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A new and efficient synthetic method for the herbicide carfentrazone-ethyl based on the Heck reaction

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Abstract The herbicide carfentrazone-ethyl (**1**) was prepared by a new and improved synthetic method. The common and inexpensive reagent ethyl acrylate was employed to replace commercially unavailable ethyl 3-hydroxy-2-methylenebutanoate, which was used in the synthetic route reported previously. Starting from iodination of 1-(4-chloro-2-fluorophenyl)-4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazole (**2**), an intermediate 1-(4-chloro-2-fluoro-5-iodophenyl)-4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazole (**3**) was afforded in an excellent yield. Then, an intermediate ethyl 3-[2-chloro-5-(4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)-4-fluorophenyl]-2-propenoate (**4**) was synthesized by Heck coupling of **3** with ethyl acrylate. Next, oxidative addition–elimination of **4** with *OXONE*®/HCl-Et_3N in one pot produced ethyl 2-chloro-3-[2-chloro-5-(4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)-4-fluorophenyl]-2-propenoate (**5**). Finally, the target product **1** was obtained via reduction of **5** by H_2. This new synthetic method exhibits the advantages of mild conditions, atom economy, low-cost, and efficiency.

Keywords Carfentrazone-ethyl · Herbicide · Triazolinone · Heck reaction · *OXONE*® · Hydrogenation

Introduction

Carfentrazone-ethyl (**1**) (Fig. 1) [1, 2], chemically known as ethyl α,2-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)]-4-fluorobenzenepropanoate is a kind of commercial herbicide, which is widely utilized due to

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its safety, low toxicity, and high efficiency. It exhibits excellent post-emergence cereal and corn herbicidal activities [3–6] and has been mainly used in the control of broadleaf weeds and sedge weeds, such as cleavers, abutilon, hearts quinoa, petunias, etc. Furthermore, it also shows good herbicidal activity against weeds resistant to sulfonylurea herbicides, which attracts sustained attention in the field of pesticide chemistry [7].

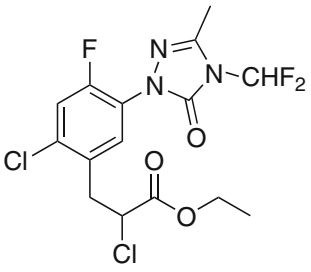
In the past two decades, synthetic chemists made great efforts in the preparation of **1**. Early in 1990, FMC Corporation firstly disclosed a synthetic method for preparing **1** by using 1-(4-chloro-2-fluorophenyl)-4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazole (triazolinone **2**) as a starting material, which comprised nitration, reduction, diazotization, and Meerwein arylation [8]. Later, in 1997, Ager and coworkers [9] modified the above method in order to develop an industrial synthetic route by selecting different reagents, catalysts, and solvents in the process of diazotization. In 1999, Crispino and coworkers [10] developed another synthetic method (shown in Scheme 1) by using triazolinone **2** as the raw material, which reacted with iodine crystals in the presence of oleum to afford an intermediate 1-(4-chloro-2-fluoro-5-iodophenyl)-4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazole (**3**). Then, compound **3** was coupling with ethyl 3-hydroxy-2-methylenebutanoate in the presence of a palladium catalyst and a tertiary amine via Heck reaction and subsequently rearranged to give an intermediate ethyl α-acetyl-2-chloro-5-[4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl]-4-fluorobenzenepropanoate (**6**). Finally, product **1** was obtained by substitution-elimination of **6**. In fact, this method has not been commercialized yet, possibly because the raw material ethyl 3-hydroxy-2-methylenebutanoate using in Heck reaction was not commercially available. In addition, taking atom economy into account, extra efforts should also be made to improve this method.

Actually, as one of the widely used methods forming a C–C bond in modern organic synthesis, the Heck reaction has recently been developed to a convenient method in mild conditions with high yields [11]. In this work, we present an improved method by modification of the reported route in Scheme 1, employing the inexpensive and readily available reagent ethyl acrylate to replace the commercially unavailable reagent ethyl 3-hydroxy-2-methylenebutanoate. Starting from triazolinone **2**, the target compound **1** was synthesized via iodination, Heck coupling, oxidative addition–elimination and reduction, as shown in Scheme 2. This new method has potential application in preparing product **1** in mild conditions with low cost and high efficiency.

