Microwave-Assisted Convenient Synthesis of α,β-Unsaturated Esters and Ketones *via* Aldol-Adduct Elimination

by **Pathi Suman**, **Rayala Nageswara Rao**, and **Bhimapaka China Raju***

Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, India
(phone: +914027191725; fax: +91402716512; e-mail: chinarajuiict@yahoo.co.in)

Various fluorinated 3-oxo ester/1,3-diketones were reacted with carbonyl compounds, in presence of piperidine and under microwave irradiation, to afford (*E*)-α,β-unsaturated esters and ketones in good yields. The systematic study reveals that the reaction proceeded through the formation of aldol adduct. The method provides a new and simple way for C,C bond formations.

Introduction. – (*E*)-α,β-Unsaturated esters and ketones are important intermediates for the synthesis of natural products and biologically important heterocyclic compounds [1]. *Wittig* and *Horner–Wadsworth–Emmons* reactions are the classical methods to produce (*E*)-α,β-unsaturated esters [2]. *Knoevenagel* condensation of non-fluorinated 3-oxo esters with aldehydes depending on the reaction conditions resulted in the formation of mono/dimethylene-3-oxo esters [3], whereas fluorinated 3-oxo esters (ethyl 4,4,4-trifluoro-3-oxobutanoate) seldom lead to the (*E*)-3-phenyl-2-(2,2,2-trifluoroacetyl)prop-2-enoate, and 2,6-bis(trifluoromethyl)tetrahydropyrans or 4-aryl-(alkyl)-3,5-dialkoxycarbonyl-2,6-dihydroxy-2,6-bis(fluoroalkyl)tetrahydropyrans [4]. However, to the best of our knowledge, there is no method available in the literature for the synthesis of (*E*)-α,β-unsaturated esters/ketones by the reaction of carbonyl compounds with fluorinated 3-oxo ester/1,3-diketones such as ethyl 4,4,4-trifluoro-3-oxobutanoate/1,1,1-trifluoropentane-2,4-dione.

Results and Discussion. – Our studies recently focused on feasible reactions of carbonyl compounds/salicylaldehydes with 3-oxobutanoates bearing chloro or trifluoro substituents. In this context, we studied the reactivity of salicylaldehydes with ethyl 4-chloro-3-oxobutanoate using piperidine to provide 2*H*-chromenes [5], interim these derivatives were successfully converted to corresponding 2,3-dihydrobenzoxepine-4-carboxylates [6]. We also studied the reactivity of various carbonyl compounds with ethyl 4,4,4-trifluoro-3-oxobutanoate using piperidine in CH_2Cl_2 at room temperature to provide a series of (*E*)-α,β-unsaturated esters, and the established method was successfully applied for the synthesis of variety of (*E*)-α,β-unsaturated ketones [7]. As part of our program to synthesize biologically active heterocyclic compounds and discovery of new synthetic methodologies [8], and in an extension of our previous work [7], here, we report synthesis of (*E*)-α,β-unsaturated esters and ketones by the reaction

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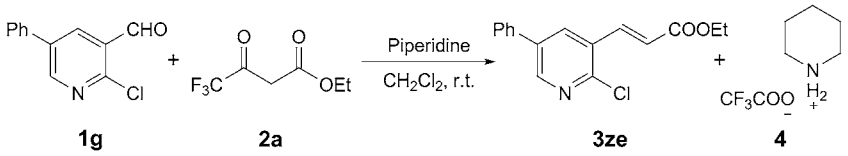
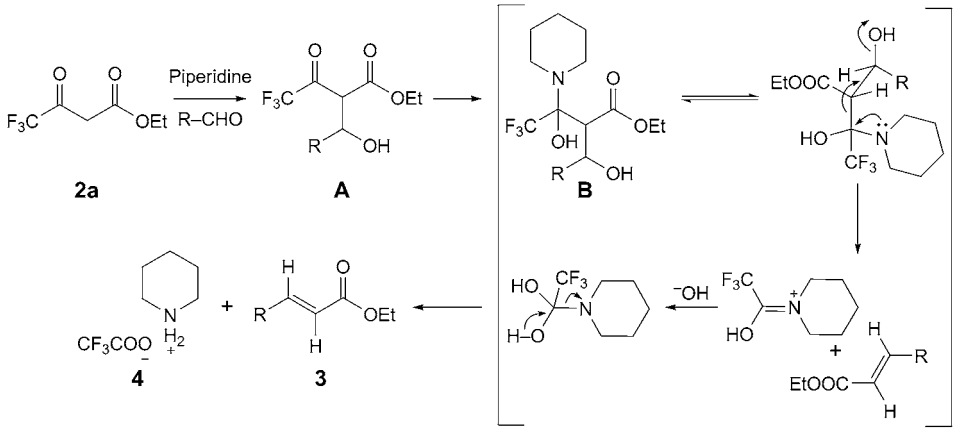
of carbonyl compounds with various oxobutanoates such as ethyl 4,4,4-trichloro-3-oxobutanoate, 1,1,1,5,5,5-hexafluoropentane-2,4-dione, 4,4,4-trifluoro-1-(naphthalene-2-yl)butane-1,3-dione, and 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione using piperidine in CH_2Cl_2 at room temperature/ under reflux conditions. Further, the method was modified by applying microwave irradiation, and the results are presented below.

