DOI: 10.1002/adsc.201601001
Advanced Synthesis & Catalysis

An Iron(II) Chloride-Promoted Radical Cascade Methylation or α-Chloro-β-methylation of *N*-Arylacrylamides with Dimethyl Sulfoxide

Zejiang Li,[a,*] Xiaosong Cui,[+a] Lin Niu,[+a] Yingming Ren,[+a] Menghua Bian,[+a] Xuebiao Yang,[+a] Biao Yang,[+a] Qinqin Yan,[a,*] and Jincan Zhao[a]

[a] College of Chemistry & Environmental Science, Hebei University, Baoding, Hebei 071002, People's Republic of China
E-mail: lizejiang898@126.com or yanqin_9397@126.com

[+] These authors contributed equally to this work.

Received: September 8, 2016; Revised: October 26, 2016; Published online: ■■ ■■, 0000

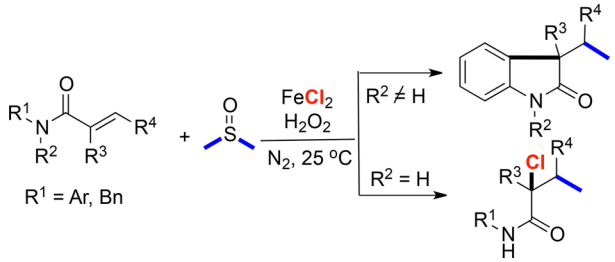
Supporting information for this article can be found under: http://dx.doi.org/10.1002/adsc.201601001.

Abstract: A free radical-initiated methylation and/or α-chloro-β-methylation of *N*-arylacrylamides with dimethyl sulfoxide under the analogous Fenton reaction condition has been developed, which provides an effective and facile cascade strategy for the synthesis of oxindoles and chlorinated amides.

Keywords: *N*-arylacrylamides; α-chloro-β-methylation; cyclization; methylation; radical reactions

The so-called "magic methyl effect" makes methylation very popular in synthetic organic chemistry.[1] The introduction of a methyl group into organic molecules could improve their biological and chemical properties.[2] In the past decades, although several methylating protocols have been achieved by using methyl-metal reagents,[3] MeI,[4] DMSO,[5] MeCOOH,[6] peroxides[7–8] etc. as methylating reagents, more practical methods remain highly desirable.

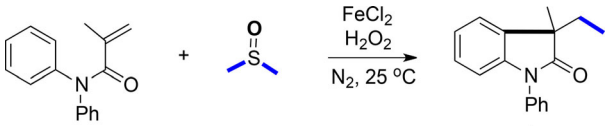
Oxindole and its derivatives have drawn much attention from chemists.[9,10] Recently, alkyl-substituted oxindoles which are prepared from cascade methylation of *N*-arylacrylamides by employing oxides or peroxides as the methyl source have been reported by Liu,[7,8] Zhu,[11] Cheng,[12] Li,[13] Chen,[14,15] and others. But challenging problems such as high-cost methyl reagents and oxidants remain to be addressed so far. Herein, in combination with our studies on radical cascade reactions,[16] we have developed a system which holds the advantages of common and economical methyl sources as well as oxidants, and easy operation. After a lot of attempts, we successfully accomplished the first example of a free radical cascade methylarylation or α-chloro-β-methylation of *N*-arylacrylamides by making use of dimethyl sulfoxide as methyl regent, iron(II) chloride as catalyst and chlorine source, and hydrogen peroxide as oxidant, which is similar to the Fenton reaction conditions (Scheme 1).[17]



Scheme 1. Methylation or methylchlorination of alkenes with dimethyl sulfoxide.

