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Iron-catalyzed hydroaminocarbonylation of alkynes: Selective and efficient synthesis of primary α,β-unsaturated amides

Zijun Huang[a,b,*], Jia Tang[a], Xiongwei Jiang[a], Tianle Xie[a], Minmin Zhang[a], Donghui Lan[a], Shaofeng Pi[a], Zhengde Tan[a], Bing Yi[a,*], Yuehui Li[b,*]

[a] Hunan Province Key Laboratory of Environmental Catalysis and Waste Rechemistry, College of Materials and Chemical Engineering, Hunan Institute of Engineering, Xiangtan 411104, China

[b] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Suzhou Research Institute of LICP, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou 730000, China

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ABSTRACT

α,β-Unsaturated primary amides are important intermediates and building blocks in organic synthesis. Herein, we report a ligand-free iron-catalyzed hydroaminocarbonylation of alkynes using NH_4HCO_3 as the ammonia source, enabling the highly efficient and regioselective synthesis of linear α,β-unsaturated primary amides. Various aromatic and aliphatic alkynes are transformed into the desired linear α,β-unsaturated primary amides in good to excellent yields. Further studies show that using NH_4HCO_3 as the ammonia source is key to obtain good yields and selectivity. The utility of this route is demonstrated with the synthesis of linear α,β-unsaturated amides including vanilloid receptor-1 antagonist TRPV-1.

α,β-Unsaturated amides are important structural motifs ever present in wide range of natural products and materials science frameworks [1–8]. For instance, α,β-unsaturated amides derivatives display biological activities applied in the treatment of psychological diseases and showed remarkable potential for the treatment of cancer (Fig. 1) [9–11]. Besides, α,β-unsaturated amides are versatile building blocks in organic synthesis [12–17]. Synthetic methods for α,β-unsaturated amides preparation has attracted broad interest due to important applications in medicine and organic synthesis. The development of greener, low-cost, energy-efficient and selective synthetic methods for α,β-unsaturated amides preparation has attracted broad interests.

Traditional synthetic methods for unsaturated amides are generally, based on nucleophilic substitution of amines with carboxylic acids derivatives and acyl chlorides or cyclization with amic acids in the presence of activating reagents (Scheme 1a) [18–23]. Transition metal catalyzed hydroaminocarbonylation provides a high atom- and step-economy pathway for producing high value-added unsaturated amides [24–37]. Reports on catalytic hydroaminocarbonylation of alkynes have been documented in literature by reacting primary and secondary amines for the preparation of the corresponding α,β-unsaturated amides with high chemo- and region-selectivity (Scheme 1b) [38–46]. However, noble metals, costly ligands or additives were necessary to achieve reasonable yields and good regioselectivity [27,38,39,41-43]. The development of more efficient carbonylation methods for the synthesis of unsaturated primary amides remains desirable.

Solid ammonium salts are cheaper and easy-to-handle ammonia source widely applied in aminocarbonylation reactions to produce various amide compounds [47–56]. Recently, we have developed the efficient iron-catalyzed aminocarbonylation of alkynes to produce succinimides with NH_4HCO_3 [54]. Huang and co-workers developed a palladium-catalyzed aminocarbonylation method for transforming alkenes with NH_4Cl into the corresponding amides [55]. Besides, Huang *et al.* reported a selective palladium-catalyzed hydroaminocarbonylation reaction between alkynes and NH_4Cl to branched α,β-unsaturated primary amides [56]. Liu's group reported a hydroaminocarbonylation reaction with alkynes and NH_4HCO_3 to generate branched α,β-unsaturated primary amides (Scheme 1c) [37]. Nevertheless, developing non-noble metal-catalyzed hydroamin-ocarbonylation with NH_4HCO_3 for the preparation linear α,β-unsaturated primary amides has not been achieved up to date. Herein, we report the first example of ligand-free iron-catalyzed hydroaminocarbonylation of alkynes to generate linear α,β-unsaturated primary amides using NH_4HCO_3 as ammonia source (Scheme 1d).

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* Corresponding authors.
E-mail addresses: huangzijun@hnie.edu.cn (Z. Huang), bingyi2004@126.com (B. Yi), yhli@licp.cas.cn (Y. Li).

