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Preparation of highly substituted (β-acylamino)acrylates *via* iron-catalyzed alkoxycarbonylation of *N*-vinylacetamides with carbazates†

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An efficient iron(II)-catalyzed alkoxycarbonylation reaction between *N*-vinylacetamides and carbazates is reported. The corresponding useful highly substituted (β-acylamino)acrylates could be obtained in reasonable to good yields and stereoselectivity under mild reaction conditions.

(β-Acylamino)acrylate derivatives are useful building blocks in organic synthesis which have been used widely for the asymmetric synthesis of β-amino acids and chiral amines.[1] Accordingly, the synthesis of this class of compounds has attracted much attention.[2] Common methods to access this class of compounds include the condensation of β-ketoester with an amine source[3] and the Pd-catalyzed α-arylation of β-amido-acrylate.[4] However, these methods suffer from a limited substrate scope and difficulties in controlling the *E*/*Z* selectivity of the product. Therefore, a more efficient and general method to access (β-acylamino)acrylate derivatives is highly desirable. We envisage that the direct C–H alkoxycarbonylation of *N*-vinylacetamides will provide one of the most direct entries to this class of compounds. However, the Pd-catalyzed C–H carbonylation of *N*-vinylacetamides with carbon monoxide led to the formation of 1,3-oxazin-6-ones.[5] An attractive strategy is to use carbazate, a very useful source of ester groups discovered by Taniguchi and coworkers, as the carbonylation reagent.[6] During the past few years, carbazates have been widely used by many groups including those of Tian,[7] Li,[8] Du,[9] Zhu,[10] *etc.* Inspired by these seminal studies and due to our interest in developing direct C–H bond functionalization of *N*-vinylacetamides,[11] herein, we report a new and simple method to prepare highly substituted (β-acylamino)acrylates using *N*-vinylacetamides and carbazates catalyzed by cheap and low toxicity iron catalysts.

Initially, our attempt involved the search for optimized reaction conditions by carrying out the reaction of *N*-vinylacetamide **1a** with carbazate **2a**. The observed results are shown in Table 1. Using 20 mol% [Fe(Pc)] (iron(II)phthalocyanine) as a catalyst, the desired product (*Z*)-methyl 3-acetamido-3-phenylacrylate **3a** could be obtained only in low yields when PIDA (phenyliodine diacetate), BQ (benzoquinone), TBPB (*tert*-butyl benzoperoxoate) DTBP (di-*tert*-butyl peroxide) or DCP (dicumyl peroxide) was used as an oxidant in acetonitrile at 80 °C (Table 1, entries 1–5). To our delight, the desired product could be obtained in 68% yield when TBHP (*tert*-butyl hydroperoxide) was used as the oxidant with Cs_2CO_3 as the additive. Furthermore, after reducing the catalyst loading to 10 mol% and the base amount to one equivalent, the yield of the desired product only decreased slightly at 60 °C (Table 1, entry 11). However, other tested bases (Table 1, entries 12–16), iron catalysts (Table 1, entries 17–19) or used solvents (Table 1, entries 20–22) did not favour the transformation to the desired product. It was found that increasing TBHP loading and increasing the reaction concentration could not improve the product yield significantly. Control experiments were also carried out and the iron catalyst was found to be necessary to afford the product (Table 1, entry 26). Finally, the optimized conditions were established to be: [Fe(Pc)] (10 mol%), Cs_2CO_3 (1 equiv.), and TBHP (2.0–2.4 equiv.) at 60 °C in CH_3CN for 2 hours.

The optimized reaction conditions were then applied to various acyclic *N*-vinylacetamides (Table 2). It was found that the substituents on the phenyl ring of the *N*-vinylacetamide did not affect the yields of the reaction of **1** with **2a**. Different halide substituents were tolerated in the final products which permit their further functionalization in subsequent steps. However, the substituents at the *ortho*-position could lead to a slightly decreased *Z*/*E* selectivity of the products. In addition, different heteroaryls such as benzofurans, furans and thiophene substituted *N*-vinylacetamides were also applied as substrates in this reaction, the corresponding products could be isolated in reasonable yields and with high stereoselectivities. Furthermore, *N*-vinylacetamide **1p** with a cyclohexyl group could also be used well and afforded the desired product **3p** in 63% yield and in a 92/8 ratio of *Z*/*E* selectivity.

