.^{9b} In this procedure, the best results were obtained for the hydration of phenylacetylene in the presence of FeCl_3 (10 mol %) and H_2O (3 equiv) in 1,2-dichloroethane (DCE). This catalyst despite its efficiency has some disadvantages such as prolonged reaction times (67 h) for attaining good yields (80%) and the generation of α -chlorostyrene as a by-product. Although, the direct hydration of alkynes catalyzed by triflimide iron(III) has

been reported,^{9c} this triflimide-based catalyst system was generated in situ by the reaction of FeCl_3 with 3AgNTf_2 . Furthermore, the *p*-toluenesulfonic acid-catalyzed hydration of alkyne was reported.¹⁰ In this reaction, rapid hydration requires the use of activated internal alkynes and microwave irradiation (MWI).

In our studies of the use of iron salts as a catalyst, our initial plan was to synthesize a vinylsulfonate moiety through the iron π -activation of C–C triple bonds (Scheme 1).

When phenylacetylene and *p*-toluenesulfonic acid in DCE were reacted in the presence of catalytic amount of FeCl_3 , acetophenone was selectively obtained in good yield. Overall, indirect hydration of an alkyne is accomplished by regioselective hydrosulfonylation and subsequent hydrolysis of the generated vinyl tosylate. Herein, we report an effective Fe(II)-catalyzed hydration for the Markovnikov hydration of an alkyne in the presence of methanesulfonic acid (Scheme 2).

The construction of methyl ketone was initiated with 4-pentyl-phenylacetylene as a model system to explore the reaction (Table 1). Initially, the use of various metal iron salts as a catalyst was investigated for the formation of a ketone in the presence of MsOH . Catalytic amounts of FeBr_2 , FeCl_2 , $\text{Fe}(\text{acac})_2$, FeCl_3 , FeBr_3 , $\text{Fe}(\text{acac})_3$, $\text{Fe}(\text{OTf})_3$, and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ produced the desired compound in good yields of 66–88% at 60 °C (entries 1–8). Among

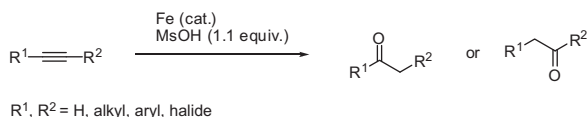


Scheme 1.

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* Corresponding author. Tel.: +82 33 250 6477; fax: +82 33 250 6470.

E-mail address: lky@kangwon.ac.kr (K. Lee).



Scheme 2. Iron-catalyzed hydration of alkyne.

the catalysts investigated, $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ produced the desired product with the highest yield of 92% (entry 9); however, at room temperature, the reaction yield decreased to 75% (entry 10). Next, the effects of various acids were investigated for 4-pentylphenylacetylene. When using *p*-TsOH, a relatively lower isolated yield of 78% was obtained (entry 11). No reaction occurred when using AcOH and CSA (entries 12 and 13, respectively). When using TfOH, sluggish conversion of the alkyne was achieved with 59% yield (entry 14). We confirmed that hydration was not caused by a Brønsted-acid-mediated process, because the reaction did not occur in the presence of MsOH without iron salts, and trace amounts of ketone could be detected by TLC analysis (entry 15). Then, various solvents were investigated to determine the feasibility of the reaction with $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$. The addition of water did not lead to higher conversions; in fact, the use of DCE with water led to longer reaction time (entry 16). The use of acetonitrile, THF, dioxane, MeOH, and toluene resulted in low yields (entries 17–21); furthermore, no reaction occurred when using DMF. The best results were obtained using $\text{FeCl}_2 \cdot \text{H}_2\text{O}$ from 4-pentylphenylacetylene; this reaction produced 4-pentylacetophenone in 92% yield in only 1 h at 60 °C (entry 9).

Next, we investigated the scope and limitation of this indirect hydration reaction catalyzed by $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ in the presence of MsOH using a variety of alkynes. The obtained results are shown in Table 2. Electron-rich aromatic alkynes rather than phenylacetylene were obtained from their corresponding aryl ketones in good to excellent yields (entries 2 and 3). 4-Ethynylphenol as unprotected alcohol was also hydrated in moderate yield (entry 4). On

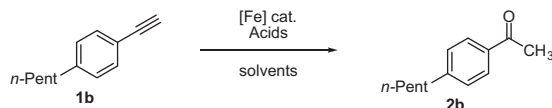
the other hand, substitution of an electron-withdrawing group such as trifluoromethyl-, chloro-, or bromo-, on the phenyl ring resulted in reasonable yields (entries 6–8). Aliphatic alkynes required longer reaction times than aromatic alkynes (entries 9 and 10). Conjugated enynes allowed hydration only at their C–C triple bond to produce the corresponding enone (entry 11). Furthermore, (bromoethynyl)-benzene was also hydrated to form 2-bromoacetophenone in good yields (entry 12). The hydration of internal alkynes proceeded efficiently to give the corresponding ketones, although these reactions required longer reaction times in comparison with those of terminal alkynes (entries 13 and 14). Notably, methylphenylacetylene gave propiophenone exclusively without the formation of 1-phenyl-2-propanone (entry 15). The hydration of 1,3-diethynylbenzene exclusively gave 1,3-diacylbenzene (entry 16).

We then examined the reactivity of terminal vs. internal alkyne and aromatic vs. aliphatic alkyne. The reaction of equimolar mixture of phenylacetylene (**1a**) and diphenylacetylene (**1n**) with 1.1 equiv of MsOH under the optimum conditions selectively produced acetophenone (**2a**) in 63% yield. Furthermore, the reaction of phenylacetylene (**1a**) and 1-dodecyne (**1i**) gave acetophenone (**2a**) in 64% yield and 2-dodecanone (**2i**) in 9% yield, respectively, (Scheme 3).

