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SHORT COMMUNICATION

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Iron-Catalyzed α-Methylenation of Ketones with *N*,*N*-Dimethylacetamide: An Approach for α,β-Unsaturated Carbonyl Compounds

Yi-Ming Li,*[a] Shao-Jie Lou,[b] Qin-Hua Zhou,[a] Lian-Wen Zhu,[a] Long-Feng Zhu,[a] and Lei Li[a]

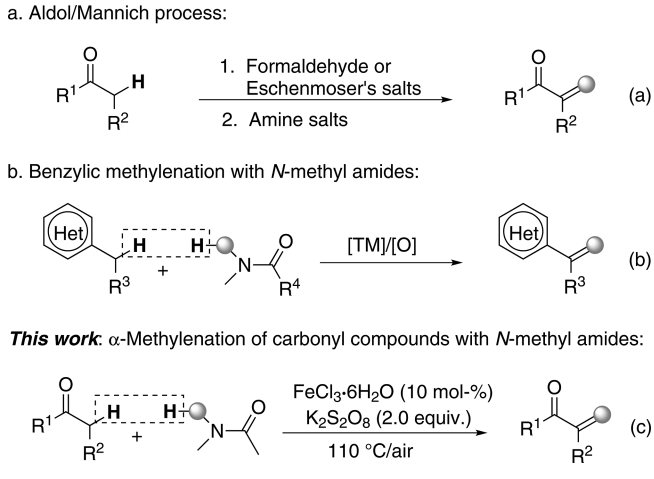
Keywords: Methylenation / CDC reaction / α, β-unsaturated carbonyls / Iron-catalysis / One-carbon source

In this study, we developed a general iron-catalyzed α-methylenation of ketones by using *N*,*N*-dimethylacetamide as the one-carbon source. Various ketones, including aryl and alkyl ketones, enones, and dicarbonyl compounds were well tolerated to yield the corresponding α,β-unsaturated carbonyl compounds in the presence of an iron catalyst, peroxides, and *N*,*N*-dimethylacetamide under aerobic conditions.

Introduction

α,β-Unsaturated ketones are skeletons extensively found in various biologically active compounds.[1] They are also widely utilized in organic synthesis because of their unique reactivities. As a broadly used Michael acceptor, α,β-unsaturated ketones are commonly employed in nucleophilic additions, Michael reactions, and Baylis–Hillman reactions.[2] They also function as substrates in Heck reactions and Diels–Alder reactions with an α-methylene moiety.[3] Among the synthetic methods reported for the construction of α,β-unsaturated ketone fragments, the α-methylenation of simple ketones is the most efficient one to yield α,β-unsaturated derivatives.[4]

Several approcahes to synthesize α-methylene ketones have been developed. These approaches include amine salt catalysed/mediated α-methylenation with formaldehyde or paraformaldehyde[5] and Mannich-type reaction with readily prepared Eschenmoser's salts followed by elimination[6] (Scheme 1a). Much achievement has been accomplished with the catalytic system, but novel one-carbon sources have been less developed. Transition-metal-catalyzed cross-dehydrogenative-coupling (CDC) reactions have emerged as powerful and efficient tools for C–C bond construction, because they obviate the need of pre-functional substrates.[7] Environment-benign iron catalysts have received considerable attention because of their significant reactivity in CDC reactions.[8] We recently developed an iron-catalyzed benzylic methylenation of 2-alkylazaarenes to produce 2-vinylazaarenes by using *N*-methyl amides as a novel one-carbon source.[9] An iminium intermediate was generated from *N*-methyl amides (DMA or DMF) in the presence of an iron catalyst and $K_2S_2O_8$. The in situ iminium cation further reacted with nucleophilic 2-alkylazaarenes and underwent subsequent elimination to yield the final α-methylenated product. Miura et al. recently reported a similar copper-catalyzed α-methylenation of benzylpyridines with *N*,*N*-dimethylacetamide (DMA) as the one-carbon source (Scheme 1b).[10] Nevertheless, the scope of substrates is still limited and less explored. Ketones are nucleophiles widely used in various CDC reactions.[11] However, the coupling of ketones and *N*-methyl amides is rare. Considering the importance of α,β-unsaturated carbonyl compounds, we envisioned to develop a direct and efficient approach to convert simple ketones to their α,β-unsaturated derivatives by



Scheme 1. Novel one-carbon source for α-methylenation of ketones. [TM] = transition metal.