Experimental

All solvents and reagents for synthesis were purchased from commercial sources and used without further purification except that *N,N*-dimethylformamide (DMF) was distilled by calcium hydride. The starting material **2** was an industrial product from Jiangsu Kuaida Agrochemical Co., Ltd with the content of 97 % tested by HPLC. Reactions were monitored by high-performance liquid chromatography

Fig. 1 Chemical structure of carfentrazone-ethyl (**1**)



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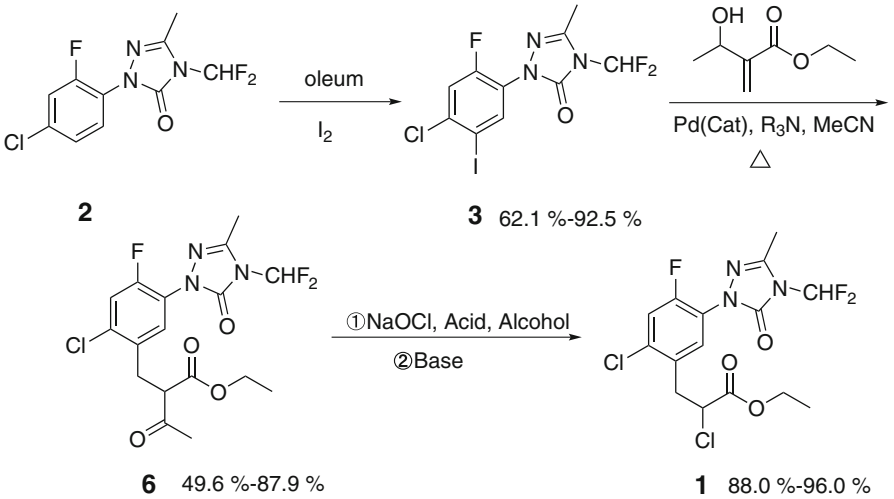


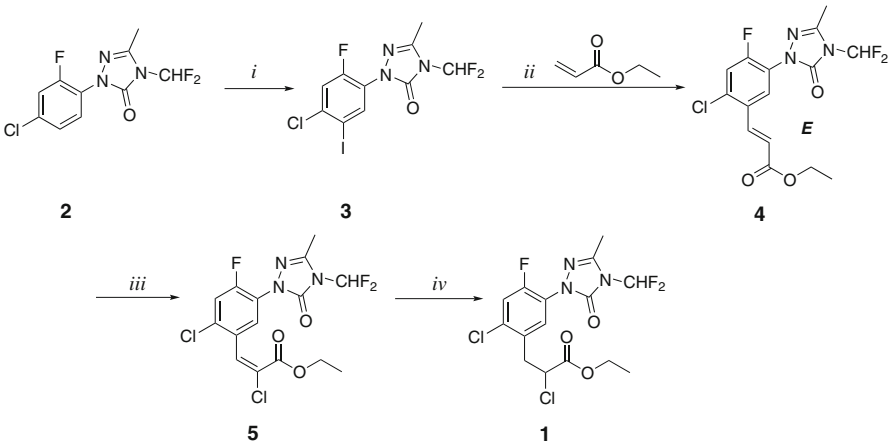
2 **3** 62.1 %-92.5 % **6** 49.6 %-87.9 % **1** 88.0 %-96.0 %

Scheme 1 Reported synthetic route of **1** by G. Crispino and coworkers

(HPLC) on a Varian 1200 chromatograph using Hypersil ODS2 (5 μm) column (150 × 4.6 mm). Content by HPLC refers to chromatographic area percentage. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400-MHz spectrometer using tetramethylsilane (TMS) as an internal standard and $CDCl_3$ as a solvent. Mass spectra were recorded on a mass spectrometry (MS) spectrometer VG12-250 MS. Melting points (m.p.) were taken on an X-4 microscope electro thermal apparatus.

