A Microwave-Accelerated Esterification of α,β-Unsaturated Acids with Alkyl or Aryl Carbonochloridate and Triethylamine in Acetonitrile as a Novel Esterifying Reagent Mixture[1])

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An efficient synthesis of α,β-unsaturated esters by treatment of the corresponding acids with alkyl or aryl carbonochloridate, triethylamine, and acetonitrile was accomplished for the first time under microwave irradiation for 10 min. The esters **1b**–**24b** were isolated in 71–97% yield.

Introduction. – In the last decade, a lot of environmentally friendly protocols have come into fore, and most importantly among them is organic synthesis under microwave irradiation, due to a lot of benefits inherent in microwaves [1]. As a corollary, some microwave-assisted esterifications of α,β-unsaturated acids have been reported with various reagents such as H^+/alcohol [2], potassium hydrogensulfate [3], silicotungstic acid [4], montomorrillonite KSF clay/H_2SO_4 [5], $PdCl_2$/P(*o*-Tol)$_3$/(bmim)PF_6/Et_3N (bmim = 1-butyl-3-methylimidazolium) [6] and polymer-supported *O*-alkyl- or *O*-benzylisourea [7]. Esterifications of α,β-unsaturated acids under microwave irradiation, beside being environmentally friendly, are also marked by a considerable reduction in reaction time in comparison to conventional [8] esterifications. In this regard, some of the methods drew our attention to the possibility to employ then in our case. Unfortunately, the promisingly high-yielding and attractive esterification of carboxylic acids with *O*-benzylisourea [7] as reagent is limited by the commercial unavailability of *O*-benzylisourea. Similarly, microwave-assisted esterification of cinnamic acids with H^+/alcohol [2] also appears to be attractive; however, when applied to 3-(2,4,5-trimethoxyphenyl)prop-2-enoic acid (**1a**) in H^+/alcohol, the method was not compatible [9] because of poor solubility of **1a** in the alcohol and rapid evaporation of alcohol during microwave irradiation, resulting in the isolation of unreacted starting material. Hence, an efficient and mild protocol for esterification of a wide range of substituted α,β-unsaturated acids remains a desirable target. We report herein a microwave-assisted synthesis of α,β-unsaturated esters utilizing commercially available alkyl or aryl carbonochloridates, Et_3N, and MeCN as a novel esterifying mixture, resulting in moderate to high yields (71–97%) after only 10 min (*Scheme 1*).

Results and Discussion. – During our endeavor on microwave-assisted synthesis of bioactive compounds [10] including cinnamic acid derivatives [11], we realized that transforming cinnamic acids into their derivatives in basic medium is advantageous

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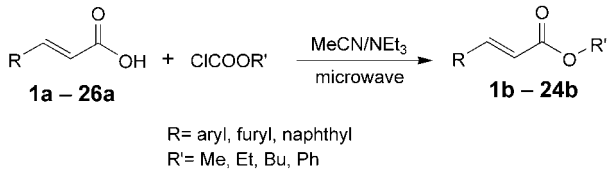
Scheme 1



since it catalyzes the reaction and facilitates dissolution of cinnamic acids. Hence, after the failure of esterification with H^+/alcohol under microwave irradiation, we focused our attention on alkyl or aryl carbonochloridate/base mixtures [12], which have been reported as a mild and well-exploited economical reagents for the preparation of a large number of organic molecules. However, to the best of our knowledge, esterification with alkyl or aryl carbonochloridate has not yet been achieved under microwave irradiation. Initially, 3-(2,4,5-trimethoxyphenyl)prop-2-enoic acid (**1a**) was added to a mixture of CH_2Cl_2, Et_3N, and ethyl carbonochloridate which upon microwave irradiation (960 W) for 4 min provided ethyl 3-(2,4,5-trimethoxyphenyl)-prop-2-enoate (**1b**) in 30% yield. Addition of a catalytic amount of *N*,*N*-dimethylpyridin-4-amine (DMAP) [12b] to the same initial mixture did not enhance the yield of **1b** but made workup more difficult (bumping of the reaction mixture after evaporation of CH_2Cl_2). Various solvents were tested in the above reaction such as $CHCl_3$, dioxane, and THF but none of them improved the yield of **1b** (*Table 1*). Similarly, DMF having a high boiling point and high dielectric constant [13], both assumed to be suitable for this reaction, did only marginally enhance the yield of **1b** to 37%.