Initially, *N*,*N*-diphenylmethacrylamide and dimethyl sulfoxide were chosen as the model molecules to test the reaction conditions (Table 1, also see the Supporting Information for details). It was found that the yield of the product in 18 hours is better than that in 6 and 12 hours (entries 1–3). No product was obtained without any catalyst (entry 4). Variation of the amount of iron(II) chloride and hydrogen peroxide greatly affected the reaction efficiency (entries 5–12). Addition of 1 mL, 2 mL and 4 mL of dimethyl sulfoxide generated the desired product **1** in 61%, 70%, and 83% yields, respectively (entries 13–15). Finally, the terminal product **1** was isolated in 85% yield under the optimal conditions: *N*-arylacrylamides (1 equiv.,

Table 1. Optimization of the typical conditions.[a]

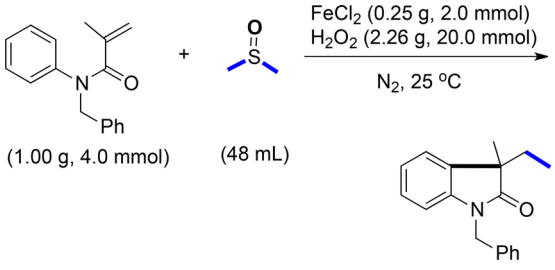


Entry	Iron(II) chloride [equiv.]	Hydrogen peroxide (30%) [equiv.]	Time [h]	Yield [%][b]
1	0.5	5	6	50
2	0.5	5	12	58
3	**0.5**	**5**	**18**	**85**
4	–	5	18	n. r.
5	0.1	5	18	6
6	0.2	5	18	59
7	0.3	5	18	64
8	1.0	5	18	75
9	0.5	1	18	47
10	0.5	2	18	69
11	0.5	3	18	73
12	0.5	4	18	75
13[c]	0.5	5	18	61
14[d]	0.5	5	18	70
15[e]	0.5	5	18	83

[a] *Reaction conditions:* *N*,*N*-diphenylmethacrylamides (1 equiv., 0.25 mmol), DMSO (3 mL), 25 °C, N_2.
[b] Isolated yields.
[c] DMSO (1 mL).
[d] DMSO (2 mL).
[e] DMSO (4 mL).

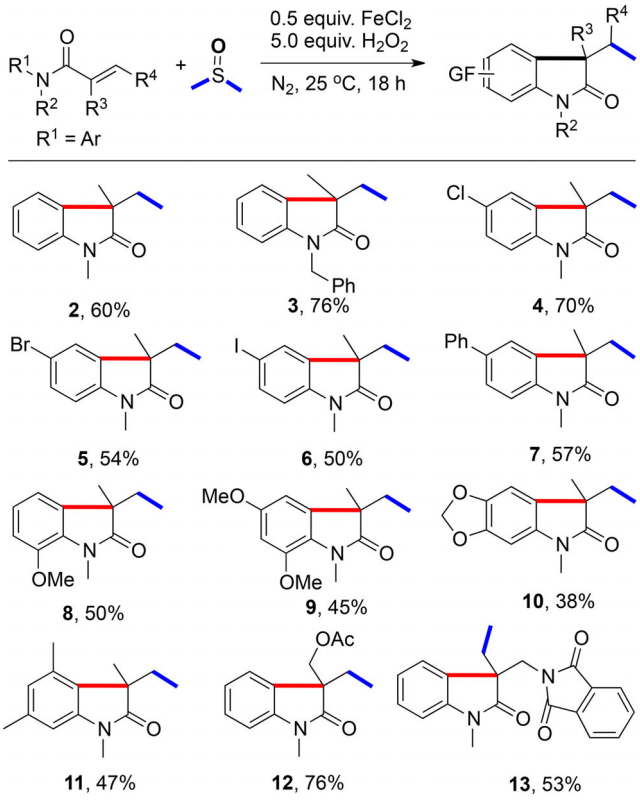
0.25 mmol), $FeCl_2$ (0.5 equiv., 0.125 mmol), H_2O_2 (30%, 5 equiv., 1.25 mmol) and DMSO (3 mL), 25 °C, N_2, 18 h, sealed tube.