General procedure for synthesis of 1-(4-chloro-2-fluoro-5-iodophenyl)-4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazole (**3**)

To a 250-ml, three-neck, round-bottom flask equipped with a mechanical stirrer and a thermometer was added 25 % oleum (12 wt % triazolinone **2** in the oleum), followed by the triazolinone **2** (0.05 mol). The mixture was cooled in an ice bath and then iodine (0.05 mol) was added. The reaction mixture was then warmed to 25–60 °C. After completion of the reaction monitored by TLC, the mixture was



Scheme 2 Modified synthetic route of 1. Reagents and conditions: (*i*) 25 % oleum ($5H_2SO_4{\cdot}2SO_3$), I_2; (*ii*) catalysts, bases; (*iii*) oxidative addition–elimination reaction, ① *OXONE*®/HCl ② Et_3N; (*iv*) H_2, Pd/C, methanol

poured into ice to give the brown precipitated solid. Then the resulting mixture was extracted with methylene chloride (2 × 50 ml). The organic extracts were combined and washed with an aqueous 10 % potassium carbonate solution, an aqueous 5 % sodium bisulfite solution, and an aqueous saturated sodium chloride solution, respectively. The organic layer was dried with magnesium sulfate, filtered, and removed the solvent under vacuum to yield the intermediate **3**. Yellow solid; m.p.: 125–127 °C (Lit. [10]: 125–127 °C); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.47 (s, 3H), 7.04 (t, $J = 58.0$ Hz, 1H), 7.38 (d, $J = 9.8$ Hz, 1H), 7.98 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 157.45, 154.88, 142.98, 139.71, 137.51, 123.24, 118.14, 107.67, 91.49, 12.74; ESI-MS *m/z*: 403.93 $(M + H)^+$.

General procedure for synthesis of ethyl 3-[2-chloro-5-(4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)-4-fluorophenyl]-2-propenoate (**4**)

A Schlenk tube equipped with a magnetic stirrer and a condenser was evacuated and filled with nitrogen three times. Then the intermediate **3** (2.50 mmol), ethyl acrylate (2.90 mmol), base and catalyst in solvent (5 ml) were placed in the tube under nitrogen atmosphere. The mixture was heated and monitored by TLC. After completion of the reaction, the mixture was allowed to cool to room temperature. Then, H_2O (10 ml) was added and the resulting mixture was extracted with ethyl acetate (3 × 20 ml). The combined organic layers were dried with magnesium sulfate and concentrated in vacuum. The crude material was purified by flash chromatography on silica gel with ethyl acetate and petroleum ether to give **4** as white solid. m.p.: 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.34 (t, $J = 7.1$ Hz, 3H), 2.49 (s, 3H), 4.28 (q, $J = 7.1$ Hz, 2H), 6.41 (d, $J = 16.0$ Hz, 1H), 7.06 (t, $J = 58.0$ Hz, 1H), 7.34 (d, $J = 9.6$ Hz, 1H), 7.78 (d, $J = 7.6$ Hz, 1H), 7.98

(d, $J = 16.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 166.10, 157.76, 155.16, 150.01, 142.91, 138.28, 135.40, 130.08, 125.74, 122.29, 119.04, 107.68, 60.99, 14.37, 12.72; ESI-MS *m/z*: 376.06 $(M + H)^+$.

General procedure for the synthesis of ethyl 2-chloro-3-[2-chloro-5-(4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)-4-fluorophenyl]-2-propenoate (**5**)

To a 250-ml, three-neck, round-bottom flask equipped with a magnetic stirrer and a thermometer was added the intermediate **4**, CCl_4 (15 ml), *OXONE*®, hydrochloric acid. The mixture was heated and the process of reaction was monitored by HPLC. Then Et_3N was added cautiously and the mixture was stirred at room temperature for 2 h. The resulting mixture was extracted with methylene chloride (2 × 50 ml). The combined organic layers were dried with magnesium sulfate and concentrated in vacuum. The crude material was purified by flash chromatography on silica gel with ethyl acetate and petroleum ether to give the desired compound **5** as white solid. m.p.: 111–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.40 (t, $J = 7.2$ Hz, 3H), 2.49 (s, 3H), 4.38 (q, $J = 7.2$ Hz, 2H), 7.07 (t, $J = 58.0$ Hz, 1H), 7.38 (d, $J = 9.2$ Hz, 1H), 8.07 (s, 1H), 8.19 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 162.60, 157.53, 154.89, 150.10, 142.89, 135.75, 131.64, 128.89, 128.56, 122.52, 118.72, 107.72, 63.10, 14.30, 12.77; ESI-MS *m/z*: 410.03 $(M + H)^+$.

