Letter

Iron-Catalyzed Carbamoylation of Enamides with Formamides as a Direct Approach to N-Acyl Enamine Amides

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Iron-Catalyzed Carbamoylation of Enamides with Formamides as a Direct Approach to *N*-Acyl Enamine Amides

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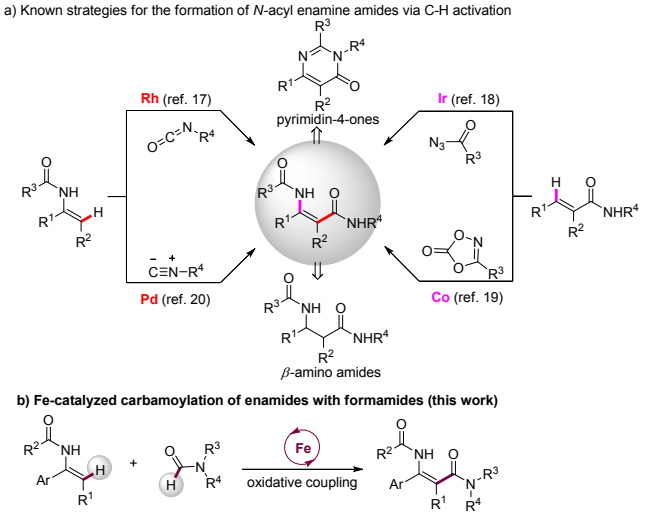
ABSTRACT: The robustness of iron catalysis enabling the unprecedented oxidative coupling reactions of enamides with formamides is described. Routing from readily accessible feedstocks, the efficient approach is implemented to furnish a broad array of value-added *N*-acyl enamine amide derivatives, which serve as versatile precursors of biologically relevant *N*-heterocycles including pyrimidin-4-ones and 4-hydroxypyridin-2-ones. Preliminary mechanistic studies supported the notion that this direct carbamoylation reaction proceeded through an aminoacyl radical species.

KEYWORDS: *oxidative coupling, enamide, formamide, iron, radicals*

Enamides are versatile reactive intermediates for the synthesis of nitrogen-containing building blocks due to their intrinsically tempered nucleophilicity.[1] Their amenability to participate in an array of selective functionalization reactions, as rendered by dual characteristics, coupled with transition metal catalysis has indisputably boosted their synthetic values.[2] Direct olefinic C–H functionalization of enamides has emerged as a useful synthetic platform to prepare various multisubstituted amine and olefin derivatives,[3] serving as the pivotal structural motifs in natural products as well as organic materials. Consequently, the use of activated coupling partners,[4] often involving halides, organometallic reagents, and acrylates, based on C–H bond functionalization have been investigated to introduce different molecular entities onto enamide scaffolds, including aryl,[5] alkenyl,[6] alkynyl,[7] alkyl,[8] acyl,[9] etc.[10] Despite these impressive progress, an appealing alternative strategy to realize the oxidative cross-coupling of enamides with simple hydrocarbons in an efficient and selective manner is highly desirable yet remains an underdeveloped area for C–C bond formation.[11]

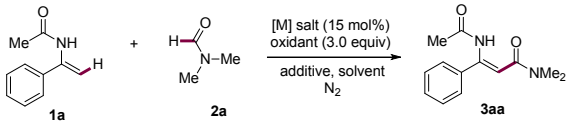
On the other hand, *N*,*N*-dimethylformamide (DMF) and its variants have been intensively exploited as a carbamoyl source via acyl C–H activation in Heck-type carbamoylation.[12] The application of this well-established protocol on unsaturated substrates, however, largely resulted in the hydrocarbamoylation adducts.[13] Only two precedent exceptions have emerged for iron-catalyzed *E*-selective carbamoylation and carbooxygenation of styrenes which assembled α,β-unsaturated amides and β-peroxy amides,[14] respectively. Inspired by the above studies, we speculated that the feasibility of the direct coupling of enamides with formamides via aminoacyl radical species in which the stereoselectivity could be controlled by the amide moiety. If realized, the protocol would grant a direct access to value-added *N*-acyl enamine amides. Notably, pertaining to the presence of *N*,*O*-functionalities in the scaffold, these compounds can be facilely derived into many important bioactive molecules such as β-amino amides upon reduction[15] and pyrimidin-4-ones upon cyclodehydration.[16] In fact, thanks to the elegant contributions by Ellman,[17] Chang,[18] Li,[19] and Luo,[20] the target molecules have been efficiently assembled via C–H activation protocols, including C–H carbamoylation of enamides with isocynates or isocyanides, as well as C–H amidation of acrylamides with acyl azides or dioxazolones (Scheme 1a). Herein, we disclose a strategically distinct approach to *N*-acyl enamine amides via the oxidative coupling between enamides and formamides by environmentally friendly iron catalysis, which notably circumvents the use of precious transition metals and toxic reagents. Further, the present transformation contributes to a new reaction pattern for enamides to forge C–C bond via a free-radical pathway in addition to C–H activation, which is relatively scarce in the enamide chemistry.

