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Development of the First Iron Chloride-Catalyzed Hydration of Terminal Alkynes

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Abstract: The development of the first iron-catalyzed hydration of terminal alkynes is described using a catalytic amount of iron(III) chloride (10 mol%). The reaction leads selectively to the corresponding methyl ketone derivatives.

Keywords: alkynes; homogeneous catalysis; hydration; iron; methyl ketones

The use of water as an inexpensive and benign reagent in organic synthesis is an important topic, and the hydration of alkynes is a typical example of such use. It is one of the most useful methods for the functionalization of unactivated alkynes, and has found numerous synthetic uses.[1] The addition of water to alkynes with Hg(II) salts to form carbonyl compounds was first reported by Berthelot in 1862, and since then, it is a classical textbook reaction.[2,3] However, the use of mercury salts is a dramatic barrier for applications in both academic and industrial work. The Markovnikov hydration of alkynes is also catalyzed by numerous complexes of transition metals such as Au,[4] Ru,[5] Rh,[6] Pt,[7] and other metals.[8] The addition of water across terminal alkynes promoted by these catalysts exclusively follows Markovnikov's rule to give methyl ketones. More recently, anti-Markovnikov hydrations of terminal alkynes to lead selectively to the corresponding aldehydes were also described using ruthenium complexes.[9]

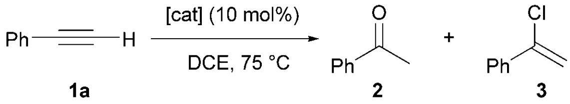
On the other hand, many catalysts are derived from heavy or rare metals and their toxicity and prohibitive prices can constitute severe drawbacks for large-scale applications. In contrast, iron is one of the most abundant metals on the earth, and consequently one of the most inexpensive and environmentally friendly ones. Although the coordination chemistry of iron has been widely developed in the past decades, it is really surprising that, until lately, iron was underrepresented in the field of homogeneous catalysis compared to the other transition metals. However, the last few years have seen a rise of the use of iron as a catalyst and very efficient processes that are now able to compete with other metal-catalyzed ones have emerged in the carbon-carbon bond formation, hydrosilylation, oxidation, even hydrogenation areas.[10]

In the course of our investigations on the use of iron compounds as environmentally friendly catalysts, we found that alkynes in the presence of a catalytic amount of an iron(III) salt can be hydrated to yield the corresponding methyl ketones in the presence of water. To the best of our knowledge, only two examples of iron-mediated hydration have been reported in the literature and both involved stoichiometric amounts.[11] However, this reaction was selective only in the case of the hydration of phenylacetylene. With the other alkynes described, the authors observed between 10 and 53% of a by-product, the 2-chloroalk-1-ene derivative, which was obtained *via* the formation of a 2-chlorovinyl-iron intermediate.[11b] Furthermore, one pioneering iron nucleophilic addition of methanol to alkynes was reported by Bassetti, but proceeded only with poor yields.[12]

Herein, we report a convenient $FeCl_3$-catalyzed Markovnikov hydration of terminal alkynes to yield to ketones with good regioselectivities.

As an initial attempt to improve this iron-catalyzed hydration of alkynes, a 1,2-dichloroethane (DCE) solution of phenylacetylene **1a** (1 mmol) was allowed to react with water (3 equiv.) at 75 °C in the presence of a catalytic amount of anhydrous $FeCl_3$ (10 mol%) under a small pressure of air (Scheme 1).

After stirring for a period of 67 h, the reaction afforded the acetophenone **2** in a GC-yield of 96% with a small amount of α-chlorostyrene **3** as a by-product (4%). We carried out then extensive investigations to



Scheme 1.

Table 1. Screening of iron salts for the catalyzed hydration of phenylacetylene.[a]

Entry	Iron salt	Solvent	Time [h]	GC yield [%][b]	
				2	**3**
1	$FeCl_2$	DCE	48	–	–
2	$FeBr_2$	DCE	40	20	0
3	$Fe(acac)_2$	DCE	6	–	–
4	$Fe(OAc)_2$	DCE	40	24	0
5	$FeCl_3{\cdot}6\,H_2O$	DCE	60	61	1
6	$FeCl_3$	DCE	67	96	4

[a] *Reaction conditions:* phenylacetylene **1a** (1 mmol), solvent (2 mL), iron salt (10 mol%), water (3 equiv.) under air.

[b] Calculated from GC response factors relative to tetradecane internal standard.

define the best reaction conditions, and Table 1 lists representative data obtained for the hydration of phenylacetylene with various commercially available iron salts. We studied the catalytic activity of various iron(II) and iron(III) salts in the course of hydrating phenylacetylene **1a** with 3 equivalents of water in DCE as solvent at 75 °C.