To demonstrate the utility of catalytic iron/MsOH, we also tested the indirect hydration of the propargylic alcohol system. 1-Phenylprop-2-yn-1-ol (**1q**) reacted smoothly to produce cinnamaldehyde (**2q**) with high yield via the Meyer–Schuster rearrangement. For 1-ethynylcyclohexenol (**1r**), dehydration proceeded initially following which the hydration of the alkyne occurred to produce an α,β -enone **2r** as the main product via Rupe rearrangement (Scheme 4).

The most plausible mechanism is that methanesulfonic acid attacks the triple bond activated by the iron salts to form a vinyl sulfonate, and then, it undergoes in situ hydrolysis to produce the ketone. This hypothesis was supported by NMR analysis in the crude mixture: it was found that the alkyne **1o** was readily

Table 1
Optimization of reaction conditions^a



Entry	Iron salt	Acid	Solvent	Temp (°C)	Time (h)	Yield ^b (%)
1	FeCl_2	MsOH	DCE	60	11	72
2	FeBr_2	MsOH	DCE	60	3	86
3	$\text{Fe}(\text{acac})_2$	MsOH	DCE	60	3.5	88
4	FeCl_3	MsOH	DCE	60	7	66
5	FeBr_3	MsOH	DCE	60	7	73
6	$\text{Fe}(\text{acac})_3$	MsOH	DCE	60	2	79
7	$\text{Fe}(\text{OTf})_3$	MsOH	DCE	60	3	75
8	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	MsOH	DCE	60	3	84
9	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	MsOH	DCE	60	1	92
10	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	MsOH	DCE	rt	7	75
11	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	TsOH	DCE	60	1.5	78
12	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	AcOH	DCE	60	18	0
13	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	CSA	DCE	60	72	0
14	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	TfOH	DCE	60	18	59
15	—	MsOH	DCE	60	28	Trace
16	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	MsOH	DCE/ H_2O	60	24	79
17	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	MsOH	CH_3CN	60	3.5	74
18	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	MsOH	THF	60	8	23
19	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	MsOH	1,4-Dioxane	60	72	57
20	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	MsOH	MeOH	60	24	35
21	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	MsOH	Toluene	60	24	31
22	$\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$	MsOH	DMF	60	24	0

^a Reaction conditions: 4-pentylphenylacetylene (1 mmol), acid (1.1 equiv), iron salt (5 mol %), and solvent (3 mL) under nitrogen atmosphere.

^b Isolated yield.

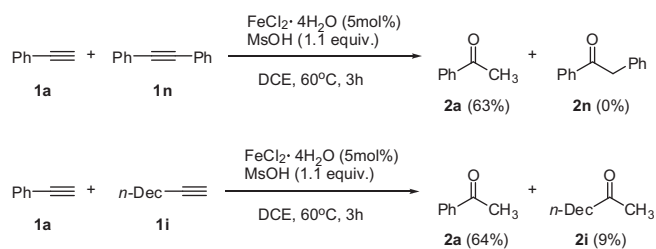
Table 2
Hydration of alkynes by catalytic iron–methanesulfonic acid^a

Entry	Substrate	Product	Time (h)	Yield ^b (%)
1	1a	2a	1.5	79
2	1b	2b	1	92
3	1c	2c	1.5	69
4	1d	2d	2	49
5	1e	2e	3.5	87
6	1f	2f	6	67
7	1g	2g	1	83
8	1h	2h	3	90
9	1i	2i	7.5	76
10	1j	2j	9	71
11	1k	2k	4.5	53
12	1l	2l	19	83 ^c
13	1m	2m	19	73 ^c
14	1n	2n	17	91 ^c
15	1o	2o	18	91 ^c
16	1p	2p	1.5	96 ^c

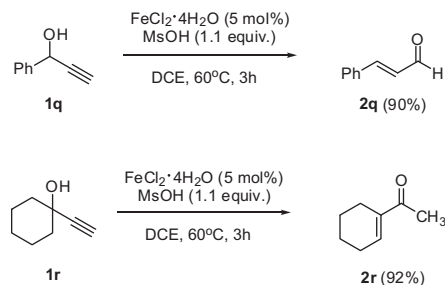
^a Reaction conditions: 4-pentylphenylacetylene (1 mmol), acid (1.1 equiv), iron salt (5 mol %), and solvent (3 mL), under nitrogen atmosphere.

^b Isolated yields.

^c 2 equiv of MsOH was used.



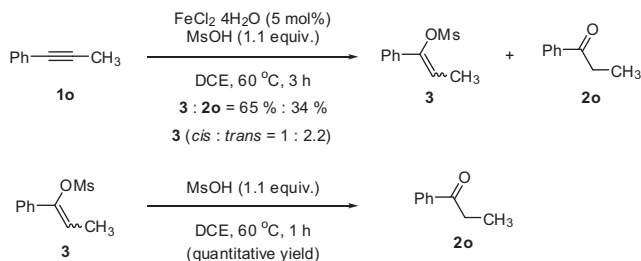
Scheme 3.



Scheme 4.

converted into the vinyl sulfonate **3** corresponding to the addition of MsOH to the C–C triple bonds, which in turn was converted into the ketone **2o** in the presence of MsOH (Scheme 5).

In summary, we have demonstrated that the FeCl₂·4H₂O and methanesulfonic acid systems show high reaction efficiency for



Scheme 5.

the indirect hydration of various alkynes in DCE. The reaction proceeds under mild conditions to produce various ketones from alkynes. Iron catalysts, which are inexpensive, non-toxic, and environmentally benign, are quite advantageous from the viewpoint of sustainable chemistry.

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