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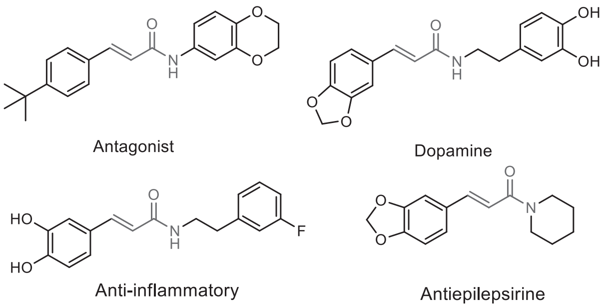
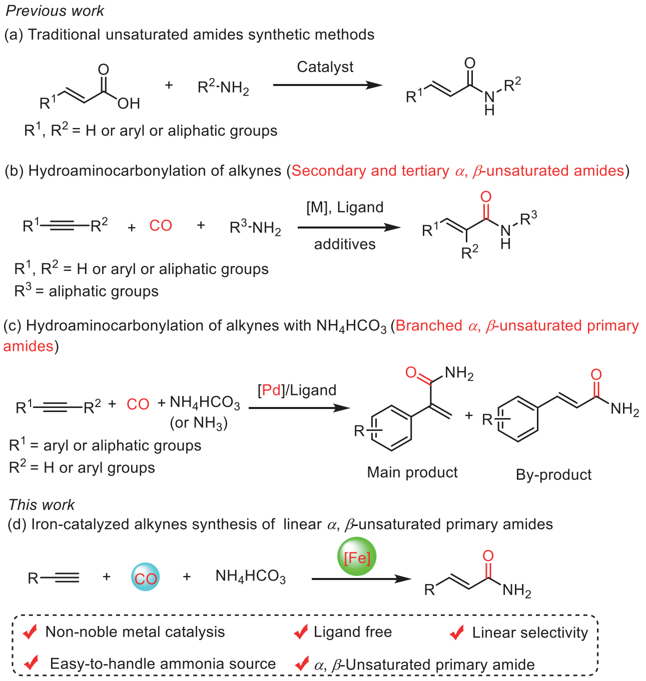


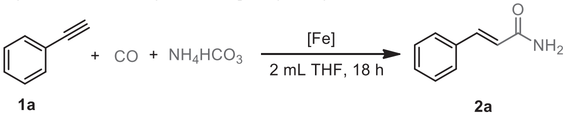
Fig. 1. Selective examples of bioactive linear α,β-unsaturated amides.



Scheme 1. Synthetic strategy of α,β-unsaturated amides.

Initially, phenylacetylene **1a** was selected as the model substrate for this hydroaminocarbonylation reaction. A series of commercially available catalysts were examined with NH_4HCO_3 used as ammonia source in the presence of CO. When iron salts such as $FeCl_3$ and $FeCl_2$ were used, no desired α,β-unsaturated amide product **2a** could be observed. To our delight, when $Fe_3(CO)_{12}$ was used as catalyst the hydroaminocarbonylation reaction proceeded successfully and gave the desired cinnamamide **2a** in 46% yield. The use of $Fe_2(CO)_9$ instead of $Fe_3(CO)_{12}$ as catalyst afforded the desired product in only 13% yield for **2a** (Table 1, entries 1–4). In addition, other metal carbonyls were found inefficient for this transformation, with no desired product could be detected (Table S1 in Supporting information). Moreover, carrying out the reaction without $Fe_3(CO)_{12}$ resulted in undetected product, while adding PPh_3 as ligand was ineffective for hydroaminocarbonylation reaction (Table 1, entries 5 and 6). We observed that reaction temperature and CO pressure played important role in this reaction. Cinnamamide **2a** was prepared in 81% yield when the reaction was performed at 140 °C under 30 bar CO (Table 1, entries 7–11). The yield was slightly decreased to 62% at 160 °C (Table 1, entry 12). Increasing the amount of NH_4HCO_3 to 5.0 mmol improved the yield significantly, and the desired product **2a** was obtained in 91% yield (Table 1, entries 13 and 14). Further screening of other reaction parameters such as solvent and the catalyst loading did not improve

Table 1
Hydroaminocarbonylation of phenylacetylene.[a]