[a] College of Biological, Chemical Sciences and Engineering, Jiaxing University,
No. 118, Jiahang Road, Jiaxing City, Zhejiang 314001, P. R. China
E-mail: lym4241986@163.com
[b] Catalytic Hydrogenation Research Center, State Key Laboratory Breeding Base of Green Chemistry – Synthesis Technology, Zhejiang University of Technology, Hangzhou 310014, P. R. China

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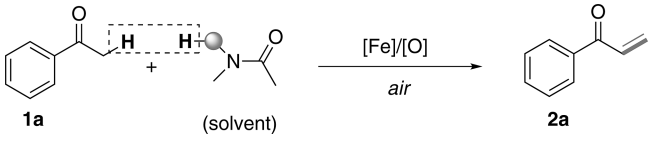
using *N*-methyl amides as novel one-carbon sources (Scheme 1c).[12]

Results and Discussion

We commenced our investigation with the use of simple acetophenone (**1a**) as the model substrate in the presence of an iron catalyst, a peroxide, and *N*,*N*-dimethylacetamide (Table 1). The α-methenylated compound **2a** was obtained in 74% isolated yield by slightly modifying our previous conditions for the benzylic methylenation of 2-alkylazaarenes (Entry 1).[9] We then explored various combinations of iron catalysts and oxidants. The results showed that $FeCl_3·6H_2O/K_2S_2O_8$ is the best catalytic system for the α-methylenation of **1a** (Entries 2–8). Control reactions revealed that no methylenation occurred in the absence of iron catalysts or peroxides (Entries 9–10). An attempt to obtain high-purity 99.99% $FeCl_3$ was also conducted to avoid metal impurities in the iron catalyst (Entry 11). α-Methylenation smoothly took place in *N*,*N*-dimethylformamide and gave a yield comparable to that with DMA (Entry 12).

Table 1. Optimization for the α-methylenation of **1a**.[a]

