

# Persulfate promoted carbamoylation of N-arylacrylamides with 4-carbamoyl-Hantzsch esters under metal-free conditions

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## Abstract

4-Carbamoyl-Hantzsch esters were used as carbamoyl radical precursors for oxidative carbamoylation of N-arylacrylamides in the presence of inexpensive persulfates. This protocol can be applied for a broad range of substrates with various functional groups, whereas a variety of 3,3-disubstituted oxindoles were obtained in good yields via an intermolecular addition/cyclization process.

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Persulfate promoted carbamoylation of N-arylacrylamides with 4-carbamoyl-Hantzsch esters under metal-free conditions

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## Comprehensive Summary

4-Carbamoyl-Hantzsch esters were used as carbamoyl radical precursors for oxidative carbamoylation of N-arylacrylamides in

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## Keywords

4-carbamoyl-Hantzsch esters | carbamoyl radicals | N-arylacrylamides | 3,3-disubstituted oxindoles | persulfate

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## Background and Originality Content

Hantzsch esters, which were previously used as a reductant, electron donor or proton source in the thermal catalytic and photochemical condition,<sup>[1]</sup> can work as a convenient radical precursor in organic synthesis. Researchers found that their derivatives could undergo a homolytic cleavage of C-C bond by various methods.<sup>[2-3]</sup> Although the utilization of 4-alkyl-Hantzsch esters as convenient alkyl radical sources in synthesizing structurally diverse organic molecules has gained great interests in recent years,<sup>[4]</sup> it still suffers from the limitation in functional groups at 4-position of 4-substituted Hantzsch esters. Notably, the photogenerated carbamoyl radical from readily available and stable 4-carbamoyl-Hantzsch ester was established recently

(Scheme 1a). For example, Melchiorre<sup>[5a]</sup> et. al. synthesized a variety of Hantzsch esters as precursors of carbamoyl radicals, which were further engaged in the direct carbamoylation of (hetero)aryl bromides by nickel and photoredox dual catalysis. Wangelin<sup>[5b-c]</sup> and Paixão<sup>[5d]</sup> focused on the carbamoyl radical addition of activated olefins, imines and azomethine imine ions with photocatalysts. Hong and co-workers<sup>[5e]</sup> suggested that 4-substituted-Hantzsch esters could react with N-amidopyridinium salts, forming an electron donor-acceptor (EDA) complex, wherein C4-functionalized pyridines were obtained in moderate to good yields without using photocatalysts. Regardless, the direct generation of carbamoyl radicals from 4-carbamoyl-Hantzsch esters without metal catalyst, photocatalyst or light irradiation has not yet been explored.

Persulfates - which served as cheap, environmentally friendly, and easily handled oxidants - have gained increasing attentions in organic synthesis for various oxidative transformations.<sup>[6-7]</sup> It can generate sulfate radical anions with strong single-electron oxidizing properties under mild conditions.<sup>[8]</sup> Therefore, we speculated that persulfates might be a feasible oxidant for 4-carbamoyl-Hantzsch esters to generate the carbamoyl radicals via SET oxidation pathway. Based on this consideration and our continuous interest in the synthesis of heterocyclic compounds,<sup>[9]</sup> we recently explored an inexpensive  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  promoted oxidative carbamoylation of N-arylacrylamides using 4-carbamoyl-Hantzsch esters as carbamoyl radical precursors. This protocol allows the construction of a diverse set of 3,3-disubstituted oxindoles in the absence of metal- or photo-catalysts (Scheme 1b). We therefore report the primary results of this work herein.