First of all, iron(II) species such as $FeCl_2$ or $Fe(OAc)_2$ were not able to promote any hydration reaction in our standard conditions and phenylacetylene **1a** remained unchanged after several days at 75 °C. Conversely, on employing anhydrous $FeCl_3$, a commercially available precursor, as the catalyst, excellent conversion was obtained (96%) and the reaction operated with perfect regioselectivity. Interestingly, the conversion was moderate (61%) when $FeCl_3{\cdot}6\,H_2O$ was used, which shows the far better Lewis acid ability of $FeCl_3$. As no superior catalyst could be identified, we decided to focus on $FeCl_3$. It must be pointed out that $FeCl_3$ must be perfectly dry and be kept under argon atmosphere to avoid its moisturization.

More interestingly, the presence of air is crucial for the progress of the reaction. If the reaction is conducted under argon at 75 °C for 60 h, only 10% conversion was observed and a mixture 1/1 of acetophenone **2** and α-chlorostyrene **3** was obtained. On the contrary, when the reaction was performed under air, the conversion was complete, and acetophenone **2** was the major product. If the same reaction was performed under a small pressure of air, without water as reagent, no ketone was detected and only non-identified oligomers were observed.

Table 2. Screening of solvents for the hydration of phenylacetylene.[a]

Entry	Solvent	Time (h)	Conv. [%][b]	GC yield [%][b]	
				2	**3**
1	DCE	67	100	**96**	**4**
2	$CHCl_3$	67	0	–	–
3	Cl_3CCH_3	67	0	–	–
4	CH_3CN	67	54	4	0
5	THF	67	36	2	0
6	*i*-PrOH	67	0	0	0
7	Toluene	67	43	13	8
8	NMP	67	0	0	0
9	AcOEt	67	37	11	5
10	Dioxane	67	10	2	0
11	CH_3NO_2	67	14	14	1
12	$(MeO)_2CO$	67	0	0	0

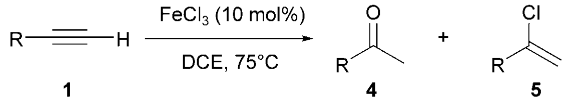
[a] *Reaction conditions:* phenylacetylene **1a** (1 mmol), solvent (2 mL), $FeCl_3$ (10 mol%), water (3 equiv.) under air.

[b] Calculated from GC response factors relative to tetradecane internal standard.

To get more information on the optimal catalyst conditions, we carried out also intensive investigations to define the best solvent for this transformation. Twelve different solvents were tested at 75 °C for 67 h using 10 mol% of dry $FeCl_3$ as catalyst in the presence of 3 equivalents of water (Table 2).

1,2-Dichloroethane (DCE) has been found to be a far better solvent than the other classic organic ones tested. Acetophenone **2** was obtained in 96% GC yield and only 4% of α-chlorostyrene **3** as by-product was detected. In other classic solvents, the conversions were moderate and, surprisingly, no reaction occurred in other chlorinated solvents ($CHCl_3$, CCl_3CH_3), isopropanyl alcohol, or *N*-methylpyrrolidone (NMP). More remarkably, even if the conversions were moderate in all the cases except for DCE, the GC yield of the desired acetophenone **2** was dramatically lowered (1–16%)! These results clearly indicated that if the hydration reaction did not occur, a degradation process could take place to convert phenylacetylene **1a** into a non-identified oligomer.

From a kinetic point of view, methyl ketone and 2-chloroalk-1-ene are formed simultaneously in a 1/1 ratio at the beginning of the reaction and after a maximum concentration of the 2-chloroalk-1-ene has been reached, the latter is then converted into acetophenone. This observation was already made by Postel in the stoichiometric version of this hydration reaction.[11a] It must be pointed that this hydration of α-chlorostyrene **3** is also a catalytic reaction. Indeed, when the α-chlorostyrene **3** is treated using 10 mol% of dry $FeCl_3$ under the reaction conditions (3 equiv. of water in DCE at 75 °C for 4 days, under air) acetophenone **2** was obtained quantitatively as single product of the reaction. Furthermore, without the iron cat-



Scheme 2.

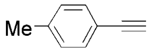
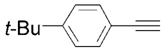
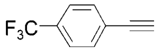
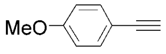
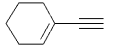
alyst under air, less than 5% of acetophenone **2** was detected, in the same reaction conditions.

Using dry $FeCl_3$ salt as catalyst, the scope of the Markovnikov hydration of various 1-alkynes **1** was examined in DCE at 75 °C. (Scheme 2 and Table 3).

Reactions using 10 mol% of $FeCl_3$ gave the desired ketones in excellent regioselectivities and good yields. Linear terminal alkynes furnished the corresponding methyl ketones with complete regioselectivity and good yields (entries 6 and 7).