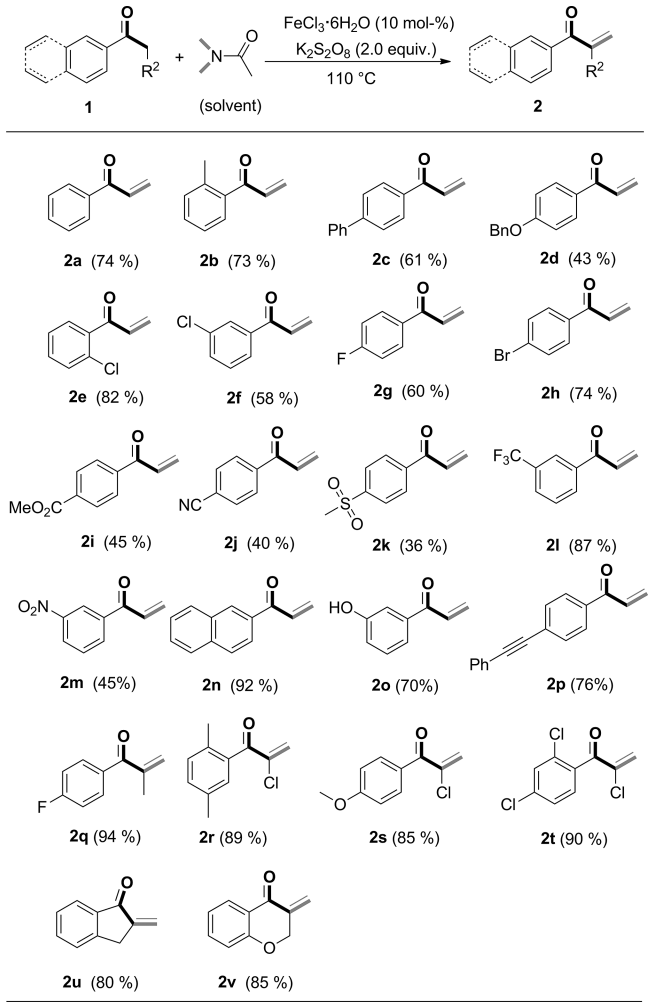


Entry	[Fe]	[O]	Yield of **2a** [%][b]
1	$FeCl_3·6H_2O$	$K_2S_2O_8$	77 (74[c])
2	$FeCl_3·6H_2O$	$Na_2S_2O_8$	67
3	$FeCl_3·6H_2O$	$(NH_4)_2S_2O_8$	58
4	$FeCl_3·6H_2O$	TBHP	43
5	$FeCl_3$	$K_2S_2O_8$	73
6	$FeCl_2$	$K_2S_2O_8$	70
7	$Fe(NO_3)_3·9H_2O$	$K_2S_2O_8$	n.d.[d]
8[e]	$FeCl_3·6H_2O$	$K_2S_2O_8$	n.d.
9	–	$K_2S_2O_8$	n.d.
10	$FeCl_3·6H_2O$	–	n.d.
11	$FeCl_3$ (99.99%)	$K_2S_2O_8$	74
12[f]	$FeCl_3·6H_2O$	$K_2S_2O_8$	75

[a] Reaction conditions: **1a** (0.2 mmol), [Fe] (0.02 mmol), [O] (0.4 mmol), DMA = *N*,*N*-dimethylacetamide (1.0 mL), 110 °C, 4 h, under air (unless otherwise noted). [b] GC–MS yields. [c] Isolated yield. [d] n.d. = not detected. [e] Under argon. [f] DMF = *N*,*N*-dimethylformamide as the one-carbon source.

Under optimized conditions, the scope of the α-methylenation protocol was explored with various ketones. Substituted aryl ketones were first investigated. Both electron-donating and electron-withdrawing substituents in phenyl methyl ketones were tolerated to produce the corresponding α,β-unsaturated derivatives in moderate to good yields (Table 2). Methylenation of halo-, carboxy-, methylsulfonyl-, cyano-, and nitro-substituted substrates smoothly took place under these conditions, which would provide opportunities for further derivatization of the final products (**2a**–**2m**). In addition, the scope of the substrates could be extended to a naphthyl ketone with high yield (**2n**). Interestingly, oxidable functional groups, e.g. hydroxy and alkynyl are compatible with the present oxidation system (**2o**, **2p**). Subsequently, sterically hindered α-substituted aryl ketones were investigated. Propiophenone smoothly underwent α-methylenation in 94% yield (**2q**). Notably, α-chloro aromatic ketones were also well tolerated with the chloro substituent remaining intact (**2r**–**2t**). Benzocyclic ketones, including 1-indanone and 4-chromanone, were also suitable substrates to furnish their α,β-unsaturated derivatives in good yields (**2u**–**2v**).

Table 2. α-Methylenation of aromatic ketones.[a]



[a] Reaction conditions: **1** (0.5 mmol), $FeCl_3·6H_2O$ (0.05 mmol), $K_2S_2O_8$ (1.0 mmol), DMA (2.0 mL), 110 °C, 4 h, under air, isolated yields.

Intriguingly, substituted *ortho*-hydroxyacetophenones **1w**–**1y** underwent intramolecular cycloaddition after the first α-methylenation to afford 4-chromanones **II**, which then underwent a second α-methylenation to give the adducts **2v**, **2x**, **2y** in good yields in the presence of 4.0 equiv. of oxidant (Figure 1). Thus, a novel and facile way was developed to construct α-methylenated chromanones from simple *ortho*-hydroxyacetophenones.