General procedure for the synthesis of the herbicide carfentrazone-ethyl (**1**)

To a 100-ml, three-necked, round-bottom flask was added the compound **5** (1.50 mmol) and Pd/C. Then the flask was purged, flushed, and maintained with hydrogen atmosphere. After CH_3OH (15 ml) added into the mixture, the resulting mixture was heated to 35 °C. The mixture was filtered and concentrated in vacuum. The crude product was then purified by flash chromatography on silica gel with ethyl acetate and petroleum ether to give the product **1** as yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.26 (t, $J = 7.2$ Hz, 3H), 2.47 (s, 3H), 3.28 (dd, $J_1 = 14.0$ Hz, $J_2 = 8.0$ Hz, 1H), 3.50 (dd, $J_1 = 14.0$ Hz, $J_2 = 6.8$ Hz, 1H), 4.19–4.26 (m, 2H), 4.55 (dd, $J_1 = 8.0$ Hz, $J_2 = 6.8$ Hz, 1H), 7.06 (t, $J = 58.0$ Hz, 1H), 7.31 (d, $J = 9.6$ Hz, 1H), 7.47 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 168.61, 156.41, 153.84, 149.83, 142.52, 134.66, 130.59, 122.29, 118.32, 107.60, 62.29, 54.81, 37.94, 13.82, 12.63; ESI-MS *m/z*: 412.05 $(M + H)^+$.

Ethyl 2-chloro-5-[4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1H-1,2,4-triazol-1-yl]-4-fluorobenzenepropanoate (**8**)

^{1}H NMR (400 MHz,$CDCl_3$,δ ppm): 1.23 (t, $J = 7.2$ Hz, 3H), 2.45 (s, 3H), 2.63 (t, $J = 7.6$ Hz, 2H), 3.04 (t, $J = 7.6$ Hz, 2H), 4.12 (q, $J = 7.2$ Hz, 2H), 7.04 (t, $J = 58.0$ Hz, 1H), 7.26 (d, $J = 9.6$ Hz, 1H), 7.41(d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 171.32, 155.12, 152.48, 149.09, 141.63, 134.14, 127.51,

121.22, 117.36, 106.71, 59.80, 32.75, 27.31, 13.27, 11.69; ESI–MS *m/z*: 378.08 $(M + H)^+$.

Results and discussion

Our synthetic route for **1** is depicted in Scheme 2. The starting material **2** was treated with iodine in the oleum to produce **3**. The intermediate **3** reacted with ethyl acrylate to furnish the intermediate ethyl 3-[2-chloro-5-(4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)-4-fluorophenyl]-2-propenoate (**4**) in the absence of ligands under N_2 atmosphere via Heck reaction according to the research of Bradley et al. [12]. Then, oxidative addition–elimination of **4** with *OXONE*®/HCl-Et_3N in one-pot gave the intermediate ethyl 2-chloro-3-[2-chloro-5-(4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)-4-fluorophenyl]-2-propenoate (**5**) based on the study of Kim et al. [13]. Finally, the intermediate **5** was reduced by H_2 in the presence of Pd/C [14] in methanol to afford the target compound **1**.

Synthesis of the intermediate **3** with iodine in the oleum

The iodination of the triazolinone **2** to produce **3** was carried out in the 25 % oleum [10] (12 wt % triazolinone **2** in the oleum) using two forms of iodine at different temperature from 25 to 60 °C in good to excellent yields. The results are summarized in Table 1. With regard to the influence on the forms of iodine, the reaction needed a longer reaction time using graininess of iodine than powder of iodine, which probably increased the contact area between **2** and iodine to accelerate the rate of the reaction (Table 1, entries 1–2). The investigation on the effects of the temperature over the reaction revealed that the yields of **3** firstly increased from 25 to 35 °C and then decreased slowly from 35 to 60 °C (entries 3–8). However, the reaction time was shortened sharply from 28 to 2.5 h, probably because the oleum, as a solvent and an oxidant, has more activity at high temperature, whereas too high temperature might cause volatilization of oleum to reduce the yield of **3** slightly. Thus, the iodination reaction at 35 °C using powder of iodine provided **3** with the highest yield of 97.6 % and 96.8 % purity by HPLC.