In a model reaction, 2-chloro-5-phenylnicotinaldehyde (**1g**; 1 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (**2a**; 1.2 mmol), and piperidine (1.2 mmol) in CH_2Cl_2 (4 ml) at room temperature furnished a product (90% yield; *Scheme 1*), identified as ethyl (*E*)-3-(2-chloro-5-phenylpyridin-3-yl)prop-2-enoate (**3ze**) [7], presumably *via* an aldol adduct or *Knoevenagel* intermediate. Systematically, a series of experiments were conducted to study the reaction mechanism, and the progress of the reactions was monitored by LC/MS and ^{1}H-NMR. The LC/MS data (*Zorbax SB C3*, 150 × 4.6 mm, 5 μm; MeCN/H_2O 70 : 30; 1 ml/min) indicated that the reaction proceeded through the formation of aldol primary adduct (**A**; (4.396 min; 27%; *Scheme 2*). The ^{1}H-NMR experiment was carried out in an NMR tube with $CDCl_3$, and the formed aldol adduct was analyzed; the signal of H–C(2) (between the two C=O groups of primary aldols) appeared as *doublet* at δ(H) 3.24 ($J = 11.9$) and H-atom signal of the HO–C*H* group appeared as *triplet*-like signal at δ(H) 4.90 ($J = 11.9$). Piperidyl H-atom signals were detected as two separate *singlet*s at δ(H) 8.60 and 8.08. The ester Me signal appeared as *triplet* at δ(H) 1.24 ($J = 6.9$), and CH_2O gave rise to a *quartet* at δ(H) 4.08 ($J = 6.9$). Further attack of piperidine at trifluoroacetyl C=O C-atom of aldol primary adduct (**A**) led to the intermediate **B**. The *in situ* stereoselective elimination of piperidinium

Scheme 1



Scheme 2. *Proposed Mechanism for Tandem Aldol-Adduct Elimination*



trifluoroacetate afforded (*E*)-α,β-unsaturated ester **3** (*Scheme 2*). The eliminated piperidinium trifluoroacetate salt was analyzed by ^{19}F- and ^{1}H-NMR spectroscopy. The ^{19}F-NMR spectrum exhibited a *singlet* at δ(F) −76.17 (*Fig. 1*) for piperidinium trifluoroacetate salt, in agreement with the corresponding value of the prepared salt, δ(F) −76.25; *Fig. 2*[1]). The ^{1}H-NMR spectrum displayed a *multiplet* at δ(H) 1.60–1.72,

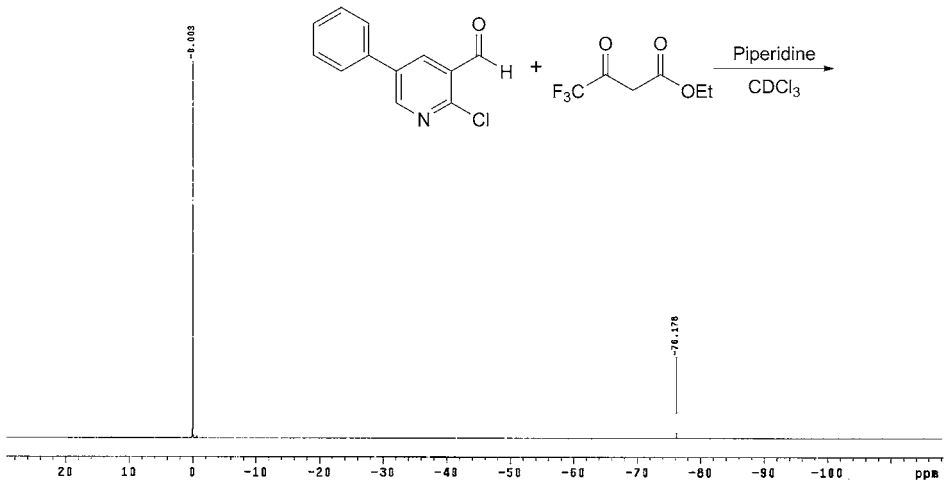


Fig. 1. *^{19}F-NMR Spectrum of NMR tube reaction* ($CFCl_3$ as internal standard)

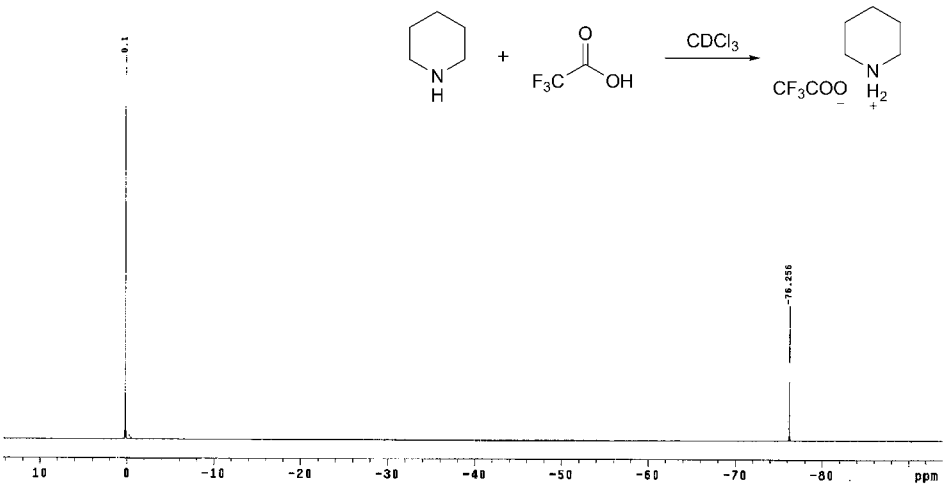


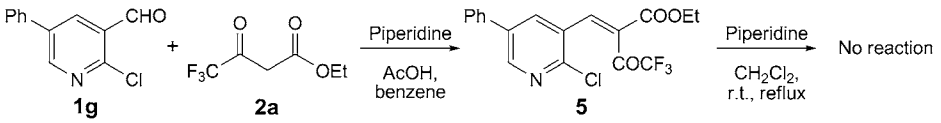
Fig. 2. *^{19}F-NMR Spectrum of the prepared piperidinium trifluoroacetate* ($CFCl_3$ as internal standard)

[1]) Standard piperidinium trifluoroacetate salt was prepared by mixing piperidine and CF_3COOH in $CDCl_3$ at low temperatures.

corresponding to two H-atoms, another *multiplet* at δ(H) 1.74 – 1.90 corresponding to four H-atoms, and the H-atoms adjacent to an N-atom due to the deshielding gave rise to a further *multiplet* at δ(H) 3.12 – 3.22.