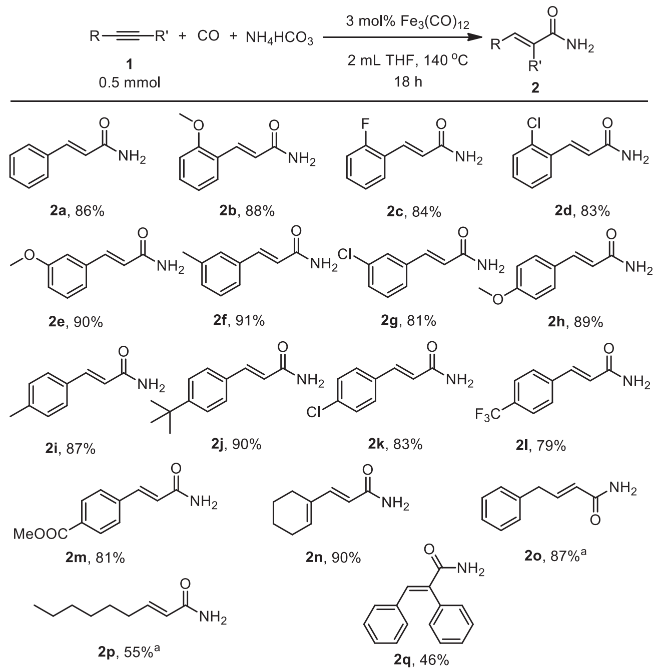
Entry	[Fe] (mol%)	CO (bar)	Temp. (°C)	Yield (%)[b]
1	$Fe_3(CO)_{12}$ (3)	10	120	46
2	Fe_2CO_9 (3)	10	120	13
3	$FeCl_3$ (5)	10	120	0
4	$FeCl_2$ (5)	10	120	0
5[c]	$Fe_3(CO)_{12}$ (5)	10	120	Trace
6	-	10	120	0
7	$Fe_3(CO)_{12}$ (3)	5	120	24
8	$Fe_3(CO)_{12}$ (3)	20	120	65
9	$Fe_3(CO)_{12}$ (3)	30	120	71
10	$Fe_3(CO)_{12}$ (3)	30	130	77
11	$Fe_3(CO)_{12}$ (3)	30	140	81
12	$Fe_3(CO)_{12}$ (3)	30	160	62
13[d]	$Fe_3(CO)_{12}$ (3)	30	140	85
14[e]	$Fe_3(CO)_{12}$ (3)	30	140	91 (86)[f]
15[e]	$Fe_3(CO)_{12}$ (2)	30	140	84

[a] Reaction conditions: phenylacetylene (**1a,** 0.5 mmol), NH_4HCO_3 (1.0 mmol), $Fe_3(CO)_{12}$ (3 mmol%), THF (2.0 mL), 18 h.
[b] Yield was determined by GC using dodecane as an internal standard.
[c] 12 mol% PPh_3.
[d] NH_4HCO_3 (3.0 mmol).
[e] NH_4HCO_3 (5.0 mmol).
[f] Isolated yield.

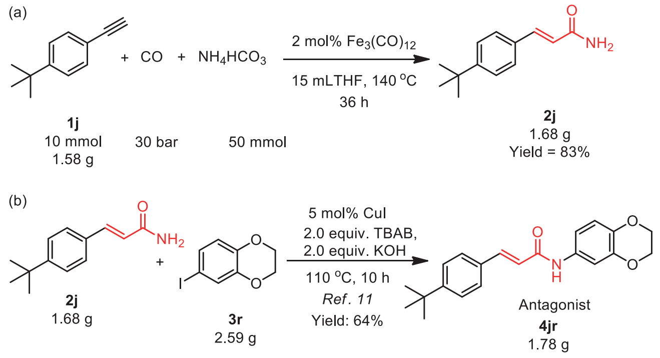
the reaction yield (Table 1, entry 15 and Table S2 in Supporting information). We also examined the effect of the ammonium salts and found $(NH_4)_2CO_3$ and $HCOONH_4$ proved to be effective as ammonia source. However, NH_4Cl or NH_4OAC were found inefficient for the hydroaminoca-rbonylation reaction (Table S3 in Supporting information).

