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Efficient synthesis of β -enaminoesters via highly stereoselective Reformatsky reaction with disubstituted formamides as novel electrophiles

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ABSTRACT

An efficient synthesis of various β -enaminoesters has been achieved via Reformatsky reaction with disubstituted formamides as novel electrophiles. The exclusive β -enaminoester *E*-isomers were obtained in 60–72% yield.

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β-Enaminoesters, ¹ a class of versatile intermediates for the synthesis of the heterocycles, ² are common pharmacophores in a number of important medicinal agents. Many of their derivatives, including anticonvulsant, ³ anti-inflammatory, ⁴ and particularly the antibacterial fluorinated quinolone, ⁵ possess a wide range of biological activities. Despite the importance of enaminones as valuable biologically active compounds, their synthesis has received little attention so far. β-Enaminoesters are generally prepared by condensation of amines with β-ketoesters or alkynes. ^{6,7} However, the drawbacks are well documented including incomplete reaction, long reaction time, and discrimination between E and E double-bond geometric isomers. ⁸

The Reformatsky reaction is one of the fundamental reactions in organic synthesis. 9,10 It is well recognized $^{10-13}$ that the Reformatsky reagents as nucleophiles reacted with a number of electrophiles including aldehydes, ketones, nitriles, amides, and imides affording β -hydroxy or α,β -unsaturated products. However, there have been few studies on disubstituted formamides as electrophiles in the Reformatsky reaction. In this Letter, we report an efficient method to synthesize β -enaminoesters via Reformatsky reaction with disubstituted formamides as novel electrophiles for the first time. The afforded β -enaminoesters were E-isomers exclusively (Scheme 1).

The solvent of this reaction was studied with ethyl bromoacetate and DMF as the model substrates, and the reaction was carried out with Zn dust. Results are summarized in Table 1. The ether solvents such as Et₂O and 1,4-dioxane (entries 1 and 2) gave the product in low yield, and the nonpolar solvent toluene led to uncompleted reaction (entry 3). As shown in Table 1, THF was the better solvent, and the corresponding product was obtained in 62% yield (entry 4). Because of the low reactivity of ethyl chloroacetate, no product was detected at all in THF (entry 5), but **3b** was obtained in 43% yield in toluene because of higher reaction temperature (entry 6). Similarly, ethyl iodoacetate gave the same product in 65% yield (entry 7) (Scheme 2).

DMF could be appropriate as a solvent in some specific Reformatsky reactions when more reactive electrophiles such as aldehydes and ketones are used.¹⁰ We found that DMF also could be used as an electrophile, but 2 equiv of Reformatsky reagent were needed to make sure that DMF was absolutely transformed. Generally, the reaction was monitored by TLC and GC–MS.

Reformatsky reagents and disubstituted formamides formed the dehydrated adducts spontaneously to afford enaminoesters $\bf 3a-h$ in 60–72 yield. The results are summarized in Table 2. Among all the formamides tested, *N*-methyl-*N*-phenylformamide gave the best yields of about 70% (entries 10–12). Methyl bromoacetate ($\bf 2a$) gave methyl β -enaminoesters. Also, the reaction of ethyl iodoacetate $\bf 2c$ gave the desired products in a little better yield.

Scheme 1.

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Table 1Reaction of haloacetates with DMF

Entry ^a	X	Solvent(reflux)	Yield ^b
1	Br	Et ₂ O	41
2	Br	1,4-Dioxane	45
3	Br	Toluene	50
4	Br	THF	62
5	Cl	THF	0
6	Cl	Toluene	43
7	I	THF	65

 $[^]a$ Reaction condition: 10 mmol of $\alpha\text{-haloacetate}, 5$ mmol DMF, 15 mmol Zn dust, 0.1 mmol $I_2,$ and 10 mL THF were refluxed for 5 h.

The structures of β -enaminoesters were confirmed by ¹H NMR spectra. The characteristic coupling constant of the two protons on the double bond is about 13 Hz, which indicates that the products are *E*-isomers instead of the *Z* isomers.

In summary, the first synthetically useful, convenient, and cost-effective Reformatsky reaction of disubstituted formamides and α -haloacetates is presented here. The exclusive β -enaminoester *E*-isomers were prepared from different formamides and α -haloacetates in 60–72% yield via Reformatsky reaction.

General procedure: The reagents were obtained from commercial sources. THF, DMF, diethyl ether, toluene, and 1,4-dioxane were dehydrated with Na or CaH₂. Zinc dust was activated by trimethyl chlorosilane. The ¹H and ¹³C NMR spectra were recorded at 500 and 125 MHz, respectively, in CDCl₃ with a Bruker AM 500 spectrometer.