Scheme 1. Direct Synthesis of *N*-Acyl Enamine Amides



Preliminary investigation began with the oxidative coupling of *N*-(1-phenylvinyl)acetamide (**1a**) with DMF (**2a**) as model substrates. To our delight, the coupling product **3aa** was obtained in 46% yield using 1 equiv of **1a**, DMF as solvent, *tert*-butyl hydroperoxide (TBHP) as oxidant in the presence of $FeCl_3$ (15 mol%) at 65 °C. After extensive screening of iron salts, we found that $FeCl_2$ catalyzed the reaction in higher yield (entries 1–7). Other inexpensive first-row transition metal salts, such as $CuCl_2$, $MnCl_2$, and $CoCl_2$, proved less efficient (entries 8–10). In addition, no desired product was observed when other common oxidants were employed (entries 11–13) by using $FeCl_2$ as catalyst, except for di-*tert*-butyl peroxide (DTBP), which delivered 81% yield of **3aa** as the optimum (entry 14). Control experiment in the absence of $FeCl_2$ gave no product (entry 15). Despite the satisfactory results obtained under the neat conditions at the current stage, we were interested in pursuing the reaction with stoichiometric amounts of DMF instead of behaving as a solvent. Our focus was then to identify an adequate medium for this transformation. Using 1,2-dichloroethane (DCE) as solvent, a decreased amount of DMF (12 equiv) led to a sluggish conversion (entry 16). Pleasingly, elevating the temperature to 80 °C and increasing the loading of DTBP to 5.0 equiv, remarkably improved the yield from 13% to 45% (entries 17 and 18). A subsequent solvent modification showed that chlorobenzene was the best choice, furnishing a compromised 49% yield of **3aa** (entries 19–23). Considering the beneficial role of base for radical-mediated C–C double bond formation, a set of bases were examined, among which KOAc was found to be suitable promoter (entries 24–28). Attempts to decrease the stoichiometry of DMF affected the reaction negatively (entry 29).

Table 1. Optimizations for the oxidative coupling of 1a and 2a[a]



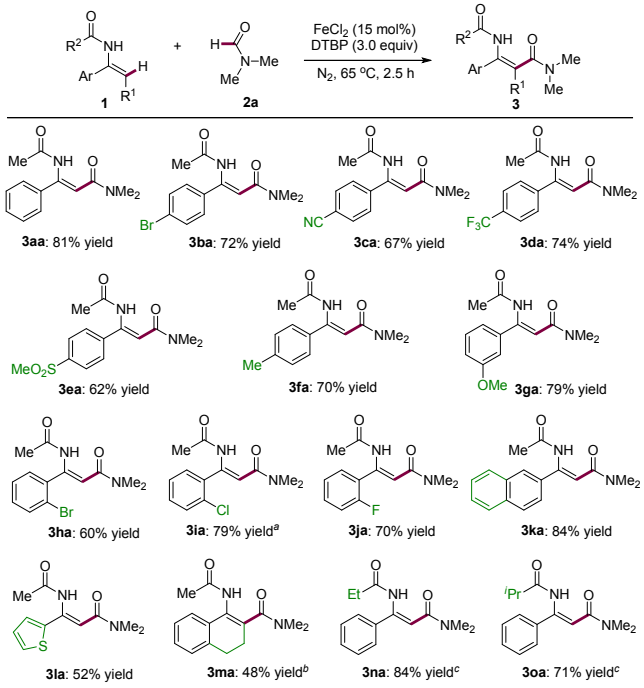
Entry	[M] salt	Oxidant (equiv)	Additive	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	$FeCl_3$	TBHP (3.0)	-	DMF	65	2.5	46
2	$FeBr_3$	TBHP (3.0)	-	DMF	65	2.5	20
3	$Fe(OTf)_3$	TBHP (3.0)	-	DMF	65	2.5	<5
4	$FeBr_2$	TBHP (3.0)	-	DMF	65	2.5	35
5	FeI_2	TBHP (3.0)	-	DMF	65	2.5	n.d.
6	$Fe(OTf)_2$	TBHP (3.0)	-	DMF	65	2.5	23
7	$FeCl_2$	TBHP (3.0)	-	DMF	65	2.5	72
8	$CuCl_2$	TBHP (3.0)	-	DMF	65	2.5	16
9	$MnCl_2$	TBHP (3.0)	-	DMF	65	2.5	12
10	$CoCl_2$	TBHP (3.0)	-	DMF	65	2.5	13
11	$FeCl_2$	BPO (3.0)	-	DMF	65	2.5	n.d.
12	$FeCl_2$	CHP (3.0)	-	DMF	65	2.5	n.d.
13	$FeCl_2$	$K_2S_2O_8$ (3.0)	-	DMF	65	2.5	n.d.
14	**$FeCl_2$**	**DTBP (3.0)**	**-**	**DMF**	**65**	**2.5**	**81**
15	-	DTBP (3.0)	-	DMF	65	2.5	n.d.
16[b]	$FeCl_2$	DTBP (3.0)	-	DCE	65	2.5	13
17[b]	$FeCl_2$	DTBP (3.0)	-	DCE	80	13	40
18[b]	$FeCl_2$	DTBP (5.0)	-	DCE	80	13	45
19[b]	$FeCl_2$	DTBP (5.0)	-	DMSO	80	13	6
20[b]	$FeCl_2$	DTBP (5.0)	-	Toluene	80	13	17
21[b]	$FeCl_2$	DTBP (5.0)	-	THF	80	13	12
22[b]	$FeCl_2$	DTBP (5.0)	-	^{t}AmOH	80	13	24