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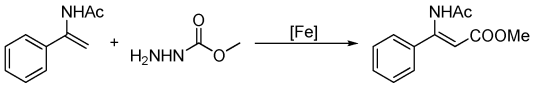
Table 1 Optimization of the reaction conditions of alkoxycarbonylation of acyclic *N*-vinylacetamide with carbazate **2a**[a,b]



1a 2a 3a

Entry	Catalyst (mol%)	Oxidant[b]	T (°C)	Base (equiv.)	Solvent	t (h)	Yield[c] (%)
1	[Fe(Pc)] (20)	PIDA	80		CH_3CN	3	30
2	[Fe(Pc)] (20)	BQ	80		CH_3CN	3	37
3	[Fe(Pc)] (20)	TBPB	80		CH_3CN	3	35
4	[Fe(Pc)] (20)	DTBP	80		CH_3CN	3	Trace
5	[Fe(Pc)] (20)	DCP	80		CH_3CN	3	Trace
6	[Fe(Pc)] (20)	TBHP	80		CH_3CN	3	41
7	[Fe(Pc)] (20)	TBHP	80	Cs_2CO_3 (2.0)	CH_3CN	3	68
8	[Fe(Pc)] (20)	TBHP	60	Cs_2CO_3 (2.0)	CH_3CN	3	68
9	[Fe(Pc)] (10)	TBHP	60	Cs_2CO_3 (2.0)	CH_3CN	3	68
10	[Fe(Pc)] (5)	TBHP	60	Cs_2CO_3 (2.0)	CH_3CN	3	66
11	[Fe(Pc)] (10)	TBHP	60	Cs_2CO_3 (1.0)	CH_3CN	3	68
12	[Fe(Pc)] (10)	TBHP	60	Na_2CO_3 (1.0)	CH_3CN	3	47
13	[Fe(Pc)] (10)	TBHP	60	CH_3COOK (2.0)	CH_3CN	3	51
14	[Fe(Pc)] (10)	TBHP	60	LiOH (2.0)	CH_3CN	3	62
15	[Fe(Pc)] (10)	TBHP	60	$KHCO_3$ (2.0)	CH_3CN	3	58
16	[Fe(Pc)] (10)	TBHP	60	K_3PO_3 (1.0)	CH_3CN	3	65
17	$FeCl_3$ (20)	TBHP	60	Cs_2CO_3 (1.0)	CH_3CN	3	Trace
18	$FeCl_2$ (20)	TBHP	60	Cs_2CO_3 (1.0)	CH_3CN	3	22
19	$FeBr_2$ (20)	TBHP	60	Cs_2CO_3 (1.0)	CH_3CN	3	26
20	[Fe(Pc)] (10)	TBHP	60	Cs_2CO_3 (1.0)	THF	3	47
21	[Fe(Pc)] (10)	TBHP	60	Cs_2CO_3 (1.0)	Toluene	3	47
22	[Fe(Pc)] (10)	TBHP	60	Cs_2CO_3 (1.0)	CH_2Cl_2	3	56
23[d]	[Fe(Pc)] (10)	TBHP	60	Cs_2CO_3 (1.0)	CH_3CN	3	68
24[e]	[Fe(Pc)] (10)	TBHP	60	Cs_2CO_3 (1.0)	CH_3CN	3	68
25[e,f]	[Fe(Pc)] (10)	TBHP	60	Cs_2CO_3 (1.0)	CH_3CN	2	68
26		TBHP	60	Cs_2CO_3 (1.0)	CH_3CN	2	Trace

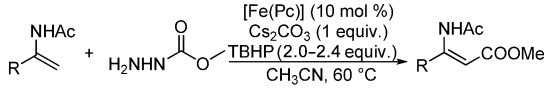
[a] Reaction conditions: the mixture of **1a** (0.2 mmol), **2a** (0.8 mmol), oxidant (2.0 equiv.) and base in solvent (1.5 mL). [b] TBHP was used with 2.0–2.4 equiv. (5–6 M in decane). [c] Isolated yields. [d] Solvent (1.0 mL). [e] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), TBHP (2.0–2.4 equiv., 80 μL, 5–6 M in decane), solvent (1.0 mL). [f] A 94 : 6 *Z*/*E* ratio was determined from ^{1}H NMR spectra of the crude product.

Finally, ethyl hydrazinecarboxylate and benzohydrazide were used as carbonyl sources in the current reaction,[12] products **3q** and **3r** were efficiently formed in 62% and 60% yields, respectively. After establishing the current simple and efficient method for preparation of highly substituted (β-acylamino)acrylates, a gram-scale reaction between **1a** and **2a** was tested. To our delight, the product **3a** could also be obtained in a steady 61% yield (please see the details in the ESI†).