Synthesis of the intermediate **4** based on the Heck reaction

The intermediate **4** was obtained from the intermediate **3** with ethyl acrylate in the absence of ligands via the Heck reaction [12]. Structurally, the coupling product **4** was *E* configuration for the coupling constant of the hydrogen on the C–C double bond is 16.0 Hz [15], which was similar to the structures of most reported products synthesized by the Heck reaction [16, 17]. By the way, an isolated by-product was observed. The by-product was proved to be a small amount of the compound **2**. It was speculated that the deiodination of **3** formed **2** during the Heck reaction.

Further, the coupling reaction of **3** using commercially available catalysts and different bases in various solvents was investigated as shown in Table 2. Recently, many new and convenient catalysts such as CuCl [18] and Pd/C [19] were reported

Table 1 Effects of reaction conditions[a,b] on the yield of the compound **3**

Entry	Temperature (°C)	Time (h)	I_2-form	Yield[c] (%)
1	25	42	Graininess	80.2
2	35	17	Graininess	89.4
3	25	28	Powder[d]	82.1
4	30	23	Powder	88.9
5	35	6	Powder	97.6
6	40	3	Powder	94.8
7	50	2.5	Powder	93.9
8	60	2.5	Powder	92.6

[a] Reaction conditions: the triazolinone **2** (0.05 mol), iodine (0.05 mol) in the 25 % oleum (12 wt % triazolinone **2** in the oleum)

[b] The 25 % oleum was prepared by 50 % oleum and the concentrated sulfuric acid

[c] Isolated yield

[d] The graininess of iodine was grinned in a mortar by pestle to give the powder of iodine

to have good effects on the Heck reaction, but both of them gave a poor performance in our reaction system (Table 2, entries 1–2). Conversely, the catalyst $Pd(OAc)_2$ gave the higher yield of **4** than $Pd(PPh_3)_4$ and $(PPh_3)_2PdCl_2$ (entries 3–5). Moreover, Et_3N was more favored to the reaction than K_2CO_3 (entries 5–6). It is clear from the table that DMF as a solvent displayed a better effect than MeCN and DMF/H_2O (entries 5, 7–8). In addition, the molar ratio of catalyst $Pd(OAc)_2$ to **3** was optimized in DMF using Et_3N as a base. The results indicated that molar ratio of catalyst $Pd(OAc)_2$ had a slight effect on the yield of **4** (entries 9–15). Even when the number of equivalent of $Pd(OAc)_2$ decreased to 1 ‰ equiv., the yield of **4** still exceeded 85 %, only by prolonging reaction time from 3 h to 33 h. Although the change of molar ratio of $Pd(OAc)_2$ made little difference to the yield of **4** (entry 15), it would cut cost to make it possible to develop an acceptable and low-cost protocol. Taking all these into account, using 2 ‰ equiv. of $Pd(OAc)_2$ and Et_3N as a base in DMF gave the better yield of **4** in 87.7 % yield.

Synthesis of the intermediate **5** by oxidative addition–elimination reaction

The compound **5** was synthesized from the compound **4** with *OXONE*®/HCl-Et_3N in one pot [13], which was a new method for the preparation of α-chloro-α,β-unsaturated carbonyl compounds, compared to direct addition–elimination method with Cl_2. The preparation of **5** comprised two-steps in one pot where **4** was firstly oxidized by *OXONE*®/HCl to give an intermediate ethyl α,β,2-trichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl]-4-fluorobenzenepropanoate (**7**). Then, the elimination of **7** was conducted by Et_3N to give **5** as shown in Scheme 3.