### Scheme 1 Carbamoylations using 4-carbamoyl-Hantzsch esters as radical precursors

#### Results and Discussion

The investigation started by employing 4-carbamoyl Hantzsch ester derivative (**1a**) and N-methyl-N-phenylmethacrylamide (**2a**) as the model substrates. To our delight, this carbamoylation proceeded smoothly when  $\text{Na}_2\text{S}_2\text{O}_8$  was used as an oxidant in  $\text{CH}_3\text{CN}$  at 50 °C, and the desired product **3a** was obtained in 56% yield (Table 1, entry 1). Several solvents were subsequently tested for this reaction.  $\text{H}_2\text{O}$ , acetone, and DMSO were failed to give the desired product **3a** with high yields (Table 1, entries 2-4). Nevertheless, when  $\text{CH}_3\text{CN}$  and  $\text{H}_2\text{O}$  were combined together (ratio 1:1), the yield of **3a** reached up to 70% (Table 1, entry 5). After this, some other oxidants were screened. The experiments indicated  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  as the best one (Table 1, entries 6-8). Using 2 equiv. of  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  as the oxidant, 92% yield of **3a** could be obtained, but the reaction could not take place in the absence of an oxidant (Table 1, entries 7, 9-10). Increasing the temperature from 50 °C to 80 °C could not further improve the yield of the desired product for this transformation, which only gave 60% of **3a**. Moreover, no desired product **3a** was detected when this reaction was carried out at room temperature (Table 1, entries 11-12). Switching the reaction atmosphere from  $\text{N}_2$  to air, the corresponding product **3a** was not observed (Table 1, entry 13). Based on the above studies, the optimal reaction conditions were obtained as follows: **1a** (0.24 mmol), **2a** (0.2 mmol),  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  (0.4 mmol) in  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  (1:1, 2 mL) under  $\text{N}_2$  atmosphere at 50 °C for 12 h. Under the optimal conditions, an isolated yield of 88% could be achieved for **3a** (Table 1, entry 14).

**Table 1** Optimization of reaction conditions<sup>a</sup>

entry	oxidant (equiv.)	solvent	yield (%) <sup>b</sup>
1	$\text{Na}_2\text{S}_2\text{O}_8$ (2)	$\text{CH}_3\text{CN}$	56
2	$\text{Na}_2\text{S}_2\text{O}_8$ (2)	$\text{H}_2\text{O}$	18
3	$\text{Na}_2\text{S}_2\text{O}_8$ (2)	acetone	16
4	$\text{Na}_2\text{S}_2\text{O}_8$ (2)	DMSO	42
5	$\text{Na}_2\text{S}_2\text{O}_8$ (2)	$\text{CH}_3\text{CN}:\text{H}_2\text{O}=1:1$	70
6	$\text{K}_2\text{S}_2\text{O}_8$ (2)	$\text{CH}_3\text{CN}:\text{H}_2\text{O}=1:1$	74
7	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (2)	$\text{CH}_3\text{CN}:\text{H}_2\text{O}=1:1$	92
8	$\text{PhI}(\text{OAc})_2$ (2)	$\text{CH}_3\text{CN}:\text{H}_2\text{O}=1:1$	0
9	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (1)	$\text{CH}_3\text{CN}:\text{H}_2\text{O}=1:1$	82
10	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (0)	$\text{CH}_3\text{CN}:\text{H}_2\text{O}=1:1$	nr
11 <sup>c</sup>	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (2)	$\text{CH}_3\text{CN}:\text{H}_2\text{O}=1:1$	0

12 <sup>d</sup>	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (2)	CH <sub>3</sub> CN:H <sub>2</sub> O=1:1	60
13 <sup>e</sup>	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (2)	CH <sub>3</sub> CN:H <sub>2</sub> O=1:1	0
14 <sup>f</sup>	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (2)	CH <sub>3</sub> CN:H <sub>2</sub> O=1:1	92(88) <sup>g</sup>

<sup>a</sup> Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), oxidant, solvent (0.1 M), 50 , 12 h under N<sub>2</sub> atmosphere. <sup>b</sup> The yields were determined by <sup>1</sup>H NMR with CH<sub>2</sub>Br<sub>2</sub> as internal standard. <sup>c</sup> At room temperature. <sup>d</sup> At 80 . <sup>e</sup> Under air. <sup>f</sup> 0.2 mmol scale. <sup>g</sup> Isolated yield.

With the optimized conditions in hand, the scope of this reaction was further examined. As shown in Scheme 2, a wide range of 4-carbamoyl-Hantzsch esters were competent in this reaction, which afforded the corresponding 3,3-disubstituted oxindoles in good yields. Tertiary amides bearing piperidine (**3a**), morpholine (**3b**), pyrrolidine (**3c**) and the acyclic tertiary amide (**3d**) were all obtained successfully in good yields. For secondary amides with cyclic or acyclic substituents (**3e**-**3k**), the reactions gave the corresponding products in satisfactory yields. Interestingly, the reaction of N-arylcetylamide with Hantzsch ester bearing a heteroaryl group was also effective, providing the product **3j** in acceptable yield. We also tried some secondary amides bearing electron-donating methyl (**3m**) or electron-withdrawing CF<sub>3</sub> group (**3n**) at the aromatic ring, both of which transferred smoothly to the desired 3,3-disubstituted oxindoles. Besides, it is worth to point out that simple 4-alkyl-Hantzsch ester was also compatible, providing the desired product **3o** in 81% yield.

