Microwave-Assisted One-Pot Synthesis of α-Fluoro-α,β-Unsaturated Esters under Solvent-Free Conditions

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Abstract: A microwave-assisted approach for the synthesis of α -fluoro- α , β -unsaturated esters from ethyl bromofluoroacetate, aldehydes, and triphenylphosphine in the presence of Zn–Cu under solvent-free conditions was achieved. The reaction was accomplished within five minutes with good product yields.

Key words: microwave irradiation, solvent-free, α -fluoro- α , β -un-saturated ester

Microwave irradiation has been used in organic synthesis since 1986¹ and is now accepted as a method for reducing the reaction times for a large variety of reactions.² It has also been widely applied in the formation of carbon–carbon double bond, including Wittig,³ Heck,⁴ condensation reactions,⁵ Knoevenagel reaction,⁶ or dehydration of aldol compounds.⁷

As many fluorinated compounds have biological activities,⁸ extensive studies on the preparation of fluorine-containing analogues,9 particularly for the fluorinecontaining alkenes,¹⁰ have been carried out extensively in recent years. There are already existing methods to construct fluoro-substituted carbon-carbon double bond,¹¹ and the reaction can be conducted in the presence of metallic reagents, such as Et₂Zn,¹² Pd(PPh₃)₄,¹³ VOCl₃,¹⁴ Mg(0)¹⁵ These methods are suitable for certain synthetic conditions in many cases, however, some of these procedures are associated with one or more disadvantages such as tedious process,16 long reaction time,13 expensive metallic reagents, and difficult product separation,¹⁷ which might limit the scale of an experiment. Thus, there is still a necessity to find new methodologies that are fast and inexpensive to carry out the reaction in a large scale. Herein, we wish to report a microwave-assisted method for the one-pot synthesis of ethyl α -fluoro- α , β -unsaturated esters in the presence of Zn–Cu¹⁸ under solvent-free conditions.



Scheme 1 Synthesis of α -fluoro- α , β -unsaturated ester

SYNLETT 2008, No. 15, pp 2376–2378 Advanced online publication: 22.08.2008 DOI: 10.1055/s-2008-1078213; Art ID: W06908ST © Georg Thieme Verlag Stuttgart · New York The synthesis of ethyl α -fluoro- α , β -unsaturated esters was carried out using ethyl bromofluoroacetate, triphenylphosphine, and aldehydes under microwave irradiation. Initial studies were carried out using 4chlorobenzaldehyde (**2b**) as the model substrate to explore the reaction conditions (Scheme 1). We first examined the effect of different metallic reagents under the one-pot conditions. The reaction was carried out at 110 °C, inside a 1000 W microwave oven using dry DMF as solvent. The results are summarized in Table 1.

Table 1 Results of Different Metallic Reagents with Ethyl Bromofluoroacetate, Triphenylphosphine, and 4-Chlorobenzaldehyde

Solvent	Metallic reagent	Time (min)	Yield (%) ^a
DMF	_	20	40
DMF	-	40	41
DMF	Zn	20	52
DMF	Zn	40	52
DMF	Fe	20	43
DMF	Fe	40	44
DMF	Zn–Cu	20	60
DMF	Zn–Cu	40	61

^a Isolated yield, product characterized by ¹H NMR, IR, and MS.

As shown in Table 1, although the reaction could proceed even without metallic reagents, addition of metallic reagents would improve the yield dramatically. We were pleased to find that Zn–Cu was a good reagent for the onepot reaction. Similar yields were observed even if the reaction time was extended to 40 minutes.

Then, we further investigated the solvent effect in the presence of Zn–Cu under the microwave-irradiation conditions. The results are summarized in Table 2.

As shown in Table 2, the results indicated that the reaction under solvent-free conditions afforded ethyl α -fluoro- α , β unsaturated ester in the best yield, thus solvent-free conditions were chosen as our optimal conditions to examine the reaction scope.

We further studied the effect at different temperatures and powers of microwave in the presence of Zn–Cu under solvent-free conditions. The results are summarized in

Table 2	Results of Dif	ferent Solvents	with Ethyl	Bromofluoroace-
tate, Triph	enylphosphine	e, and 4-Chloro	benzaldehy	de

Solvent	Metallic reagent	Temp (°C)	Time (min)	Yield (%) ^a
_	Zn–Cu	110	20	73
DMF	Zn–Cu	110	20	60
MeCN	Zn–Cu	80	20	53
[Bmin]PF ₆	Zn–Cu	110	20	59
THF	Zn–Cu	60	20	50
CH ₂ Cl ₂	Zn–Cu	40	20	51
C ₆ H ₆	Zn–Cu	80	20	40

^a Isolated yield.

Table 3. As shown in Table 3, the results indicated that the yield was improved at 150 °C with a microwave power of 1000 W. At the same time, we found the reaction time could be reduced to five minutes with a stronger power and at a higher temperature.