In the initial trial, we found the intermediate **7** was critical to the yield of **5**. So, we focused our attention on optimization of **7** and the reaction was monitored by HPLC (Table 3). Oxidants such as H_2O_2 [20] and NaClO were used in quantity for

Table 2 Effects of reaction conditions[a] on the yield of the compound **4**

Entry	*n*(**3**):*n*(EA):*n*(Cat.):*n*(Base)	Catalyst	Base	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	1.00:1.15:0.27:3.00	CuCl	Et_3N	DMF	120	48	Trace
2	1.00:1.50:0.03:2.50	5 %Pd/C	K_3PO_4	EtOH/H_2O	80	48	0
3	1.00:1.15:0.01:3.00	$(PPh_3)_2PdCl_2$	Et_3N	DMF	120	9	66.1
4	1.00:1.15:0.005:3.00	$Pd(PPh_3)_4$	Et_3N	DMF	120	18	80.6
5	1.00:1.15:0.005:3.00	$Pd(OAc)_2$	Et_3N	DMF	120	3	86.6
6	1.00:1.15:0.005:3.00	$Pd(OAc)_2$	K_2CO_3	DMF	120	10	73.4
7	1.00:1.50:0.05:2.00	$Pd(OAc)_2$	K_2CO_3	DMF/H_2O[c,d]	82	72	22.3
8	1.00:1.50:0.05:3.00	$Pd(OAc)_2$	Et_3N	MeCN	82	48	52.1
9	1.00:1.15:0.05:3.00	$Pd(OAc)_2$	Et_3N	DMF	120	3	93.6
10	1.00:1.15:0.03:3.00	$Pd(OAc)_2$	Et_3N	DMF	120	3	89.1
11	1.00:1.15:0.02:3.00	$Pd(OAc)_2$	Et_3N	DMF	120	3	86.4
12	1.00:1.15:0.01:3.00	$Pd(OAc)_2$	Et_3N	DMF	120	3	90.8
13	1.00:1.15:0.003:3.00	$Pd(OAc)_2$	Et_3N	DMF	120	6	88.3
14	1.00:1.15:0.002:3.00	$Pd(OAc)_2$	Et_3N	DMF	120	6	87.7
15	1.00:1.15:0.001:3.00	$Pd(OAc)_2$	Et_3N	DMF	120	33	85.9

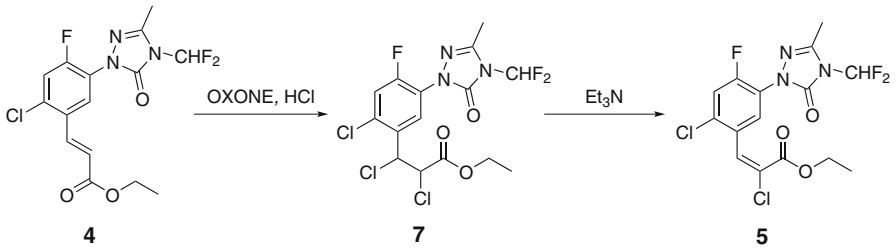
EA ethyl acrylate

[a] Reaction conditions: the compound **3** (2.50 mmol), ethyl acrylate (2.90 mmol), base and catalyst in solvent (5 ml) were placed in the Schlenk tube and the mixture was heated under nitrogen atmosphere until **3** was consumed totally monitored by TLC

[b] Isolated yield

[c] Biphasic reaction

[d] Added Bu_4NBr as phase transfer catalyst



4 7 5

Scheme 3 Preparation of **5** from **4** by oxidative addition–elimination method in one-pot with *OXONE*®/HCl-Et_3N

the oxidative addition and failed to get **7** with no reaction. Instead, using 2 equiv. of *OXONE*® in 2 mol/l HCl at 40 °C produced a trace of **7** (Table 3, entry 1). Encouragingly, increasing to 10 equiv. of *OXONE*® generated **7** in 58.8 % yield (entry 5). It was noteworthy that yield of **7** did not increase any more until 28 h. Furthermore, the amount of HCl and its concentration were investigated using 10 equiv. of *OXONE*®. It was observed that 24 equiv. of HCl achieved the better yield of **7** (entries 5, 7–11). When the amount of HCl was 24 equiv., the concentration of HCl was 1 mol/l to give better results than that was 2 mol/l (entries 5, 9). The effect of temperature was also examined. The reaction proceeded in 1 mol/l HCl at room temperature to provide **7** in 41.9 % yield, which was lower than the yield of **7** at 40 °C (entries 5, 14). Meanwhile, the reaction time was prolonged to 72 h at room temperature. Contrarily, the reaction proceeded in 2 mol/l HCl at room temperature to obtain the better yield than that at 40 °C (entries 11, 15), probably due to the faster volatilization of HCl at 40 °C. In addition, two different adding ways of *OXONE*®/HCl were investigated. One adding way was that *OXONE*® and HCl were first to be mixed at 0 °C and then the mixture was added into the reaction system to give **7** in 51.7 % yield (entry 12). The other was that *OXONE*® and HCl were directly added into the reaction system in one portion to generate **7** in 58.8 % yield (entry 5). Thus, using 10 equiv. of *OXONE*® in 1 mol/l HCl at 40 °C gave the better yield of **7** in 58.8 % yield, while about 7 % of **4** were remained. There were remainders with content of 34 % in the reaction. The structures of these remains have not been confirmed. They might be some by-products. To confirm their structures and to reduce these by-products will be our next work.