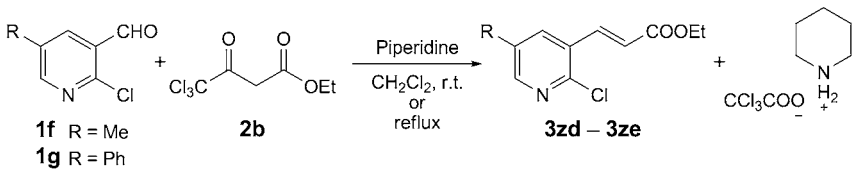
Knoevenagel product **5** (15% yield) was prepared as outlined in *Scheme 3* [9] by the condensation of **1g** (1 mmol) with **2a** (1 mmol), in AcOH and piperidine (1 mmol) and using dry benzene (*Scheme 3*). Compound **5** was characterized by ^{1}H-NMR, and an attempt was carried out with **5** (1 mmol) and piperidine (1.2 mmol) in CH_2Cl_2 at room temperature. The progress of the reaction was monitored by TLC, and formation of the desired product **3ze** was not detected (^{1}H-NMR). Even under reflux, the attempt did not give the desired compound **3ze** (TLC and ^{1}H-NMR), and starting material **5** was recovered. Thus, the present reaction proceeded only through the formation of primary aldol adduct; further attack of piperidine at trifluoroacetyl C=O C-atom, followed by *in situ* stereoselective elimination of piperidinium trifluoroacetate provided (*E*)-α,β-unsaturated ester (*Schemes 1 – 3*). Having obtained the results with piperidine, next we have tested various secondary amines such as pyrrolidine, piperazine, 1-methylpiperazine, 1-phenylpiperazine, 1-benzylpiperazine, morpholine, ^{i}Pr$_2$NH, Et$_2$NH, and Me$_2$NH in the reaction of **1g** with **2a** in CH_2Cl_2 at room temperature. Among these, pyrrolidine was found to be better (40 h, 82% yield) to give **3ze**, compared to other bases (2 – 4 equiv., 60 – 70 h, 15 – 30%). Piperidine in combination of CH_2Cl_2 turned out as the better system, and 1 mol of piperidine was essential to form piperidinium trifluoroacetate to provide (*E*)-α,β-unsaturated esters and ketones [7].

Scheme 3



Having succeeded in the preparation of (*E*)-α,β-unsaturated esters with ethyl 4,4,4-trifluoro-3-oxobutanoate; next ethyl 4,4,4-trichloro-3-oxobutanoate (**2b**) was tested with carbonyl compounds to evaluate the feasibility of the reaction. Accordingly, under optimized conditions **2b** was reacted with **1f** and **1g**, and the products **3zd** and **3ze**, respectively, were obtained in low yields (48 h, 58%; *Scheme 4*), presumably due to the less powerful withdrawing effect of the CCl_3 group compared to CF_3 group present in the 3-oxo ester. These results encouraged us to carry out the reactions of various aromatic and heteroaromatic carbonyl compounds, **1a** and **1b**, and **1c** – **1j**, respectively, with various oxobutanoates such as 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**2c**), 4,4,4-trifluoro-1-(naphthalene-2-yl)butane-1,3-dione (**2d**), and 4,4,4-trifluoro-1-(furan-2-

Scheme 4



yl)butane-1,3-dione (**2e**) under optimized conditions resulting in formation of series of new products **3a**–**3t** in very good yields (*cf. Scheme 5* and *Table 1*). The synthesis of 1,1,1-trifluoro-4-phenylbut-3-en-2-one (**3b**) was reported in the literature by the reaction of benzaldehyde with 1,1,1-trifluoropentane-2,4-dione or 1,1,1-trifluoroacetone with piperidine/AcOH in benzene [9][10], and by *Wittig* reagent [11], whereas the present simple preparation of **3b** involves the reaction of benzaldehyde with 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**2c**) using piperidine in CH_2Cl_2 at ambient/reflux

Scheme 5

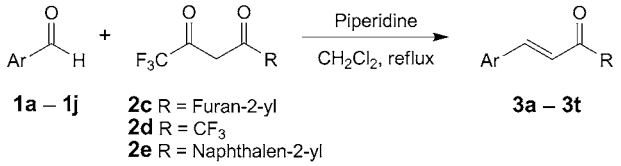
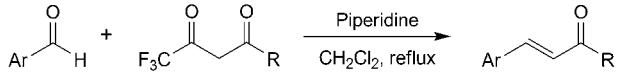


Table 1. *Synthesis of (*E*)-α,β-Unsaturated Ketones*[a])



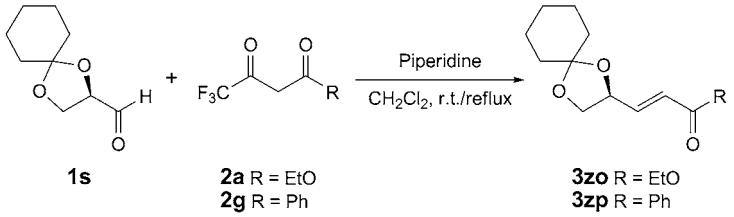
Entry	Compound **1**	Ar	Compound **2**	R	Product **3**	Yield [%][b])[c])
1	**1a**	Ph	**2c**	Furan-2-yl	**3a**	87
2	**1a**	Ph	**2d**	CF_3	**3b**	70
3	**1b**	4-Br–C_6H_4	**2e**	Naphthalen-2-yl	**3c**	88
4	**1c**	Pyridin-2-yl	**2e**	Naphthalen-2-yl	**3d**	89
5	**1d**	Pyridin-4-yl	**2e**	Naphthalen-2-yl	**3e**	91
6	**1e**	Pyridin-3-yl	**2c**	Furan-2-yl	**3f**	85
7	**1d**	Pyridin-4-yl	**2c**	Furan-2-yl	**3g**	84
8	**1f**	2-Chloro-5-methylpyridin-3-yl	**2d**	CF_3	**3h**	68
9	**1f**	2-Chloro-5-methylpyridin-3-yl	**2e**	Naphthalen-2-yl	**3i**	83
10	**1f**	2-Chloro-5-methylpyridin-3-yl	**2c**	Furan-2-yl	**3j**	86
11	**1g**	2-Chloro-5-phenylpyridin-3-yl	**2d**	CF_3	**3k**	65
12	**1g**	2-Chloro-5-phenylpyridin-3-yl	**2e**	Naphthalen-2-yl	**3l**	84
13	**1g**	2-Chloro-5-phenylpyridin-3-yl	**2c**	Furan-2-yl	**3m**	83
14	**1h**	2-Chloro-5-(4-methoxyphenyl)-pyridin-3-yl	**2e**	Naphthalen-2-yl	**3n**	85
15	**1i**	2-Chloroquinolin-3-yl	**2e**	Naphthalen-2-yl	**3o**	82
16	**1i**	2-Chloroquinolin-3-yl	**2c**	Furan-2-yl	**3p**	86
17	**1i**	2-Chloroquinolin-3-yl	**2d**	CF_3	**3q**	67
18	**1j**	2-Chloro-8-methylquinolin-3-yl	**2e**	Naphthalen-2-yl	**3r**	83
19	**1j**	2-Chloro-8-methylquinolin-3-yl	**2c**	Furan-2-yl	**3s**	84
20	**1j**	2-Chloro-8-methylquinolin-3-yl	**2d**	CF_3	**3t**	64