23[b]	$FeCl_2$	DTBP (5.0)	-	PhCl	80	13	49
24[b]	$FeCl_2$	DTBP (5.0)	CsOAc	PhCl	80	13	58
25[b]	$FeCl_2$	DTBP (5.0)	DABCO	PhCl	80	13	32
26[b]	$FeCl_2$	DTBP (5.0)	KO^{t}Bu	PhCl	80	13	<5
27[b]	$FeCl_2$	DTBP (5.0)	K_2CO_3	PhCl	80	13	13
28[b]	**$FeCl_2$**	**DTBP (5.0)**	**KOAc**	**PhCl**	**80**	**13**	**68**
29[c]	$FeCl_2$	DTBP (5.0)	KOAc	PhCl	80	13	51

[a]Unless otherwise noted, reaction was performed with **1a** (0.2 mmol), Fe salt (15 mol%), oxidant (3.0 equiv), and additive (30 mol%) in solvent (0.8 mL) under N_2. Isolated yield. [b]12 equiv of **2a** used. [c]8 equiv of **2a** used. n.d. = not detected. BPO = dibenzoyl peroxide. CHP = cumyl hydroperoxide.

Using the optimal conditions uncovered in Table 1, entry 14, the substrate generality with respect to the enamides was examined in the Fe-catalyzed oxidative coupling with **2a** (Scheme 2). A variety of *N*-vinylacetamides tested underwent carbamoylation smoothly under our catalytic protocol, providing various *N*-acyl enamine amides in good yields and with complete *Z*-selectivity, irrespective of the electronic and steric properties of substituents on the phenyl ring. Functional moieties of synthetic potential such as halides, methoxy, trifluoromethyl, sulfonyl, and cyano groups, were well tolerated. Naphthalenyl and thiophenyl substituted enamides could also deliver the coupling products in 84% and 52% yields (**3ka** and **3la**), respectively. Nonetheless, by switching to cyclic enamide, moderate conversion into the corresponding product **3ma** was observed even after a prolonged reaction time. Along with *N*-acetyl enamides (**1a–m**), replacing substitution pattern with other acyl groups at the nitrogen atom, such as *N*-propionyl and isobutyryl substituents, did not influence the reaction efficiency (**3na** and **30a**).