Subsequently, the intermediate **7** was eliminated by addition of Et_3N cautiously to afford **5**. The elimination proceeded rapidly to give at least 90 % conversion of **7**. The yields of **5** were also listed in Table 3. Overall, the one-pot reaction gave the highest isolated yield of **5** in 56.7 % yield (entry 5).

Synthesis of carfentrazone-ethyl (**1**) by reduction of the intermediate **5**

The intermediate **5** was a kind of α-halo-α,β-unsaturated esters which were reported to be reduced by bio-catalytic methods to give α-halo saturated ester [21]. However, the bio-reduction methods often used expensive enzymes as catalysts. So, in our initial attempts, organic catalytic methods to prepare **1** were used (Table 4). Firstly,

Table 3 Effects of reaction conditions[a] on the yield of the intermediate **7** and **5**

Entry	n(**4**):n(*OXONE*®)	$n_{HCl} = C_{HCl} \cdot V_{(HCl)}$ (mmol = mol/l × ml)	Temperature (°C)	Content of **7** by HPLC[b] (%)	Yield of **5**[c] (%)
1	1.0:2.0	2 × 0.5	40	5.6	Trace
2	1.0:5.0	1 × 12	40	25.3	22.5
3	1.0:6.0	1 × 12	40	26.6	24.0
4	1.0:8.0	1 × 12	40	38.9	35.1
5	1.0:10.0	1 × 12	40	58.8	56.7
6	1.0:12.0	1 × 12	40	53.8	50.4
7	1.0:10.0	1 × 6	40	29.3	26.2
8	1.0:10.0	1 × 3	40	11.2	Trace
9	1.0:10.0	2 × 6	40	52.6	51.5
10	1.0:10.0	2 × 9	40	44.2	40.5
11	1.0:10.0	2 × 12	40	41.6	37.6
12[d]	1.0:10.0	1 × 12	40	51.7	47.4
13[d]	1.0:10.0	2 × 6	40	41.3	36.4
14[e]	1.0:10.0	1 × 12	r.t	41.9	39.7
15[e]	1.0:10.0	2 × 12	r.t	54.2	52.6

[a] Reaction condition: the compound **4** (0.5 mmol), *OXONE*® in CCl_4 (15 ml) and HCl (12 mmol) were allowed to react for 28 h and then Et_3N (16 ml) was added to stir for 2 h at room temperature

[b] The content of the intermediate **7** was monitored by HPLC in the oxidative addition and mobile phase was a mixture of methanol/water in the ratio 70:30 (v/v); wavelength: 245 nm; flow rate: 1 ml/min

[c] Isolated yield of the compound **5**

[d] Reagent *OXONE*® and HCl were first to be mixed at 0 °C, then was added to the system

[e] The reaction time was prolonged to 72 h at room temperature

$NaBH_4$/CuCl as catalysts in methanol [22] were attempted, while we failed to get **1** and an isolated by-product was proved to be ethyl 2-chloro-5-[4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl]-4-fluorobenzenepropanoate (**8**) by NMR and mass spectrometry (Table 4, entry 1). Then, reaction was unsuccessful using $NaBH_4$/ZnO [23] as catalysts in absence of solvent (entry 2). Thereafter, choosing $NaBH_4$ [24] as a catalyst led to none of expected **1** (entry 3).