[a]) Conditions: aldehyde (1 mmol), trifluoro 1,3-diketones (1.2 mmol), piperidine (1.2 mmol). [b]) Yields of isolated products; not optimized. [c]) (*E*)-Isomer (^{1}H-NMR).

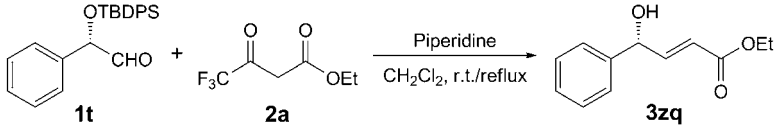
conditions. The preparation of new unsaturated trifluoromethyl ketones such as **3h**, **3k**, **3t**, and **3q** has also been achieved by the present method. Substituted cinnamaldehydes **1p** and **1q** were also tested with **2a** and **2f** at room temperature/reflux conditions; however, the desired product could not be obtained.

Further, the method was applied to the synthesis of chiral derivatives **3zo** and **3zp**, starting from **1s** with **2a** and **2g**, respectively, in CH_2Cl_2 at room temperature under optimized conditions. Compound **3zo** is an important chiral synthon utilized for the synthesis of various natural products (*Scheme 6*) [12]. Compound **3zq** [13] was successfully prepared by the reaction of **2a** with **1t** under similar conditions (deprotection of ^{t}BuPh$_2$Si (TBDPS); *Scheme 7*).

Scheme 6



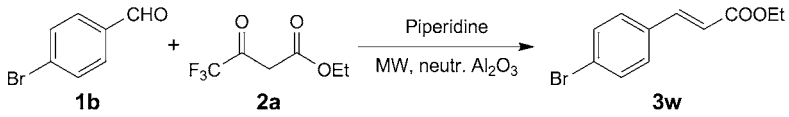
Scheme 7



Having succeeded in the synthesis of a series of (*E*)-α,β-unsaturated esters and ketones by conventional methods, next we studied the microwave-assisted synthesis of (*E*)-α,β-unsaturated esters and ketones under solvent-free conditions. Microwave-assisted reactions are considered to be superior to conventional reactions due to substantial rate enhancement for the synthesis of various natural products and heterocyclic compounds. Moreover, majority of the microwave-assisted reactions proceed solvent-free; hence, they are considered to be clean, efficient, and economical [14]. Solvent-free syntheses of (*E*)-α,β-unsaturated esters and ketones by the reaction of carbonyl compounds with ethyl 4,4,4-trifluoro-3-oxobutanoate (**2a**), 4,4,4-trifluoro-1-(naphthalene-2-yl)butane-1,3-dione (**2d**), 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione **2e**), 1,1,1-trifluoropentane-2,4-dione (**2f**), and 4,4,4,-trifluoro-1-phenylbutane-1,3-dione (**2g**) have not been reported so far.

We performed the microwave (MW)-assisted reactions in *CEM* [15] *Discover* microwave apparatus. Aldehyde **1b** (1 mmol), **2a** (1.2 mmol), and piperidine (1.2 mmol) were dissolved in Et_2O, neutral Al_2O_3 was added, and the solvent was removed under reduced pressure below 28°. The adsorbed solid was taken up for irradiation with 100 W. We monitored the progress of the reaction by TLC and found that the conversion poor in 2–9 min (15–28%; *Table 2*, *Entries 1–4*); however, the conversion was improved to 90% with 150-W irradiation (16 min; *Table 2*, *Entries 5–9*) to give ethyl (*E*)-3-(4-bromophenyl)acrylate (**3w**).

Table 2. *Optimization of Microwave-Assisted Reactions*[a])

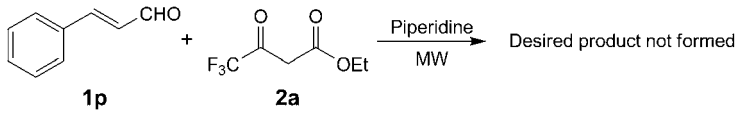


Entry	Time [min]	Power [W]	Yield [%][b])
1	3	100	Trace
2	5	100	15
3	7	100	21
4	9	100	28
5	5	150	34
6	7	150	37
7	10	150	59
8	14	150	88
9	16	150	90
10[c])	14	150	90
11[d])	300	–	92

[a]) Conditions: aldehyde (1 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (1.2 mmol), piperidine (1.2 mmol). [b]) Yields of isolated products; not optimized. [c]) Piperidine (1.5 mmol). [d]) CH_2Cl_2, r.t.