With the optimized reaction conditions in hand, we explored the scope of alkyne substrates for the synthesis of linear α,β-unsaturated primary amides (Scheme 2). Gratifyingly, a range of alkynes are suitable substrates to react with NH_4HCO_3 and CO under the optimized reaction conditions. The desired linear α,β-unsaturated primary amides **2a**-**2q** were obtained in 46%–91% yields. The electronic properties of the substituents on the aromatic ring of the aromatic alkynes have weaker influence on the reactivity and selectivity. The results of *meta*- and *para*-substituted aromatic alkynes showed insignificant electronic effects. And surprisingly, the reaction of sterically hindered 1-ethynyl-2-methoxybenzene (**1b**) provided the desired linear α,β-unsaturated primary amides in good yield (**2b**, 88%). Moreover, aromatic alkynes bearing electron-withdrawing substituents such as fluoro- and chloro– groups have less influence on the reactivity (**2c**, 84%; **2d**, 83%; **2g**, 81%; **2k**, 83%). Similarly, aromatic alkynes with strong electron withdrawing groups like trifluoromethyl and esters substitution afforded linear α,β-unsaturated primary amides in moderate yields (**2l**, 79%; **2m**, 81%). To our delight, aliphatic alkynes were also transformed in moderate to good yields, *e.g.*, **2n**, **2o** and **2p**. Trace amounts of succinimide was detected under the optimized reaction conditions. The method could be applied for the internal alkyne 1,2-diphenylethyne (**1q**) to give moderate yield (46%).

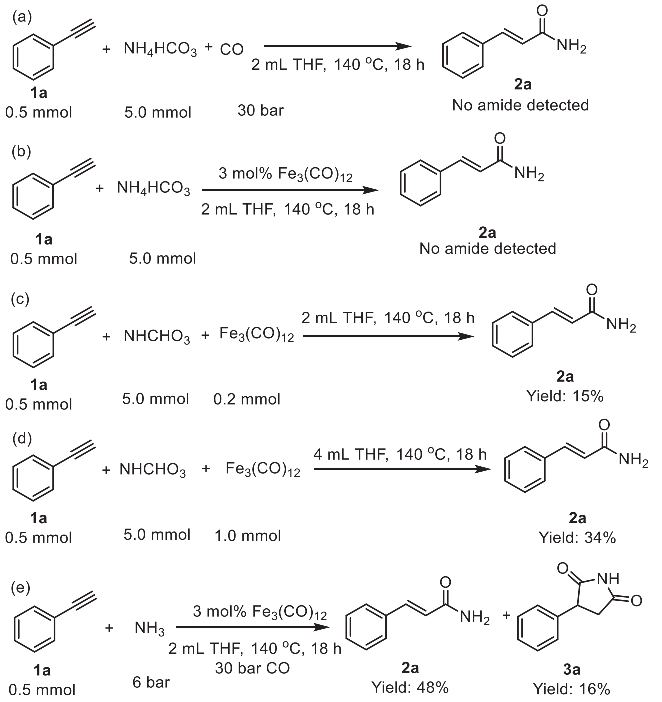
To demonstrate the synthetic utility of this method, vanilloid receptor-1 antagonist TRPV-1 was prepared. 3-(4-(*tert*–Butyl)phenyl)acrylamide **2j** preparation proceeded smoothly at gram-scale and 1.68 g of **2j** was obtained under the slightly modified reaction conditions in 83% yield (Scheme 3a). The subsequent coupling reaction of 3-(4-(*tert*–butyl)phenyl) acrylamide afforded



Scheme 2. Substrate scope for hydroaminocarbonylation of alkynes using NH_4HCO_3. Reaction conditions: alkyne (**1**, 0.5 mmol), CO (30 bar), NH_4HCO_3 (5.0 mmol), $Fe_3(CO)_{12}$ (0.015 mmol), THF (2.0 mL), 140 °C, 18 h, isolated yield. [a] Yield was determined by GC using dodecane as an internal standard.



Scheme 3. Scale-up reaction.



Scheme 4. Control experiments.