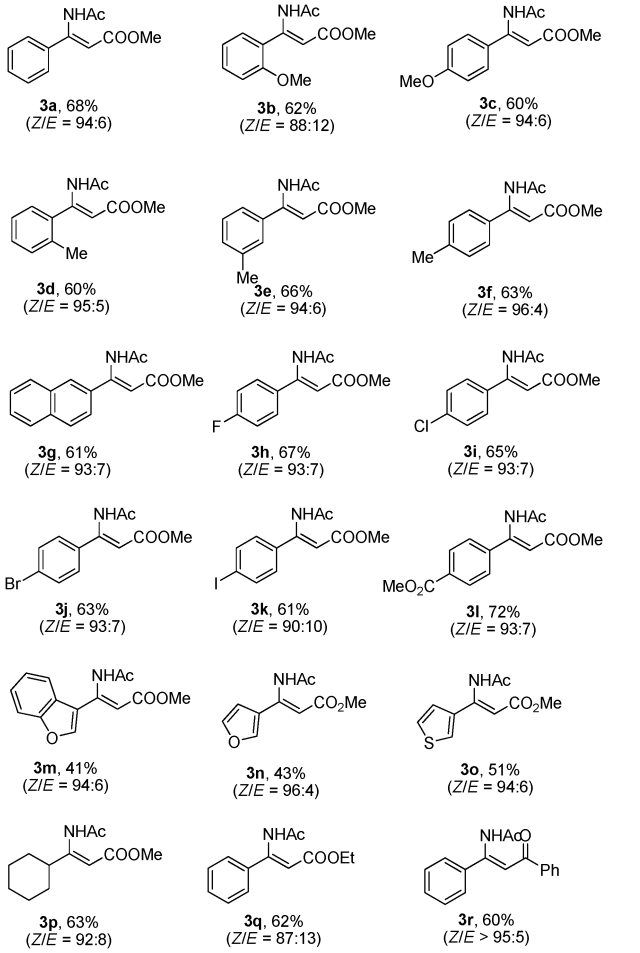
When the optimized reaction conditions were employed for the alkoxycarbonylation reaction of cyclic *N*-vinylacetamide **4a**, unfortunately, only very poor yield (<10%) of the product was obtained accompanied by the decomposed starting material. After careful investigation (Table 3), we found that the choice of base was crucial for the product yield. Next, different bases were further examined in the reaction and finally one equivalent of K_2CO_3 was found to be suitable for affording product **5a** in an acceptable yield at room temperature. Other bases such as LiOH, KOH or K_3PO_4 were found to be less effective in affording the desired product.

With the further optimized reaction conditions in hand, various cyclic *N*-vinylacetamides were tested for the preparation of tetra-substituted (β-acylamino)acrylate derivatives (Table 4).

Table 2 Iron-catalyzed direct alkoxycarbonylation of **1** with different carbazates[a,b,c]



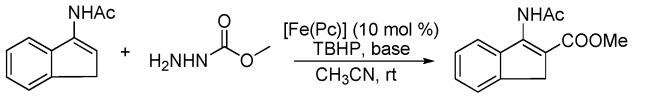
1 2a 3



[a] Reaction conditions: the mixture of **1a** (0.3 mmol), **2a** (0.6 mmol), TBHP (2.0–2.4 equiv., 120 μL, 5–6 M in decane), Cs_2CO_3 (1.0 equiv.) and [Fe(Pc)] in 1.5 mL of CH_3CN was heated at 60 °C for 2 hours. [b] Isolated yields. [c] The ratios of *Z*/*E* shown in parentheses were determined from the crude ^{1}H NMR spectra of the corresponding reactions.

The selected protecting group on the nitrogen atom is important for the product yield; as more bulky protecting groups will decrease the yield. Moreover, it was noticed that the electronic effect from the substituents on the phenyl ring of the cyclic *N*-vinylacetamides on the product yield is quite different from that observed in acyclic *N*-vinylacetamides. For example, with the halide or ester substituent, only moderate yields of the products could be realized. It seems that the steric effect from the substituted methyl group at the 3-position is not sensitive for the generation of the product, 61% yield of **5j** could be observed. Variation on the ring size was also studied; the substrates with a six- or seven-membered ring could also be smoothly transferred into the target products in 50% and 62% yields, respectively (Table 4, entries **5k** and **5l**).