To evaluate the efficiency of this methodology, reactions of various substituted aromatic (*Table 3*, *Entries 1–8*), aliphatic (*Table 3*, *Entry 9*), and heteroaromatic (*Table 3*, *Entries 10–29*) carbonyl compounds with oxobutanoates, such as **2a**, **2d**, **2e**, **2f**, and **2g**, were studied to give the corresponding (*E*)-α,β-unsaturated esters and ketones **3c**–**3zn** in good yields. Further, the method was extended to the reaction of cinnamaldehyde (**1p**) with **2a** under optimized conditions. A colorless solid was obtained, and spectral evaluation indicated that the formed compound was not the desired (*E,E*)-unsaturated ester (^{1}H-NMR; *Scheme 8*). However, reactions of cinnamaldehydes **1p**–**1r** with 1,3-diketones **2d**, **2f**, and **2g** afforded the corresponding (*E,E*)-unsaturated ketones **3zj**–**3zn** (*Scheme 9*, and *Table 3*, *Entries 30–34*). Thus, the synthesized compounds were well characterized on the basis of their spectral data; the data of known compounds **3u**, **3w**, **3y**, **3z**, **3za**, **3zh**, **3zc**, **3zd**, **3ze** [7], **3b** [11], **3a**, **3c**, **3t**, **3g**,

Scheme 8



Scheme 9

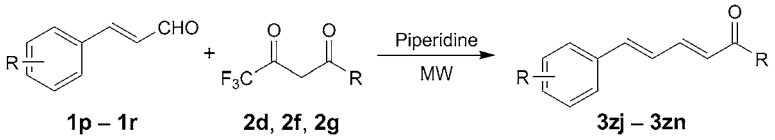
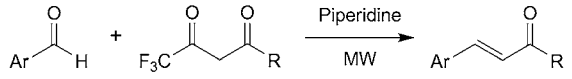


Table 3. *Microwave-Assisted Synthesis of (*E*)-α,β-Unsaturated Esters and Ketones*[a])



1 **2** **3**

Entry	**1**	Ar	**2**	R	Product **3**	Yield [%][b])[c])
1	**1a**	Ph	**2a**	EtO	**3u**	90
2	**1a**	Ph	**2f**	Me	**3v**	87
3	**1b**	4-Br–C_6H_4	**2a**	EtO	**3w**	89
4	**1b**	4-Br–C_6H_4	**2g**	Ph	**3x**	87
5	**1b**	4-Br–C_6H_4	**2e**	Naphthalen-2-yl	**3c**	88
6	**1k**	4-MeO–C_6H_4	**2a**	EtO	**3y**	89
7	**1l**	4-Cl–C_6H_4	**2a**	EtO	**3z**	88
8	**1l**	4-Cl–C_6H_4	**2f**	Me	**3za**	86
9	**1m**	Pentyl	**2a**	EtO	**3zb**	71
10	**1c**	Pyridin-2-yl	**2a**	EtO	**3zc**	90
11	**1c**	Pyridin-2-yl	**2e**	Naphthalen-2-yl	**3d**	86
12	**1d**	Pyridin-4-yl	**2e**	Naphthalen-2-yl	**3e**	84
13	**1e**	Pyridin-3-yl	**2c**	Furan-2-yl	**3f**	85
14	**1d**	Pyridin-4-yl	**2c**	Furan-2-yl	**3g**	83
15	**1f**	2-Chloro-5-methylpyridin-3-yl	**2a**	EtO	**3zd**	90
16	**1f**	2-Chloro-5-methylpyridin-3-yl	**2e**	Naphthalen-2-yl	**3i**	83
17	**1f**	2-Chloro-5-methylpyridin-3-yl	**2c**	Furan-2-yl	**3j**	86
18	**1g**	2-Chloro-5-phenylpyridin-3-yl	**2a**	EtO	**3ze**	92
19	**1g**	2-Chloro-5-phenylpyridin-3-yl	**2e**	Naphthalen-2-yl	**3l**	84
20	**1g**	2-Chloro-5-phenylpyridin-3-yl	**2c**	Furan-2-yl	**3m**	83
21	**1h**	2-Chloro-5-(4-methoxyphenyl)pyridin-3-yl	**2g**	Ph	**3zf**	91
22	**1h**	2-Chloro-5-(4-methoxyphenyl)pyridin-3-yl	**2e**	Naphthalen-2-yl	**3n**	85
23	**1i**	2-Chloroquinolin-3-yl	**2e**	Naphthalen-2-yl	**3o**	82
24	**1i**	2-Chloroquinolin-3-yl	**2c**	Furan-2-yl	**3p**	86
25	**1j**	2-Chloro-8-methylquinolin-3-yl	**2e**	Naphthalen-2-yl	**3r**	83
26	**1j**	2-Chloro-8-methylquinolin-3-yl	**2c**	Furan-2-yl	**3s**	84
27	**1n**	6-Bromo-1,3-benzodioxol-5-yl	**2g**	Ph	**3zg**	86
28	**1n**	6-Bromo-1,3-benzodioxol-5-yl	**2e**	Naphthalen-2-yl	**3zh**	82
29	**1o**	5-Bromo-1-[(*tert*-butoxy)carbonyl]-1*H*-indole-3-yl	**2e**	Naphthalen-2-yl	**3zi**	85
30	**1p**	Ph–CH=CH (*E*)	**2f**	Me	**3zj**	60
31	**1p**	Ph–CH=CH (*E*)	**2g**	Ph	**3zk**	63
32	**1p**	Ph–CH=CH (*E*)	**2e**	Naphthalen-2-yl	**3zl**	58
33	**1q**	4-NO_2–C_6H_4–CH=CH (*E*)	**2g**	Ph	**3zm**	48
34	**1r**	2-MeO–C_6H_4–CH=CH (*E*)	**2g**	Ph	**3zn**	51

[a]) Conditions: aldehyde (1 mmol), trifluoro 1,3-diketo ester/ketone (1.2 mmol), piperidine (1.2 mmol), Microwave irradiation (150 W). [b]) Yields of isolated products; not optimized. [c]) (*E*)-isomer (^{1}H-NMR).

3v, **3zj**, **3x**, **3zk**, **3zl**, **3zm**, **3zn** [16], **3zo**, **3zp** [12], and **3zq** [13] were compared with those in the literature. New compounds **3d**, **3e**, **3h**–**3t**, and **3zf**–**3zi** were identified by means of their ^{1}H- and ^{13}C-NMR, MS, IR, and ESI-HR-MS data (see *Exper. Part*).

Conclusions. – In conclusion, an efficient method has been established for the synthesis of (*E*)-α,β-unsaturated esters and ketones by the reaction of carbonyl compounds with trifluoro-oxobutanoates/1,3-diketones. The reactions proceed through the formation of aldol primary adduct and *in situ* stereoselective elimination of piperidinium trifluoroacetate. The method also opens a new way for C,C bond formations.