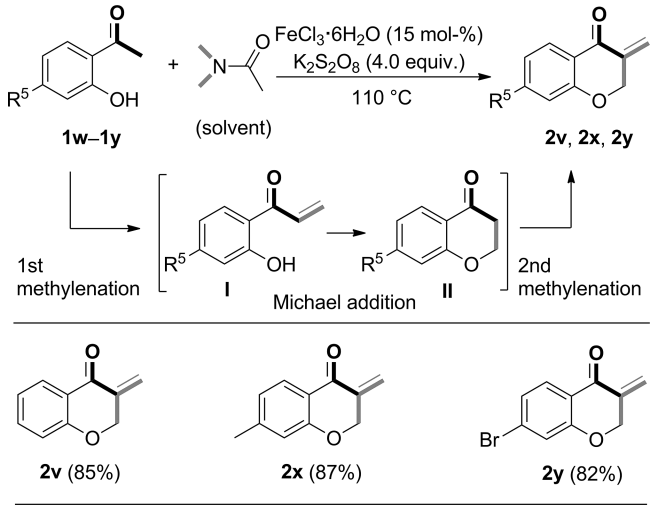
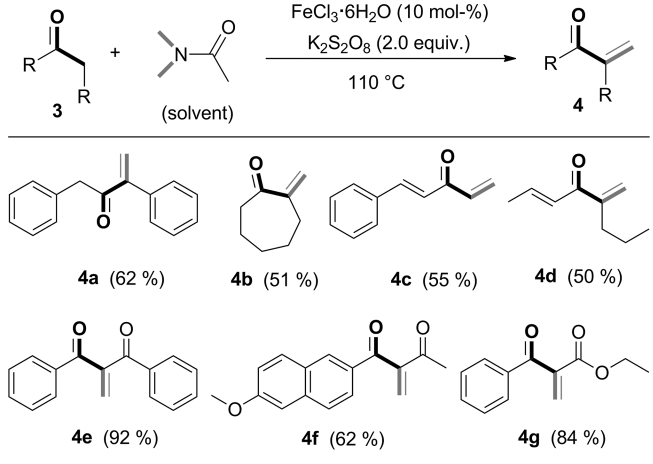


Figure 1. Two-fold α-methylenation of *ortho*-hydroxyacetophenones. Reaction conditions: **1** (0.5 mmol), $FeCl_3·6H_2O$ (0.075 mmol), $K_2S_2O_8$ (2.0 mmol), DMA (2.0 mL), 110 °C, 4 h, under air, isolated yields.

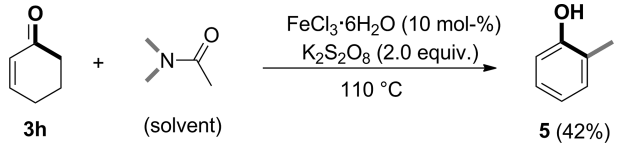
Other ketones with various substituents were then explored (Table 3). Symmetric ketones such as dibenzyl ketone and cycloheptanone produced the monomethylenated products in moderate yields (**4a**, **4b**). Noteworthy, no α,α-dimethylation derivative was detected when starting from the substrates **4a** and **4b**, even when 4.0 equiv. of oxidant were used. Enones were also applicable under these conditions to afford dienones in moderate yields (**4c**, **4d**). Dicarbonyl compounds are good substrates because of their acidic α-hydrogen atoms (**4e**–**4g**).

Table 3. α-Methylenation of various ketones.[a]



[a] Reaction conditions: **3** (0.5 mmol), $FeCl_3·6H_2O$ (0.05 mmol), $K_2S_2O_8$ (1.0 mmol), DMA (2.0 mL), 110 °C, 4 h, under air, isolated yields.