General procedure for synthesis of ethyl β -(N-methyl-N-phenylamino)-acrylate (3h): Under dry nitrogen atmosphere, a mixture of ethyl bromoacetate (1.7 g, 10 mmol) and N-methyl-N-phenyl formamide (0.68 g, 5 mmol) in anhydrous THF (20 mL) was added to the mixture of Zn dust (3 equiv) and I_2 (cat 0.1 equiv) over 30 min. The mixture was refluxed in THF until the staring material was consumed, as determined by GC and TLC. The reaction mixture was poured into 20 mL saturated aqueous ammonium chloride and was extracted (3 × 20 mL) with Et₂O. The combined ether extracts were washed with brine (60 mL) and dried over MgSO₄. The solvent was removed under vacuum, and the resulting crude product was purified by chromatography on silica gel eluted with EtOAcpetroleum ether to get ethyl β -(N-methyl-N-phenylamino)-acrylate in 70% yield.

Methyl β-dimethylamino acrylate (**3a**): 1 HNMR (CDCl₃, 500 MHz) δ 7.44 (d, J = 13 Hz, 1H), 4.51 (d, J = 13 Hz, 1H), 3.66 (s, 3H), 2.89 (s, 6H). *Ethyl* β-dimethylamino acrylate (**3b**): 1 H NMR (CDCl₃, 500 MHz) δ 7.44 (d, J = 13 Hz, 1H), 4.51 (d, J = 13 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H), 2.89 (s, 6H), 1.26 (t, J = 7.0 Hz, 3H). MS (m/z): 143, calcd for $C_7H_{13}NO_2$ [M] 143.18.

Methyl β-piperdinoacrylate (**3c**): 1 HNMR (CDCl₃, 500 MHz) δ 7.39 (d, J = 13 Hz, 1H), 4.62 (d, J = 13 Hz, 1H), 3.66 (s, 3H), 3.18–3.20 (m, 4H), 1.56–1.66 (m, 6H).

Ethyl β-piperdinoacrylate (**3d**): ^{1}H NMR (CDCl₃, 500 MHz) δ 7.39 (d, J = 13 Hz, 1H), 4.62 (d, J = 13 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 3.19 (t, J = 5 Hz, 4H), 1.57–1.62 (m, 6H), 1.25 (t, J = 7 Hz, 3H).

Methyl β-morphinoacrylate (**3e**): 1 H NMR (CDCl₃, 500 MHz) δ 7.36 (d, J = 13 Hz, 1H), 4.70 (d, J = 13 Hz, 1H), 3.70–3.72 (m, 4H), 3.67 (s, 3H), 3.20–3.22 (t, J = 5 Hz, 4H).

Ethyl β-morphinoacrylate (**3f**): 1 H NMR (CDCl₃, 500 MHz) δ 7.36 (d, J = 13 Hz, 1H), 4.69 (d, J = 13 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H),

Scheme 2.

Table 2 Reaction α -haloesters with disubstituted formamides

Entry	1	2	Product	Yield ^a (%)	Ref.
1	$\stackrel{\textstyle O}{\nearrow} H_{1a}$	2a	N OMe 3a	65	14
2	1a	2b	N OEt 3b	62	15
3	1a	2c	3b	65	15
4	\bigcup_{N} H 1p	2a	\bigcirc N \bigcirc OMe $_{3c}$	61	16
5	1b	2b	OEt 3d	60	17
6	1b	2c	3d	67	17
7	O_N H $_{1c}$	2a	$0 \longrightarrow 0 \\ OMe_{3e}$	63	16
8	1c	2b	ON OEt 3f	61	18
9	1c	2c	3f	64	18
10	O _N H _{1d}	2a	OMe 3g	72	19
11	1d	2b	O _N OEt 3h	70	20
12	1d	2c	3h	72	20

a Isolated yield of pure compound.

3.69-3.71 (m, 4H), 1.57-1.62 (m, 6H), 3.21 (t, J=5 Hz, 4H), 1.26 (t, J=7 Hz, 3H).

Methyl β-(*N*-methyl-*N*-phenylamino)-acrylate (**3g**): ¹H NMR (CDCl₃, 500 MHz) δ 7.94 (d, J = 13 Hz, 1H), 7.12–7.37 (m, 5H), 4.94 (d, J = 13 Hz, 1H), 3.71 (s, 3H), 3.24 (s, 3H).

Ethyl β-(N-methyl-N-phenylamino)-acrylate (**3h**): 1 H NMR (CDCl₃, 500 MHz) δ 7.94 (d, J = 13 Hz, 1H), 7.10–7.37 (m, 5H), 4.94 (d, J = 13 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 3.24 (s, 3H), 1.29 (t, J = 7 Hz, 3H). 13 C NMR (CDCl₃, 125 MHz) δ 169.20 (1C), 148.45 (1C), 146.60 (1C), 129.44 (2C), 124.14 (1C), 119.84 (2C), 90.45 (1C), 59.31 (1C), 36.55 (1C), 14.57 (1C). MS (m/z): 206 [M+1], calcd for $C_{12}H_{15}NO_2$ [M+H⁺] 206.11.

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b Isolated yield of pure compound.

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