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Experimental Part

General. The chemicals, trifluoro 1,3-diketones/β-keto esters (*Aldrich*), piperidine, and all the solvents were obtained from local suppliers. Column chromatography (CC): silica gel (SiO_2; 60–120 mesh). M.p.: *Mettler-Temp* apparatus; uncorrected. IR Spectra: *Perkin-Elmer-1600* FT-IR spectrometer; in KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker-Avance-300* spectrometer; in $CDCl_3$; chemical shifts, δ, in ppm rel. to Me_4Si as internal standard; *J* in Hz. ESI-MS: 7070 H spectrometer with a direct inlet system; in *m*/*z* (rel. %). ESI-HR-MS: *Agilent 6510 Q-TOF* LC/MS instrument. Microwave (MW) irradiation: *CEM*™ *Discovery* instrument.

Representative Procedure for the Synthesis of (E)-*α,β-Unsaturated Esters/Ketones.* Piperidine (1.2 mmol) was added to a stirred soln. of *2-chloro-5-methylnicotinaldehyde* (**1f**; 1.0 mmol) and *ethyl 4,4,4-trifluoro-3-oxobutanoate/4,4,4-trifluoro-1-(naphthalene-2-yl)butane-1,3-dione* (**2a**/**2d**; 1.2 mmol) in CH_2Cl_2 (2 ml), and the mixture was refluxed for 2 to 3 h (TLC). After completion of reaction, the mixture was further diluted with CH_2Cl_2, and the contents were washed with H_2O, the org. layer was separated, dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by CC (hexane/AcOEt 9 : 1) to afford the **3zd**/**3i** as a colorless solid/solid in 90/83% yield.

Representative Procedure for MW-Assisted Synthesis of (E)-*α,β-Unsaturated Esters and Ketones.* A mixture of *4-bromobenzaldehyde* (**1b**; 1.0 mmol), *ethyl 4,4,4-trifluoro-3-oxobutanoate* (**2a**; 1.2 mmol), and piperidine (1.2 mmol) was added to neutral Al_2O_3 (200 mg) in Et_2O (2 ml). The solvent was evaporated under reduced pressure at moderate temp. (28°), and then the mixture was poured into a capped 10-ml microwave vessel. The mixture was irradiated for 16 min with 150 W, monitored by TLC; after completion of the reaction, the residue was purified by flash CC to give **3w** (89%) as a colorless liquid.

*(2*E*)-1-(Naphthalen-2-yl)-3-(pyridin-2-yl)prop-2-en-1-one* (**3d**). Yield: 86%. Yellow solid. M.p. 80–82°. IR: 2925, 2853, 1661, 1608, 1467, 776. ^{1}H-NMR: 7.24–7.30 (*m*, 1 H); 7.44 (*d*, *J* = 7.6, 1 H); 7.48–7.60 (*m*, 2 H); 7.60–7.92 (*m*, 4 H); 7.98 (*d*, *J* = 8.3, 1 H); 8.12–8.18 (*m*, 1 H); 8.30 (*d*, *J* = 15.1, 1 olef. H); 8.62 (*s*, 1 H); 8.68 (*d*, *J* = 4.5, 1 H). ^{13}C-NMR: 124.2; 124.5; 125.5; 126.7; 127.8; 128.4; 128.5; 129.6; 130.4; 132.6; 135.2; 135.6; 136.7; 142.3; 150.1; 153.3; 189.5. ESI-MS: 260 ($[M+H]^+$). ESI-HR-MS: 260.107 ($[M+H]^+$, $C_{18}H_{14}NO^+$; calc. 260.1075).

*(2*E*)-1-(Naphthalen-2-yl)-3-(pyridin-4-yl)prop-2-en-1-one* (**3e**). Yield: 84%. Brown solid. M.p. 84–86°. IR: 2923, 1662, 1462, 809, 757. ^{1}H-NMR: 7.48–7.78 (*m*, 5 H); 7.82 (*d*, *J* = 15.9, 1 olef. H); 7.86–8.10 (*m*, 4 H); 8.50 (*s*, 1 H); 8.70 (*d*, *J* = 4.7, 2 H). ^{13}C-NMR: 122.1; 124.4; 126.0; 127.0; 127.9; 128.7; 128.8; 129.6; 130.2; 135.0; 135.7; 135.9; 141.3; 142.3; 150.5; 188.8. ESI-MS: 260 ($[M+H]^+$). ESI-HR-MS: 260.107 ($[M+H]^+$, $C_{18}H_{14}NO^+$; calc. 260.1075).

*(3*E*)-4-(2-Chloro-5-methylpyridin-3-yl)-1,1,1-trifluorobut-3-en-2-one* (**3h**). Yield: 68%. Colorless solid. M.p. 148–150°. IR: 2921, 2851, 1718, 1608, 1145, 980, 869. ^{1}H-NMR: 2.42 (*s*, Me); 6.98 (*d*, *J* = 16.2, 1 olef. H); 7.81 (*s*, 1 H); 8.25 (*d*, *J* = 16.2, 1 olef. H); 8.29 (*s*, 1 H). ^{13}C-NMR: 29.7; 120.2; 127.6; 132.7; 132.8; 136.5; 144.1; 149.9; 152.35; 186.4. ^{19}F-NMR: −78.16.

*(2*E*)-3-(2-Chloro-5-methylpyridin-3-yl)-1-(naphthalen-2-yl)prop-2-en-1-one* (**3i**). Yield: 83%. Pale-yellow solid. M.p. 112–114°. IR: 2921, 1660, 1604, 1464, 1170. ^{1}H-NMR: 2.42 (*s*, Me); 7.52–7.62 (*m*, 3 H); 7.84–8.08 (*m*, 6 H); 8.22 (*d*, *J* = 2.1, 1 H); 8.48 (*s*, 1 H). ^{13}C-NMR: 17.7; 124.4; 126.0; 126.7; 127.6; 128.4; 128.6; 129.3; 129.5; 130.0; 132.3; 132.5; 134.9; 135.5; 136.3; 138.7; 149.1; 150.6; 188.4. ESI-MS: 308/310 ([*M* + H]$^+$). ESI-HR-MS: 308.0863 ([*M* + H]$^+$, $C_{19}H_{15}ClNO^+$; calc. 308.0842).