Table 1. *Effect of Solvent and Ethyl Carbonochloridate (EtOCOCl)/Triethylamine Ratio*[a]) *in the Esterification of 3-(2,4,5-Trimethoxyphenyl)prop-2-enoic Acid* (**1a**) *into Ethyl 3-(2,4,5-Trimethoxyphenyl) Prop-2-enoate* (**1b**) *under Microwave Irradiation* (960 W)

Microwave irradiation	Solvent	EtOCOCl [mol-equiv.]	Yield [%]
2 min	CH_2Cl_2	1.2	30
4 min	CH_2Cl_2	1.2	no improvement
4 min	THF	1.2	25
4 min	$CHCl_3$	1.2	28
4 min	1,4-dioxane	1.2	21
4 min	DMF	1.2	37
4 min	MeCN	1.2	45
10 min	MeCN	1.2	no improvement
10 min (ice bath)	MeCN	1.2	52
10 min (ice bath)	MeCN	2	68
10 min (ice bath)	MeCN	3	88
10 min (ice bath)	MeCN	excess	no improvement
300 min (conventional)	MeCN	3	64

[a]) The amount of Et_3N was kept constant (3 mol-equiv.) in all experiments because it is the minimum amount required for dissolution of **1a**.

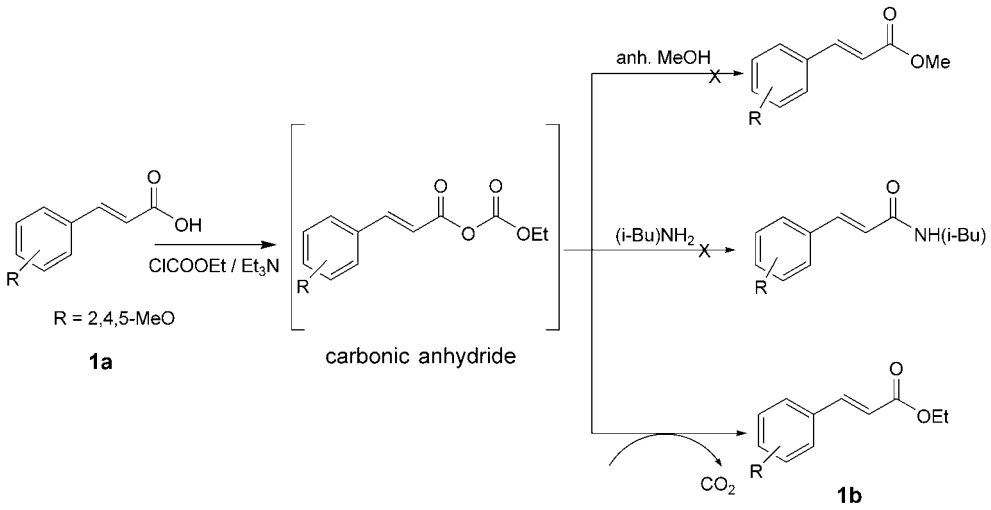
Surprisingly, the use of MeCN [14] as a solvent increased the yield of **1b** to 45% within 4 min of irradiation; thus, MeCN appeared to be the most suitable solvent for

the reaction (*Table 1*). But no further increase in the yield could be achieved even upon prolonged periods of exposure (up to 10 min). Although we assumed that the combination of Et_3N and ethyl carbonochloridate should retard evaporation of the thermolabile ethyl carbonochloridate to some extent under microwave irradiation, the persistently low product yield suggested that some evaporation of either ethyl carbonochloridate or esterified product was occurring. Hence, irradiations at various low-power levels (180–600 W) were explored, but there was no significant improvement in the yield of **1b**. This suggested that high magnetron-input power (700–960 W) led to evaporation of product, whereas a low input-power level (180–600 W) was insufficient for satisfactory esterification rates of **1a**. Thus, the above irradiations were performed in an ice bath for a prolonged time under high magnetron-input power (960 W) inside the microwave oven, indeed, the cooling should condense the volatile products but not adversely influence the superheating [15] effects associated with microwaves. Finally, the microwave-assisted (960 W) reaction of **1a** with ethyl carbonochloridate/Et_3N 1:1 (mol ratio) in MeCN under ice-bath cooling provided an 88% yield of **1b** in an optimized time of 10 min (*Table 1*). The use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or pyridine in place of Et_3N was also effective; however, there was no significant increase in yield of the product **1b**.

Under conventional conditions, the reaction of **1a** with ethyl carbonochloridate/Et_3N in MeCN at room temperature (5 h) under N_2 gave product **1b** in 64% yield; no yield improvement was achieved even upon refluxing for 10 h.

The reaction of cinnamic acid **1a** and ethyl carbonochloridate proceeds *via* the unstable intermediate carboxylic carbonic anhydride, which spontaneously releases carbon dioxide [12][16] and forms ethyl cinnamate **1b** (*Scheme 2*). We studied the mechanism in more detail by performing a series of experiments wherein **1a** was first activated with ethyl carbonochloridate/Et_3N to form intermediate anhydride, which upon addition of MeOH or isobutylamine did not form any methyl cinnamate or *N*-

Scheme 2



isobutylcinnamamide, respectively (*Scheme 2*). Instead, in both cases, ethyl cinnamate **1b** was exclusively obtained, thus confirming that the esterification mechanism is intramolecular rather than intermolecular. Performing the above experiment under microwave irradiation also confirms the involvement of an intramolecular mechanism for the formation of ester **1b**.