#### Scheme 2 Scope of 4-carbamoyl Hantzsch esters<sup>a</sup>

<sup>a</sup> Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (0.4 mmol) in CH<sub>3</sub>CN:H<sub>2</sub>O=1:1 (2 mL), 50 , 12 h under N<sub>2</sub> atmosphere, isolated yield.

This oxidative carbamoylation was also compatible with different N-arylacrylamides (Scheme 3). First, N-methyl-N-arylacrylamides bearing electron-donating or electron-withdrawing groups at *para* - or *ortho* - position of aromatic ring were tested, methoxyl-, methyl-substituted aniline, and fluoro-, chloro-substituted aniline were obtained in 51-86% yields (**3p**-**3s**, **3u** and **3w**). But nitro-substituted substrate was ineffective under the standard conditions, in which a 68% recovery yield of **2t** was obtained from the reaction mixture. Substrates with meta-substituted aryl ring afforded mixed products. For substrate with Me group at *meta* -position of aromatic ring, the reaction gave 85% of the total yield of **3v** + **3v'**. Similarly, *meta* -Cl substituted substrate also delivered the regioisomers **3x** and **3x'**. Furthermore, heterocycles like pyridine and 1,2,3,4-tetrahydroquinoline were also tolerated in this reaction (**3y** - **3z**). N-arylacrylamides with different N substituents (Et, Ph, Bn) worked smoothly (**3aa** - **3ac**). When using substrate with free N-H group at the N-arylacrylamide, no desired product could be obtained (**3ad**). It is noteworthy that the

#### Scheme 3 Scope of N-arylacrylamides<sup>a</sup>

<sup>a</sup> Reaction conditions: **1a** (0.24 mmol), **2** (0.2 mmol), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (0.4 mmol) in CH<sub>3</sub>CN:H<sub>2</sub>O=1:1 (2 mL), 50 , 12 h under N<sub>2</sub> atmosphere, isolated yield. <sup>b</sup> Recovered yield.

six-membered-ring product **3ae** was also achieved in 56% yield for this transformation.

In order to better understand the mechanism, several control experiments were conducted (Scheme 4). The free radical scavenger TEMPO was added into this system, no desired product was observed. In addition, TEMPO trapped radical product was detected by HRMS. When 1,1-diphenylethylene was introduced into the reaction system, this reaction was also significantly inhibited. These results support the radical-mediated reaction mechanism for this transformation.<sup>[10]</sup>

#### Scheme 4 Radical inhibition and trapping experiments

According to the literatures<sup>[5,10-11]</sup> and the above experiments, a plausible mechanism involving radical process was proposed herein (Scheme 5). 4-Carbamoyl Hantzsch ester **1** is first oxidized by (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, generating the carbamoyl radical **A** via a single electron transfer process.<sup>[10]</sup> Then, radical **A** reacts with N-methyl-N-phenylmethacrylamide **2a** to form alkyl radical **B**, which further undergoes an intramolecular

cyclization with the aromatic ring, leading to an intermediate **C**.<sup>[11c]</sup> Finally, the aromatization of intermediate **C** results in the formation of desired product **3** with the help of  $(\text{NH}_4)_2\text{S}_2\text{O}_8$ .

### Scheme 5 Proposed Mechanism

### Conclusions

In summary, we have developed an efficient radical cascade cyclization reaction of N-arylacrylamides and 4-carbamoyl Hantzsch esters under mild conditions. This approach can tolerate a wide range of 4-carbamoyl-Hantzsch esters (including cyclic/acyclic tertiary amides, secondary amides, and heteroaryl amides), as well as N-arylacrylamides with different functional groups. This reaction protocol showcased its advantages in using cost-effective persulfate as the radical initiator instead of an expensive photocatalyst under metal-free conditions.

### Experimental

4-Carbamoyl Hantzsch ester (0.24 mmol), N-arylacrylamide (0.2 mmol),  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  (0.4 mmol), and  $\text{CH}_3\text{CN-H}_2\text{O}$  (2 mL, v/v, 1:1) were added to a 10 mL Schlenk tube under  $\text{N}_2$ . The mixture was heated at 50 for 12 h and then cooled to room temperature. After the reaction was completed, the mixture was concentrated under reduced pressure. The resulting mixture was dissolved with ethyl acetate (5 mL) and washed with  $\text{H}_2\text{O}$  ( $3 \times 5\text{mL}$ ). The organic phase was concentrated under vacuum, and the residue was purified by column chromatography on silica gel to give the corresponding products.

### Supporting Information

The supporting information for this article is available on the WWW under <https://doi.org/10.1002/cjoc.2021xxxxx>.

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