*(2*E*)-3-(2-Chloro-5-methylpyridin-3-yl)-1-(furan-2-yl)prop-2-en-1-one* (**3j**). Yield: 86%. Colorless solid. M.p. 95–97°. ^{1}H-NMR: 2.40 (*s*, Me); 6.60 (*dd*, *J* = 1.7, 3.6, 1 H); 7.32 (*dd*, *J* = 1.0, 2.9, 1 H); 7.41 (*d*, *J* = 15.9, 1 olef. H); 7.64 (*s*, 1 H); 7.82 (*s*, 1 H); 8.08 (*d*, *J* = 15.9, 1 olef. H); 8.21 (*s*, 1 H). ^{13}C-NMR: 17.6; 112.7; 118.1; 125.2; 128.9; 132.7; 136.5; 138.1; 146.8; 149.0; 150.9; 153.2; 177.0. ESI-MS: 248/250 ([*M* + H]$^+$). ESI-HR-MS: 248.0472 ([*M* + H]$^+$, $C_{13}H_{11}ClNO_2^+$; calc. 248.0478).

*(3*E*)-4-(2-Chloro-5-phenylpyridin-3-yl)-1,1,1-trifluorobut-3-en-2-one* (**3k**). Yield: 65%. Colorless solid. M.p. 162–164°. ^{1}H-NMR: 7.06 (*d*, *J* = 15.5, 1 olef. H); 7.40–7.58 (*m*, 5 H); 8.12 (*d*, *J* = 2.5, 1 H); 8.31 (*d*, *J* = 16.1, 1 olef. H); 8.66 (*d*, *J* = 2.3, 1 H). ^{13}C-NMR: 120.8; 127.1; 128.1; 129.1; 129.4; 129.5; 129.5; 134.6; 135.5; 136.7; 144.2; 150.3; 178.6.

*(2*E*)-3-(2-Chloro-5-phenylpyridin-3-yl)-1-(naphthalen-2-yl)prop-2-en-1-one* (**3l**). Yield: 84%. Pale-yellow solid. M.p. 106–108°. IR: 2920, 1645, 1610, 1465. ^{1}H-NMR: 7.36–7.62 (*m*, 7 H); 7.68 (*d*, *J* = 15.9, 1 olef. H); 7.84–8.20 (*m*, 6 H); 8.50 (*s*, 1 H); 8.58 (*d*, *J* = 2.3, 1 H). ^{13}C-NMR: 124.0; 124.5; 126.6; 126.8; 127.2; 127.9; 128.5; 128.7; 129.0; 129.3; 129.5; 130.2; 131.0; 132.5; 134.2; 135.5; 136.2; 138.1; 138.8; 147.3; 148.5; 188.5. ESI-MS: 370/372 ([*M* + H]$^+$). ESI-HR-MS: 370.1004 ([*M* + H]$^+$, $C_{24}H_{17}ClNO^+$; calc. 370.0999).

*(2*E*)-3-(2-Chloro-5-phenylpyridin-3-yl)-1-(furan-2-yl)prop-2-en-1-one* (**3m**). Yield: 83%. Colorless solid. M.p. 116–118°. ^{1}H-NMR: 6.60 (*dd*, *J* = 1.5, 3.8, 1 H); 7.36 (*d*, *J* = 3.8, 1 H); 7.42–7.58 (*m*, 6 H); 7.62 (*d*, *J* = 15.1, 1 olef. H); 8.14 (*d*, *J* = 3.0, 1 H); 8.18 (*d*, *J* = 2.3, 1 H); 8.58 (*d*, *J* = 3.0, 1 H). ^{13}C-NMR: 112.8; 117.8; 125.6; 127.1; 128.7; 129.3; 129.6; 134.2; 136.1; 136.3; 138.1; 146.4; 148.7; 150.7; 153.5; 176.6. ESI-MS: 310/312 ([*M* + H]$^+$). ESI-HR-MS: 310.064 ([*M* + H]$^+$, $C_{18}H_{13}ClNO_2^+$; calc. 310.0635).

*(2*E*)-3-[2-Chloro-5-(4-methoxyphenyl)pyridin-3-yl]-1-(naphthalen-2-yl)prop-2-en-1-one* (**3n**). Yield: 85%. Pale yellow solid. M.p. 112–114°. IR: 2926, 1640, 1608, 1460, 1031. ^{1}H-NMR: 3.88 (*s*, MeO); 7.00 (*d*, *J* = 9.1, 2 H); 7.50–7.62 (*m*, 4 H); 7.66 (*d*, *J* = 15.9, 1 olef. H); 7.86–8.16 (*m*, 6 H); 8.50 (*s*, 1 H); 8.56 (*d*, *J* = 2.3, 1 H). ^{13}C-NMR: 55.4; 114.5; 114.8; 124.4; 126.7; 127.9; 128.3; 128.7; 128.8; 129.5; 130.4; 131.2; 132.4; 133.9; 134.8; 135.2; 135.6; 136.0; 137.5; 139.1; 148.4; 189.6. ESI-MS: 400 ([*M* + H]$^+$). ESI-HR-MS: 400.110 ([*M* + H]$^+$, $C_{25}H_{19}ClNO_2^+$; calc. 400.1104).

*(2*E*)-3-(2-Chloroquinolin-3-yl)-1-(naphthalen-2-yl)prop-2-en-1-one* (**3o**). Yield: 82%. Pale yellow solid. M.p. 182–184°. IR: 2924, 1662, 1465, 762. ^{1}H-NMR: 7.54–7.63 (*m*, 3 H); 7.72 (*d*, *J* = 15.7, 1 olef. H); 7.76 (*t*, *J* = 6.8, 1 H); 7.86–8.14 (*m*, 6 H); 8.24 (*d*, *J* = 15.7, 1 olef. H); 8.50 (*s*, 1 H); 8.54 (*s*, 1 H). ^{13}C-NMR: 123.7; 124.5; 126.4; 126.8; 127.0; 127.1; 127.8; 127.9; 123.1; 128.7; 128.8; 129.4; 129.6; 130.5; 131.7; 136.3; 139.4; 148.0; 189.7. ESI-MS: 344/346 ([*M* + H]$^+$). ESI-HR-MS: 344.0833 ([*M* + H]$^+$, $C_{22}H_{15}ClNO^+$; calc. 344.0842).