Next, the hydrogenation of **5** was attempted to be catalyzed by Pd/C in methanol. Notably, the reduction of α-chloro-α,β-unsaturated esters to give α-chloro saturated esters by the above catalytic system has not been reported yet. Fortunately, the target compound **1** was obtained using 5 % Pd/C at 35 °C in 66 % yield determined by ^{1}H NMR spectroscopy and in 48.5 % isolated yield (entry 4). The reaction simultaneously gave a by-product **8** in 33 % yield by ^{1}H NMR and in 25.1 % isolated yield (entry 4). With any decrease in quantity of 5 % Pd/C, the reaction failed to provide **1** with desired yields (entries 5–9). Moreover, prolonging reaction time did not improve the yield of **1** (entry 8), and choosing 10 % Pd/C as a catalyst gave the more yield of **8** (entry 9) (Fig. 2).

It seems likely that chlorine atom in α-position of **5** was replaced by hydrogen atom in the Pd/C-H_2 catalytic system to form the by-product **8**, and the chlorine

Table 4 Effects of reaction conditions on the yield of **1**

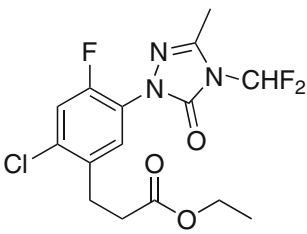
Entry	Reagent	Solvent	Temperature (°C)	*T* (h)	Results (%) **1/8/5**	Note
1	$NaBH_4$/CuCl	MeOH	0	7	0[a]/85.2[a]/trace[a]	
2	$NaBH_4$/ZnO	None	r.t	1.5	No reaction	
3	$NaBH_4$	MeOH	r.t	24	0/0/trace[a]	
4	5 % Pd/C + H_2	MeOH	35	22	48.5[a]/25.1[a]/trace[a] 66[b]/33[b]/trace[b]	m(5 % Pd/C) = 100 wt % × m(**5**)
5	5 % Pd/C + H_2	MeOH	35	22	6.6[c]/53.7[c]/0[c]	m(5 % Pd/C) = 30 wt % × m(**5**)
6	5 % Pd/C + H_2	MeOH	35	22	6.3[c]/10.1[c]/82.4[c]	m(5 % Pd/C) = 20 wt % × m(**5**)
7	5 % Pd/C + H_2	MeOH	35	22	7.4[c]/5.3[c]/83.1[c]	m(5 % Pd/C) = 10 wt % × m(**5**)
8	5 % Pd/C + H_2	MeOH	35	48	7.7[c]/6.2[c]/81.6[c]	m(5 % Pd/C) = 10 wt % × m(**5**)
9	5 % Pd/C + H_2	MeOH	35	22	No reaction	m(5 % Pd/C) = 5 wt % × m(**5**)
10	10 % Pd/C + H_2	MeOH	35	22	5.8[c]/66.3[c]/8.3[c]	m(10 % Pd/C) = 10 wt % × m(**5**)

[a] Isolated yield

[b] Yield determined by ^{1}H NMR spectroscopy

[c] HPLC yield; mobile phase was a mixture of methanol/water in the ratio 70:30 (v/v); wavelength was 245 nm; flow rate was 1 ml/min

Fig. 2 Chemical structure of by-product (**8**)



atom might cause Pd/C temporal failure [25, 26]. Thus, how to prevent the dechlorination in the reduction was the key to improve the yield of **1**, which will encourage us to find a suitable catalytic system in the future work.

Overall, the isolated yield of **1** starting from the raw material **2** through four steps was 25 %, which did not achieve the expected results.

Conclusions

In conclusion, we demonstrated a new method for the preparation of the herbicide carfentrazone-ethyl (**1**) involving iodination, Heck reaction, oxidative addition–

elimination reaction, and reduction. The inexpensive reagent ethyl acrylate was employed to replace commercially unavailable ethyl 3-hydroxy-2-methylenebutanoate to reduce costs and enhance atom economy. The hydrogenation of α-chloro-α,β-unsaturated esters furnished α-chloro saturated esters in 66 % yield determined by ^{1}H NMR. The overall isolated yield of **1** was 25 %, which did not achieve good results as expected. We thought the yield of **1** could be improved by optimizing oxidative addition–elimination reaction and reduction.

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