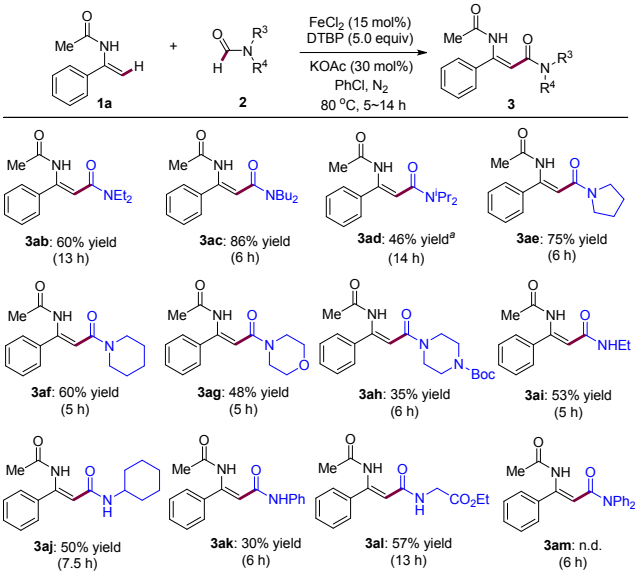
Scheme 2. Substrate Scope of Enamides



Conditions: **1** (0.2 mmol), **2a** (0.8 mL), $FeCl_2$ (0.03 mol), DTBP (0.6 mmol), N_2, 65 °C, 2.5 h. [a]24 h. [b]12 h. [c]80 °C, 13 h.

Next, the compatibility of formamide derivatives with **1a** as an enamide partner was investigated using the reaction conditions described in Table 1, entry 28. The results were summarized in Scheme 3. Broadly, both mono- and di-substituted formamides could be installed onto β-C–H bond of enamides in moderate to good yields. Specifically, beyond dialkyl chain substituted formamides (**3ab–ad**), a range of aza-cyclic derivatives embedding pyrrolidine, piperidine, morpholine, and piperazine, underwent the reaction smoothly to afford the products (**3ae–ah**). Regarding the scope of *N*-monosubstituted formamides, ethyl and cyclohexyl groups as the representative aliphatic substitution showed higher reactivity than aryl substituted derivative toward this transformation (**3ai** and **3aj** *vs.* **3ak**). *N*,*N*-diphenylformamide failed to produce the desired product under the standard conditions (**3am**). It is worth mentioning that *N*-formylglycinate of biological relevance turned out to be a competent substrate (**3al**).

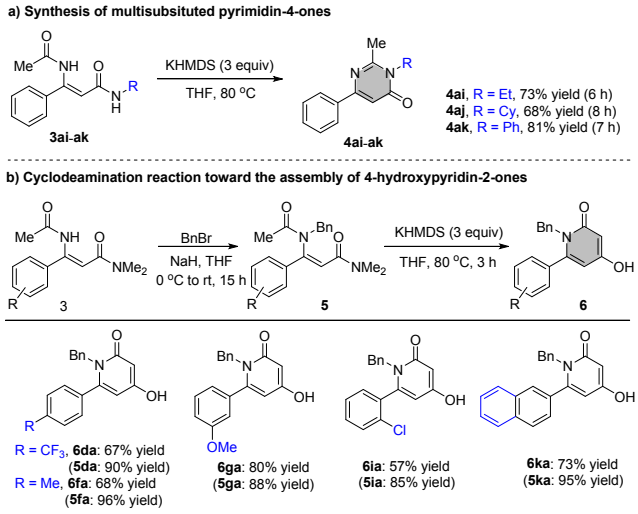
Scheme 3. Substrate Scope of Formamides



Conditions: **1a** (0.2 mmol), **2** (12 equiv), $FeCl_2$ (0.03 mmol), DTBP (0.6 mmol), KOAc (0.06 mmol), PhCl (0.8 mL), N_2, 80 °C, 5 h. [a]Without KOAc.

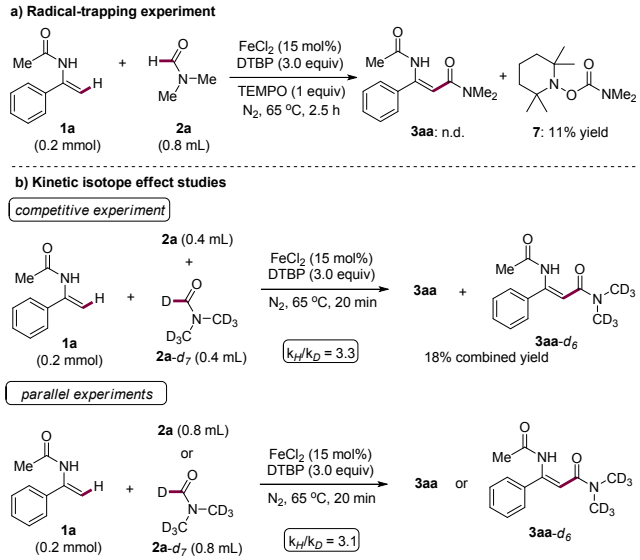
Have established the substrate generality and limitation of the present method, we sought to further illustrate the synthetic utility of the products. As can be expected from the precedent literatures,[16] subjecting the coupled products *N*-ethyl, phenyl and cyclohexyl amides (**3ai–ak**) to potassium hexamethyldisilazane (KHMDS) in THF solution afforded the cyclodehydration products (**4ai–ak**), namely pyrimidin-4-ones, which act as significant pharmacophores within drug discovery enterprise (Scheme 4a).[21] Intriguingly, exposure of benzyl protected amides **5** under the same basic conditions led to the quick assembly of 4-hydroxypyridin-2-ones **6** via cyclodeamination process. As depicted in Scheme 4b, a set of electronically and sterically varied amides **3** were exemplified to assess the breadth of this novel transformation, which serves as a convenient alternative protocol to other condensation methods for the synthesis of such privileged frameworks.[22]