Table 3 Results of Different Temperatures and Powers with EthylBromofluoroacetate, Triphenylphosphine, and 4-Chlorobenzalde-hyde

Metallic reagent	Power (W	7) Temp (°C)	Time (min)	Yield (%) ^a
Zn–Cu	500	90	20	48
Zn–Cu	700	90	20	53
Zn–Cu	800	90	20	56
Zn–Cu	900	90	20	57
Zn–Cu	1000	90	20	66
Zn–Cu	1000	110	20	73
Zn–Cu	1000	120	20	75
Zn–Cu	1000	150	5	83

^a Isolated yield.

Furthermore, we examined the effect of different heating method in the presence of Zn–Cu under solvent-free conditions. The results are summarized in Table 4. It can be seen that the yield of the reaction was improved, and the reaction time was shortened under microwave irradiation as compared to the conventional heating method.

To establish the generality of the methodology, various aldehydes were treated with ethyl bromofluoroacetate, triphenylphosphine, and Zn–Cu under the optimized conditions. The results are listed in Table 5.

It was notable that aliphatic aldehydes, except α , β -unsaturated aliphatic aldehydes, could not afford the products,¹⁹ even if the reaction time was increased to 40 minutes. Although α -fluoro- α , β -unsaturated esters could be similarly synthesized in the presence of Pd(PPh₃)₄ un-

Table 4Results of Different Heating Methods

Heating method	Metallic reagent	Time (min)	Yield (%) ^a	Z/E ^b
MW	Zn–Cu	5	83	69:31
Conventional heating method	Zn–Cu	5	60	65:35
Conventional heating method	Zn–Cu	60	75	72:28

^a Isolated yield, products characterized by ¹H NMR, IR, and MS. ^b Ratio determined by ¹H NMR (300 MHz, CDCl₃) analysis.

Table 5 Synthesis of Ethyl α-Fluoro-α,β-Unsaturated Esters

Br F	O OEt + RCHO	Ph ₃ P/Zn MW	-Cu	RHC=CFC	CO₂Et
	1 2			3	
Entry	R	Time (min)	Product	Yield (%) ^a	<i>Z</i> / <i>E</i> ^b
1	$4-O_2NC_6H_4$	5	3 a	78	68:32
2	$4-ClC_6H_4$	5	3b	83	69:31
3	$4-BrC_6H_4$	5	3c	84	61:39
4	$4-HOC_6H_4$	5	3d	67	70:30
5	$4-Me_2NC_6H_4$	5	3e	60	100:0
6	4-MeC ₆ H ₄	5	3f	66	57:43
7	$2-O_2NC_6H_4$	5	3g	69	58:42
8	$2-MeOC_6H_4$	5	3h	81	60:40
9	Ph	5	3i	70	62:38
10		5	3j	70	60:40
11		5	3k	44	86:14
12	PhCH=CH	5	31	56	68:32
13	Pr	5	3m	_	_
	Pr	20	3m	-	-
	Pr	40	3m	-	_

^a Isolated yield, products characterized by ¹H NMR, IR, and MS. ^b Ratio determined by ¹H NMR (300 MHz, CDCl₃) analysis.

der the conventional heating method, the reaction time was shortened from hours to five minutes with a slight improvement on stereoselectivity¹³ in the presence of Zn–Cu under microwave irradiation.

The ratios of Z/E isomers were determined by ¹H NMR spectra. It was reported that the signals of vinyl and ethyl protons of (Z)- α -fluoro- α , β -unsaturated esters were at a lower field than those of the corresponding *E* compounds. For example, the ¹H NMR spectrum showed that the chemical shifts of the vinyl proton and the methyl signal

of the ester group of ethyl 2-fluoro-3-(4-nitrophenyl)-(*Z*)propenoate were at $\delta = 6.98$ and 1.40 ppm, respectively, while the corresponding chemical shifts of ethyl 2-fluoro-3-(4-nitrophenyl)-(*E*)-propenoate compound were at $\delta = 6.92$ and 1.26 ppm, respectively.¹³ The results were in accordance with our results.

In conclusion, we have developed a microwave-assisted approach for the synthesis α -fluoro- α , β -unsaturated esters from ethyl bromofluoroacetate, aldehyde, and triphe-nylphosphine in the presence of Zn–Cu under solvent-free conditions. The reaction does not require the use of any volatile organic solvents as well as expensive metallic reagents. Thus, this is an economical and environmental friendly method for the synthesis of α -fluoro- α , β -unsaturated esters.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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- (19) All reactions were conducted under an XH-100A microwave synthesis/extraction instrument, which was made by Beijing Xiang Hu Science and Technology Development Co. Ltd. Triphenylphosphine (1.2 mmol), ethyl bromofluoroacetate (1.2 mmol), aldehyde (1.0 mmol), and Zn–Cu (0.1 g) were added into an oven-dried round-bottom flask. The mixture was stirred under microwave irradiation, which was set at 1000 W, 150 °C for 5 min. The product was purified by chromatography on SiO₂ with EtOAc and PE (60–90 °C).

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