With the modified conditions in hand, this system was used to investigate the substrate scope (Table 2). As can be seen, the *N*-methyl- and *N*-benzyl-substituted substrates gave the corresponding desired products in 60% and 76% yields, respectively (**2** and **3**). Halogen atoms such as Cl, Br and I substituted on the acrylamides afforded the products in moderate yields (**4**–**6**). Only the *N*-arylacrylamides with electron-donating groups could react well in the system (**7**–**11**), which also indicated that the steric effect was not so obvious. Notably, 2- [methyl(phenyl)carbamoyl]allyl acetate and 2-[(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-



(1)

Table 2. Iron-promoted free radical cascade methylation of *N*-arylacrylamides with dimethyl sulfoxide.



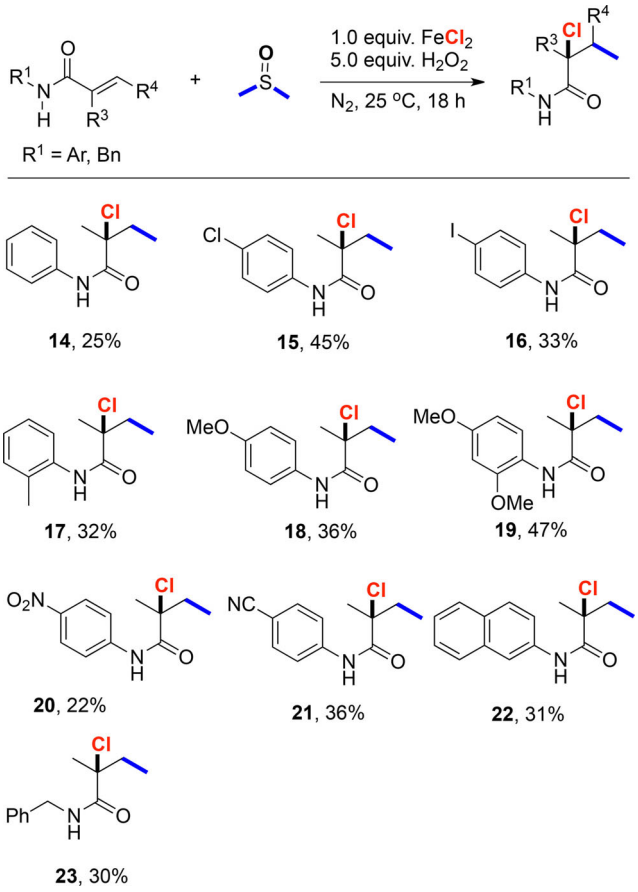
[a] *Reaction conditions:* *N*-arylacrylamides (1 equiv., 0.25 mmol), iron(II) chloride (0.5 equiv., 0.125 mmol), hydrogen peroxide (30%, 5 equiv., 1.25 mmol) and DMSO (3 mL), 25 °C, N_2, 18 h.
[b] Isolated yields.

methyl]-*N*-methyl-*N*-phenylacrylamide resulted in the products **12** and **13** in 76% and 53% yields, respectively. Meanwhile, under the best conditions, this reaction could be scaled up to the gram level easily [Eq. (1)].

We next found that N–H substituted *N*-phenylmethacrylamides underwent an α-chloro-β-methylation reaction rather than the methylarylation reaction. The reason is that it is difficult to bring in a conformation for direct N–H substituted substrates. A series of experiments was also complied to modify the reaction conditions (see the Supporting Information for details). Then, we began to study the substrate scopes under the optative condition (Table 3). We can see that substrates with both electron-donating and withdrawing groups could be tolerated in the system (**14**–**21**), although the desired products were isolated in low yields. Furthermore, *N*-naphthyl- and *N*-benzyl-substituted methacrylamides gave products **22** and **23** in 31% and 30% yields, respectively.

The reaction was inhibited when TEMPO was added to the system. It suggests that a free radical process would be involved in this system. According

Table 3. Iron-promoted free radical α-chloro-β-methylation of *N*-arylacrylamides with dimethyl sulfoxide.



[a] *Reaction conditions:* *N*-arylacrylamides (1 equiv., 0.25 mmol), iron(II) chloride (1 equiv., 0.25 mmol), hydrogen peroxide (30%, 5 equiv., 1.25 mmol) and DMSO (3 mL), 25 °C, N_2, 18 h.