The microwave-assisted esterification was applied to the preparation of a large number of esters [17] from a variety of structurally different α,β-unsaturated acids, *i.e.*, from **2a**–**26a**, and different alkyl and aryl carbonochloridates to determine the scope and limitation of the method; the corresponding esters **2b**–**24b** were isolated in moderate to high yield (71–97%; *Table 2*). Thus, α,β-unsaturated acids containing a 2-furyl or 1-naphthyl substituent, or a phenyl substituent carrying electron-withdrawing or electron-releasing groups all successfully reacted under the given esterification conditions. However, in case of the OH-substituted cinnamic acid **25a** and **26a**, no ester **25b** and **26b**, respectively, was formed even after prolonged irradiation time; some by-product was isolated which could not be elucidated. All esters **1b**–**24b** were characterized by spectroscopic techniques, and the data were in accordance with the reported values [18].

Table 2. *Alkyl Carbonochloridate Assisted Esterification of α,β-Unsaturated Acids* **1a**–**26a** *into α,β-Unsaturated Esters* **1b**–**24b** *under Microwave Irradiation* (960 W)

	R	R′	Reaction time [min]	Yield [%]
1b	2,4,5-trimethoxyphenyl	Et	10	88
2b	2,4,5-trimethoxyphenyl	Me	10	82
3b	3,4,5-trimethoxyphenyl	Et	10	83
4b	2,3,4-trimethoxyphenyl	Et	10	85
5b	3,4-dimethoxyphenyl	Et	10	84
6b	3,4-dimethoxyphenyl	Me	10	86
7b	3,4-dimethoxyphenyl	Bu	10	91
8b	3,5-dimethoxyphenyl	Et	10	85
9b	2,5-dimethoxyphenyl	Et	10	84
10b	Ph	Ph	10	82
11b	4-methoxyphenyl	Me	10	88
12b	4-methoxyphenyl	Et	10	84
13b	4-methoxyphenyl	Bu	10	82
14b	4-methoxyphenyl	Ph	10	96
15b	3-methoxyphenyl	Et	10	86
16b	4-methylphenyl	Me	10	79
17b	Ph	Et	10	74
18b	Ph	Me	10	76
19b	4-nitrophenyl	Et	10	97
20b	4-chlorophenyl	Me	10	84
21b	4-bromophenyl	Et	10	86
22b	3-chlorophenyl	Me	10	76
23b	1-naphthyl	Et	10	84
24b	2-furyl	Me	10	71
25b	4-hydroxy-3-methoxyphenyl	Et	20	–
26b	3-hydroxyphenyl	Et	20	–

Conclusions. – A novel and efficient microwave-assisted conversion of the α,β-unsaturated acids **1a**–**26a** with alkyl or aryl carbonochloridate and Et_3N in MeCN into the corresponding esters **1b**–**24b** was developed, furnishing the latter in 71–97% yield within 10 min. The method may find utility as an alternative to the currently available protocols.

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Experimental Part

General. Alkyl (methyl, ethyl or butyl) and phenyl carbonochloridate of reagent grade and MeCN of HPLC grade (*Merck*) were used without further purification. A *Kenstar* domestic microwave oven (2450 MHz, 960 W) was used for reactions. M.p.: *Mettler FP80* micromelting point apparatus; uncorrected. IR Spectra: *Perkin-Elmer* spectrophotometer. NMR Spectra: *Bruker Avance-300* spectrometer; ^1H at 300 and ^{13}C at 75.4 MHz; $CDCl_3$ soln.

Esterification of Substituted α,β-Unsaturated Acids: General Procedure. The α,β-unsaturated acid (0.005 mol) in an *Erlenmayer* flask (loose funnel at the top) was dissolved in Et_3N (0.015–0.017 mol) and MeCn (5–6 ml) and alkyl or aryl carbonochloridate (0.015 mol) was added. The mixture was placed in an ice bath and irradiated in the microwave oven for 10 min, with a pause of 15 s after every 2 min. After completion of the reaction (TLC monitoring), the mixture was cooled, washed with AcOEt (3×10 ml), and filtered. The combined AcOEt layer was washed with dil. HCl (2×10 ml), sat. $NaHCO_3$ (2×10 ml), and sat. NaCl soln., dried (Na_2SO_4), and evaporated: pure (by NMR) ester, *i.e.*, no column chromatography (CC) was required, except for phenyl cinnamates **10b** and **14b** which were subjected to CC (silica gel, hexane/AcOEt 9:1) as the crude products were comparatively impure. Spectroscopic and physical data of esters **1b**–**24b** were in accordance with the reported values [18–33].

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