Interestingly, the hydration reaction is faster with alkyl-substituted alkynes than aryl-substituted ones (compare entries 6 and 7 *vs.* 1). On the other hand, in the aryl series, when the phenylacetylene is substituted by a methyl (entry 2) or a *tert*-butyl (entry 3) group in the *para*-position, the reaction goes faster than that with phenylacetylene itself (30 and 60 h, respectively, compared to 67 h). These results seem to indicate that the presence of an electron-donating group in the *para* position of the aryl moiety accelerates the reaction. In contrast, when an electron-drawing substituent such as trifluoromethyl is placed in the *para* position of the aryl moiety, the reaction rate decreases (entry 4). This reaction tolerates the presence of an alkenyl moiety in the molecule which permits us to obtain the α,β-unsaturated methyl ketone in moderate yield (entry 8). It should be noted that, in this example, the reaction was carried out at 40 °C to avoid degradation of the α,β-unsaturated ketone. In contrast, the presence of a functional coordinating group such as hydroxy seems to inhibit the activity, because it may act as a competing ligand for the iron centre (entries 9 and 10). This result is in agreement with the one obtained with alcohol as solvents. (Table 2, entry 4) Furthermore, when the propargylic systems bear a carbonyl group such as an acetate, no reaction occurs, even after one week at 75 °C. It seems to prove that the carbonyl moiety can also coordinate the iron centre and inhibit the hydration reaction. Furthermore, when using internal alkynes under these conditions, no reaction occurs.

Table 3. Regioselective hydration of alkynes with $FeCl_3$ as catalyst.[a]

Entry	Alkyne	Time [h]	Conv. [%][b]	Ratio **4/5**[b]	Yield of **4** [%][c]
1	Ph–C≡CH	67	100	96/4	80
2		30	100	100/0	99
3		60	100	100/0	77
4		88	100	100/0	57
5		65	100	100/0	94
6	n-C_4H_9–C≡H	46	100	100/0	70
7	n-C_6H_{13}–C≡CH	48	100	98/2	87
8		40[d]	100	95/5	56
9	$HO(CMe_2)C{\equiv}CH$	70	0	–	–
10	$HO(CH_2)_4C{\equiv}CH$	70	0	–	–

[a] *Reaction conditions:* alkyne (1 mmol), DCE (2 mL), $FeCl_3$ (10 mol%), water (3 equiv.) under air.

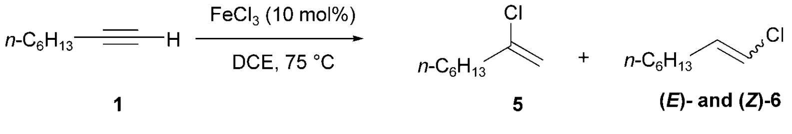
[b] Calculated from GC response factors relative to tetradecane internal standard.

[c] Isolated yields.

[d] The reaction was performed at 40 °C.

At this stage of the project, even if the origin of the catalytic activity remains unknown and if any mechanistic discussion is speculative, we might pointed out crucial role of both 1,2-dichloroethane and air in the iron catalyzed process as 1,2-dichloroethane was already known to be a mild oxidant where it plays the role of a reoxidant of the metal.[13,14] Additionally, in some palladium-catalyzed homo-coupling reactions, air was also use as re-oxidizing agent.[15]

Furthermore, we believe that the catalyzed hydration proceeds *via* an iron-Lewis acid activation of the triple bond as Miranda already demonstrated by *ab initio* calculations.[11b] One experimental result supported this opinion: when the reaction of oct-1-yne was performed in the presence of 3 equivalents of concentrated hydrochloric acid, no reaction occurs in the absence of the iron catalyst after 72 h at 75 °C under air. In contrast, when the same reaction was performed in the presence of 10 mol% of $FeCl_3$, a hydrochloration reaction took place leading to a mixture of 2-chlorooct-1-ene **5** (major product) and (*E*)- and (*Z*)-1-chlorooct-1-ene **6** (GC yield: 72%, **5**/**6** = 78/22). Octan-2-one was detected after a prolonged reaction time. (Scheme 3).



Scheme 3.

In summary, the above results show that the $FeCl_3$-catalyzed hydration of terminal alkynes leads to the formation of methyl ketone derivatives with good yields and regioselectivities. This work represents the first report of the catalytic hydration of alkynes using iron salts as the catalyst. This addition of water to a C≡C bond is a clean reaction: in general, the reaction mixture simply consists of solvent, water, and the product methyl ketone, regardless of the conversion, with only trace, if any, of 2-chloroalkene by-products. At this stage, even if the origin of the catalytic activity remains unknown, the role of 1,2-dichloroethane and air seems crucial. Further investigations into the mechanism of this reaction are now in progress.

Experimental Section

Representative Procedure

To a solution of commercially available $FeCl_3$ (16.2 mg, 10 mol%) in 1,2-dichloroethane (2 mL) were added successively 1-phenylacetylene (0.13 mL, 1.0 mmol) and water (54 mg, 3 mmol). The mixture was heated under a small pressure of air for 67 h at 75 °C and the reaction progress was monitored by GC. After cooling to room temperature, the solvent was removed under vacuum and the residue was filtered through a plug of silica, and concentrated under reduced pressure to furnish acetophenone as a colorless oil; yield: 96 mg (80%). The small pressure of air is maintained inside the Schlenk tube using a connecting U-shaped tube containing oil with two different levels, using the principle of communicating vessels (see Supporting Information).

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