[b] Isolated yields.

to the literature[18] precedent study and experimental data, a possible mechanism is shown in Scheme 2. The intermediate **A** is produced by the reaction of dimethyl sulfoxide with hydrogen peroxide. With the assistance of iron(II) chloride, intermediate **A** undergoes a heterolysis reaction and forms hydroxy ion and free radical **B**. Methyl radical and methylsulfinyl acid are gained by β-cleavage of radical **B**. Next, radical **C** is formed *via* the additon of methyl radical to the double bond of *N*-arylacrylamides. Then, radical **C** adds to the aromatic ring and generates radical **D**, which can be oxidized by iron(III) and yields the carbocation **E**. The terminal product is produced by the hydroxy ion pulling the proton from the carbocation **E**. With N–H substituted substrates, the radical **C** abstracts a chlorine atom from iron(II) chloride and gives the α-chloro-β-methylation product.

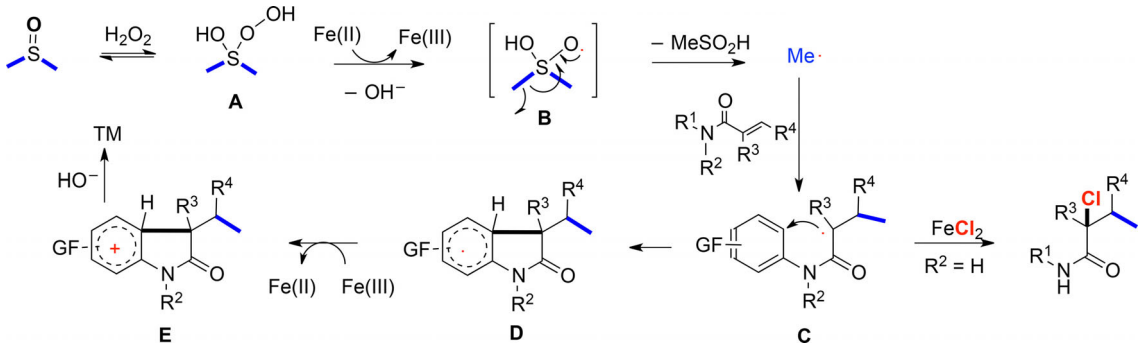
In summary, we have achieved the first economical and convenient protocol for free radical-triggered cascade methylation or α-chloro-β-methylation of *N*-arylacrylamides by means of dimethyl sulfoxide as methyl source, iron(II) chloride as both catalyst and chlorine source. Further studies on methylation reactions *via* the novel free radical approach are under way in our laboratory.

Experimental Section

General Experimental Procedure

A mixture of *N*,*N*-diphenylmethacrylamide (1 equiv., 0.25 mmol), iron(II) chloride (0.5 equiv., 0.125 mmol), hydrogen peroxide (5 equiv., 1.25 mmol) and DMSO (3 mL) was stirred at room temperature under nitrogen conditions for 18 h in a sealed tube (15 mL). After the reaction had finished, the mixture was extracted with ethyl acetate and water, evaporated under vacuum and purified by column chromatography to afford the desired methylation product.

A mixture of *N*-phenylmethacrylamide (1 equiv., 0.25 mmol), iron(II) chloride (1 equiv., 0.25 mmol), hydrogen peroxide (5 equiv., 1.25 mmol) and DMSO (3 mL) was stirred at room temperature under nitrogen conditions for 18 h in a sealed tube (15 mL). After the reaction finished, the mixture was extracted with ethyl acetate and water, evaporated under vacuum and purified by column chromatography to afford the desired α-chloro-β-methylation product.



Scheme 2. Plausible mechanism.

Acknowledgements

This project is supported by College of Chemistry & Environmental Science, Hebei University, and the Fundamental Research Funds for The Midwest Universities Comprehensive Strength Promotion Project. We also thank science technology research and development Guidance programme project of Baoding City (No. 15ZG040) for financial support.

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Adv. Synth. Catal. **2017**, *359*, 1 – 5

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