Table 3 Optimization of the reaction conditions of alkoxycarbonylation of cyclic *N*-vinylacetamide with carbazate **2a**[a,b]

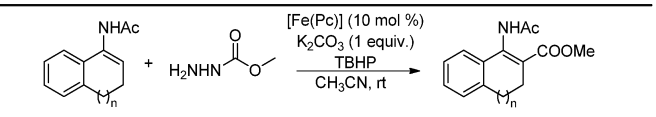


4a 2a 5a

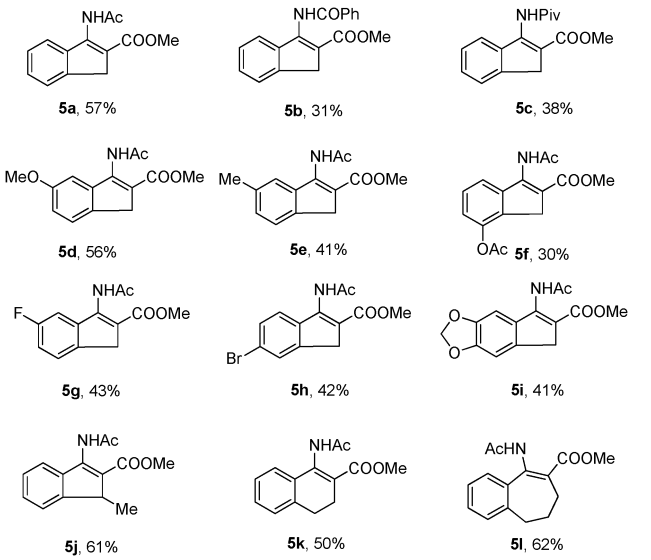
Entry	Catalyst (mol%)	Base (equiv.)	*t* (h)	Yield (%)
1	[Fe(Pc)] (10)	LiOH (1)	1	42
2	[Fe(Pc)] (10)	$LiOH·H_2O$ (1)	1	50
3	[Fe(Pc)] (10)	K_3PO_4 (1)	1	34
4	[Fe(Pc)] (10)	KOH (1)	1	Trace
5	[Fe(Pc)] (10)	K_2CO_3 (1)	1	57
6	[Fe(Pc)] (10)	Cs_2CO_3 (1)	1	Trace
7	[Fe(Pc)] (10)	K_2CO_3 (1)	0.5	54
8	[Fe(Pc)] (20)	K_2CO_3 (1)	0.5	60
9	[Fe(Pc)] (20)		1	37

[a] Reaction conditions: the solution of **4a** (0.2 mmol), **2a** (0.4 mmol), TBHP (2.0–2.4 equiv., 80 μL, 5–6 M in decane), base (1.0 equiv.) and [Fe(Pc)] in 1.0 mL of CH_3CN was run at room temperature for 1 hour. [b] Isolated yields.

Table 4 Iron-catalyzed direct alkoxycarbonylation of **4** with carbazate **2a**[a,b]

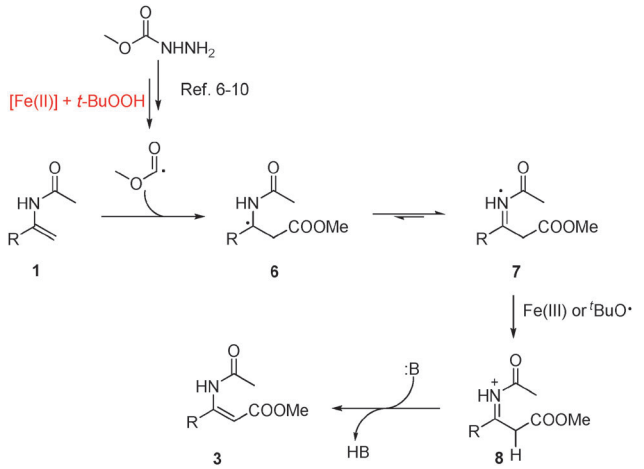


4 2a 5



[a] Reaction conditions: the solution of **4a** (0.3 mmol), **2a** (0.6 mmol), TBHP (2.0–2.4 equiv., 120 μL, 5–6 M in decane), K_2CO_3 (1.0 equiv.) and [Fe(Pc)] in 1.5 mL of CH_3CN was run at room temperature for 1 hour. [b] Isolated yields.

A plausible mechanism for the alkoxycarbonylation of *N*-vinylacetamides with carbazates could be proposed as shown in Scheme 1. After the addition of alkoxycarbonyl radical generated from carbazate with the aid of an iron catalyst[6–10] to the double bond of compound **1**, the more stable radical intermediate **7** could be further oxidized by Fe(III) or a *tert*-butyloxide radical into iminium ion **8**.[13] In the presence of base, deprotonation will lead to the formation of the desired product **3**.



Scheme 1 Proposed possible mechanism for the alkoxycarbonylation of *N*-vinylacetamide with carbazate.

In conclusion, we have developed an iron-catalyzed alkoxycarbonylation reaction of *N*-vinylacetamides with carbazates under simple and mild reaction conditions. Various acyclic and cyclic *N*-vinylacetamides as starting materials were found to be tolerated in the titled reaction. The observed good stereoselectivities and reasonable yields of the products make this method a general tool for the synthesis of highly substituted (β-acylamino)acrylate derivatives *via* direct functionalization of *N*-vinylacetamides.

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