When cyclohexenone (**3h**) was used under the standard conditions, the unexpected 2-methylphenol (**5**) was obtained. Thus, we propose that the initially α-methylenated cyclohexenone underwent a hydrogen shift to produce the methylcyclohexadienone isomer, followed by dehydrogenative aromatization under the oxidative conditions to furnish 2-methylphenol (**5**) (Scheme 2).



Scheme 2. α-Methylenation and cascade aromatization of **3h**.

Finally, a radical mechanism is proposed based on the previous report:[8] The in situ generated enol **6** attacks the iminium species **8** to form the intermediate **9**, which then undergoes C–N bond cleavage to give the product **2a** (Figure 2).

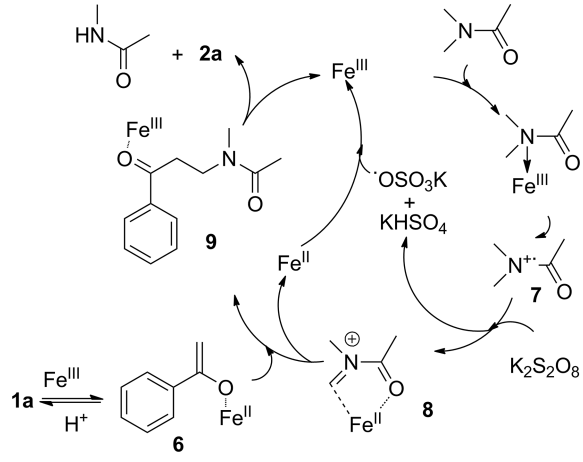


Figure 2. Proposed mechanism.

Conclusions

We developed a facile iron-catalyzed α-methylenation of ketones with DMA as a novel one-carbon source. The present methodology features a broad substrate scope, good functional-group tolerance, and simple operation, which provides a novel way to prepare useful α,β-unsaturated carbonyl compounds.

Experimental Section

Typical Procedure: Compound **1** or **3** (0.5 mmol), $FeCl_3·6H_2O$ (13.5 mg, 0.05 mmol), $K_2S_2O_8$ (270 mg, 1.0 mmol), and DMA (2.0 mL) were sequentially added to a 10 mL tube under air. The tube was sealed and the mixture stirred at 110 °C for 4 h. Upon completion of the reaction (monitored by TLC), the resulting mixture was diluted with Et_2O (15 mL) and washed with brine (3 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (100–200 mesh) by using petroleum ether/EtOAc as the eluent to yield the desired product **2** or **4**.

Supporting Information (see footnote on the first page of this article): General experimental procedures, characterization details and copies of spectra.

Acknowledgments

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[12] When we were preparing this manuscript, a similar cooper-catalyzted α-methylenation of ketones was just published: J. Liu, H. Yi, X. Zhang, C. Liu, R. Liu, G. Zhang, A. Lei, *Chem. Commun.* **2014**, *50*, 7636–7638. Though iron catalysts were inefficient when the reaction was carried out under argon, we found the iron-catalyzed α-methylenation took place smoothly under aerobic conditions with more general ketones.

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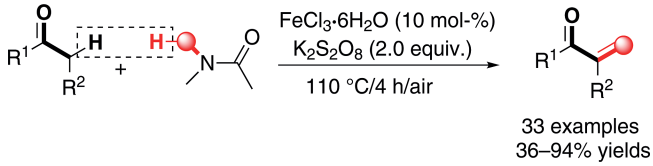

A general and facile iron-catalyzed α-methylenation of carbonyl compounds by using *N*-methyl amides as the one-carbon source was developed. Various carbonyl compounds (aryl- or alkyl-substituted, enones, 1,3-dicarbonyl compounds) were well tolerated to furnish the corresponding α,β-unsaturated carbonyl compounds in the presence of an iron catalyst, peroxides, and *N*-methyl amides under aerobic conditions.

Keywords: Methylenation / CDC reaction / α, β-unsaturated carbonyls / Iron-catalysis / One-carbon source