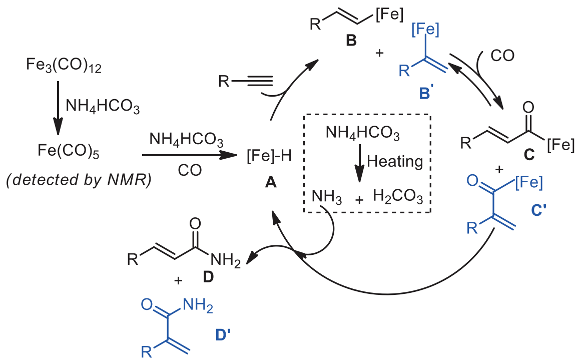


Fig. 2. Proposed reaction mechanism.

vanilloid receptor-1 antagonist TRPV-1 **4jr** on a gram scale (Scheme 3b) [57].

In order to better understand the mechanism of iron-catalyzed hydroaminocarbonylation of alkynes using NH_4HCO_3 as the ammonia source, a series of experiments were performed (Scheme 3 and Fig. S5 in Supporting information). Firstly, hydroaminocarbonylation reaction in the absence of $Fe_3(CO)_{12}$ of phenylacetylene **1a** with NH_4HCO_3 using CO was unable to provide the desired cinnamamide **2a** (Scheme 4a). Furthermore, carrying out the reaction without CO resulted in undetected cinnamamide **2a** (Scheme 4b). Cinnamamide **2a** was detected when the reaction was performed with $Fe_3(CO)_{12}$ serving as catalyst and CO source (Schemes 4c and d). Interestingly, cinnamamide **2a** and succinimides **3a** were detected when the reaction was performed with gaseous NH_3 (6 bar) serving as ammonia source instead of NH_4HCO_3 under the optimized reaction conditions (Scheme 4e). Various solid ammonium salts used as ammonia source provided different results and showed clear influence on the reactivity (Table S3 in Supporting information). It was indicated that NH_4HCO_3 promoted the formation [Fe]-H species responsible for the efficient hydroaminocarbonylation of alkynes, enabling the highly efficient and regioselective synthesis of linear α,β-unsaturated primary amides [26–28]. We established that $Fe(CO)_5$ is formed from $Fe_3(CO)_{12}$ reaction with NH_4HCO_3 based on *in situ* ^{13}C NMR experiments using NH_4HCO_3 and $Fe_3(CO)_{12}$ [54].

Based on the experimental results and recent experimental data on the hydroaminocarbonylation of alkynes and NH_4HCO_4 [24–28,54-56,58-62], we propose a possible mechanism pathway as shown in Fig. 2. Initially, the active mononuclear iron carbonyl $Fe(CO)_5$ was formed *in situ* through interactions of $Fe_3(CO)_{12}$ with NH_4HCO_3. Meanwhile, NH_3 and H_2CO_3 is released through *in situ* decomposition of NH_4HCO_3. Then, $Fe(CO)_5$, NH_4HCO_3 and CO generate the intermediate **A**. Intermediate **A** reacts with alkyne to produce intermediate **B** or **B'**. The steric hindrance of the terminal alkyne plays the major role for the formation of the kinetically favored terminal alkenyl-iron intermediate **B**. Subsequent CO insertion forms intermediate **C** and **C'**, which then affords the final carbonylation product **D** and **D'** with the presence of NH_3 released from NH_4HCO_3. Besides, the coordination of alkyne substrates and NH_3 with Fe center makes CO insertion and product **D** formation much more accessible, which is similarly observed in Beller's work using organic amines as the substrates [26].

In summary, we have demonstrated the first example of ligand-free iron-catalyzed hydroaminocarbonylation of alkynes synthesis of linear α,β-unsaturated primary amides using NH_4HCO_3 as the ammonia source. In the presence of NH_4HCO_3 and non-noble $Fe_3(CO)_{12}$ serving as catalyst, a variety of alkynes, including aromatic alkynes, aliphatic alkynes, terminal alkynes, internal alkynes, were transformed into the desired linear α,β-unsaturated primary amides in good to excellent yields. The applicability of this methodology has been demonstrated by synthesis of α,β-unsaturated amides bio-active compound. Preliminary mechanistic studies reveal the activation model involving interactions of NH_4HCO_3 with $Fe_3(CO)_{12}$. Further investigations are currently underway to apply the method to other reactions.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.01.080.

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