Scheme 4. Synthetic Utility of Some Coupling Products



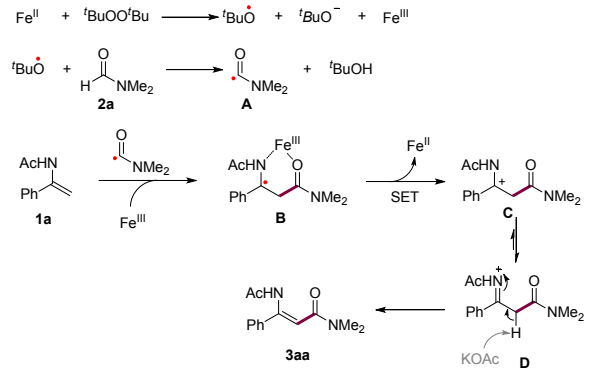
Several experiments were carried out to elucidate the mechanism of this catalytic reaction. As expected, addition of a stoichiometric amount of a known radical quencher, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), to the reaction system resulted in no detectable amidation product **3aa**; instead, carbamoylated TEMPO adduct **7** was formed in 11% yield, which indicated the intermediacy of an aminoacyl radical species in the process (Scheme 5a). Furthermore, the deuterium kinetic isotope effect (KIE) for the carbamoylation was studied to better understand the process of the C–H bond cleavage. The value of KIE = 3.3 from intermolecular competitive reaction as well as the value of KIE = 3.1 from two parallel experiments revealed that the cleavage of formyl C–H bond might be involved in the rate-determining step (Scheme 5b).

Scheme 5. Mechanistic Studies



On the basis of the above experimental findings combined with precedent reports,[14] a plausible mechanism was proposed for the current oxidative carbamoylation reaction shown in Scheme 6. The initial step involves Fe(II)-mediated decomposition of DTBP to *tert*-butoxyl radical and *tert*-butoxide anion via a single-electron-transfer (SET) redox reaction.[23] The aminoacyl radical **A** generated in situ by homolytic cleavage of formyl C(sp²)–H bond, which is clearly evidenced by a radical-trapping experiment, will then add to the double bond of enamide at the β position. Of note, iron salt could serve as Lewis acid to coordinate with the nitrogen and oxygen atoms, which thereby accounts for the exclusive stereoselectivity of the reaction. Fe(III) then oxidizes the benzylic radical **B** to the corresponding cation **C** via SET process, along with the regeneration of Fe(II) species. It is feasible that alkyl cation **C** can be isomerized to more stable iminium ion **D**. Finally, the olefinic functionality is restored upon deprotonation to afford the carbamoylation product. When the reaction was run in PhCl medium, the use of KOAc leads to the enhancement of the chemical yield might due to its beneficial role in the β-H elimination step.

Scheme 6. Proposed Mechanism for Fe-Catalyzed Oxidative Carbamoylation



In summary, the development of a practical method for the synthesis of *N*-acyl enamine amides via Fe-catalyzed oxidative coupling of enamides and formamides has been reported. Under neat conditions or PhCl as solvent, synthetically useful yields and complete *Z*-selectivities of the target products were achieved. Apart from the generality of the reaction with respect to a broad substrate scope as well as excellent functional group tolerance, conversion of the *N*-acyl enamine amides products into biologically important pyrimidin-4-ones and 4-hydroxypyridin-2-ones demonstrates the versatility of the transformation. Moreover, control experiments disclosed a preliminary radical mechanism. Further extensions of this approach and deeper mechanistic studies are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.0000000.

Detailed experimental procedures and characterization data.

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Notes

The authors declare no competing financial interest.

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