*(2*E*)-3-(2-Chloroquinolin-3-yl)-1-(furan-2-yl)prop-2-en-1-one* (**3p**). Yield: 86%. Pale-yellow solid. M.p. 168–170°. ^{1}H-NMR: 6.62 (*dd*, *J* = 2.3, 3.8, 1 H); 7.36 (*d*, *J* = 3.0, 1 H); 7.54 (*d*, *J* = 7.6, 1 H); 7.58 (*d*, *J* = 8.3, 1 H); 7.64 (*d*, *J* = 15.1, 1 olef. H); 7.72–7.80 (*m*, 1 H); 7.86 (*d*, *J* = 8.3, 1 H); 8.02 (*d*, *J* = 9.1, 1 H); 8.26 (*d*, *J* = 15.9, 1 olef. H); 8.47 (*s*, 1 H). ^{13}C-NMR: 12.9; 118.3; 125.4; 127.0; 127.3; 127.7; 128.1; 128.5; 131.7; 136.0; 136.3; 138.5; 146.3; 146.9; 147.9; 186.2. ESI-MS: 284/286 ([*M* + H]$^+$). ESI-HR-MS: 284.048 ([*M* + H]$^+$, $C_{16}H_{11}ClNO_2^+$; calc. 284.0478).

*(3*E*)-4-(2-Chloroquinolin-3-yl)-1,1,1-trifluorobut-3-en-2-one* (**3q**). Yield: 67%. Pale-brown solid. M.p. 132–134°. ^{1}H-NMR: 7.12 (*d*, *J* = 15.86, 1 olef. H); 7.62 (*t*, *J* = 6.8, 1 H); 7.78–7.90 (*m*, 2 H); 8.02 (*d*, *J* = 8.3, 1 H); 8.42 (*d*, *J* = 15.9, 1 olef. H); 8.48 (*s*, 1 H). ^{13}C-NMR: 120.3; 128.1; 128.4; 128.6; 132.6; 137.2; 137.6; 143.7; 144.6; 144.9; 148.6; 150.3; 182.0.

*(2*E*)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(naphthalen-2-yl)prop-2-en-1-one* (**3r**). Yield: 83%. Pale-yellow solid. M.p. 178–180°. IR: 2923, 1660, 1597, 1468, 1171, 743. ^{1}H-NMR: 2.78 (*s*, Me); 7.42–7.74 (*m*, 6 H); 7.82–8.00 (*m*, 3 H); 8.10 (*d*, *J* = 8.5, 1 H); 8.24 (*d*, *J* = 15.7, 1 olef. H); 8.44 (*s*, 1 H); 8.52 (*s*, 1 H). ^{13}C-NMR: 29.7; 124.0; 124.6; 125.7; 125.9; 126.7; 127.2; 127.8; 128.4; 128.6; 129.5; 130.1; 131.4; 132.6; 135.1; 135.3; 135.6; 136.1; 137.0; 139.5; 147.2; 149.4; 188.5. ESI-MS: 358/360 ([*M* + H]$^+$). ESI-HR-MS: 358.167 ([*M* + H]$^+$, $C_{23}H_{17}ClNO^+$; calc. 358.0999).

*(2*E*)-3-(2-Chloro-8-methylquinolin-3-yl)-1-(furan-2-yl)prop-2-en-1-one* (**3s**). Yield: 84%. Pale-yellow solid. M.p. 164–166°. ^{1}H-NMR: 2.76 (*s*, Me); 6.62 (*dd*, *J* = 1.5, 3.0, 1 H); 7.36 (*d*, *J* = 3.8, 1 H); 7.46 (*t*, *J* = 8.3, 1 H); 7.54 (*d*, *J* = 15.9, 1 olef. H); 7.58 (*d*, *J* = 7.6, 1 H); 7.65–7.70 (*m*, 2 H); 8.28 (*d*, *J* = 15.9, 1 olef. H), 8.44 (*s*, 1 H). ^{13}C-NMR: 41.1; 112.8; 118.2; 125.3; 127.0; 127.2; 127.7; 128.0; 128.4; 131.6; 135.9; 136.2; 138.4; 146.9; 151.0; 151.9; 186.1. ESI-MS: 298/300 ([*M* + H]$^+$).

*(3*E*)-4-(2-Chloro-8-methylquinolin-3-yl)-1,1,1-trifluorobut-3-en-2-one* (**3t**). Yield: 64%. Pale-brown solid. M.p. 128–130°. ^{1}H-NMR: 2.78 (*s*, Me); 7.12 (*d*, *J* = 15.9, 1 olef. H); 7.46 (*d*, *J* = 15.1, 1 olef. H); 7.62–7.72 (*m*, 2 H); 8.40 (*s*, 1 H); 8.45 (*s*, 1 H). ^{13}C-NMR: 29.7; 119.9; 125.8; 126.3; 126.8; 127.9; 132.2; 132.7; 137.0; 137.4; 144.9; 147.8; 149.2; 179.7.

*(2*E*)-3-[2-Chloro-5-(4-methoxyphenyl)pyridin-3-yl]-1-phenylprop-2-en-1-one* (**3zf**). Yield: 91%. Colorless solid. M.p. 125–127°. IR: 2924, 1641, 1604, 1458, 1028. ^{1}H-NMR: 3.86 (*s*, MeO); 6.98 (*d*, *J* = 15.1, 1 olef. H); 7.00 (*d*, *J* = 9.1, 1 H); 7.46–7.52 (*m*, 3 H); 7.54 (*d*, *J* = 15.9, 1 olef. H); 7.56–7.62 (*m*, 2 H); 7.99 (*d*, *J* = 8.3, 1 H); 8.03 (*d*, *J* = 6.8, 2 H); 8.08 (*s*, 1 H); 8.55 (*d*, *J* = 2.3, 1 H). ^{13}C-NMR: 55.3; 114.9; 126.6; 128.3; 128.7; 128.8; 129.8; 133.0; 133.8; 135.3; 136.0; 137.7; 139.2; 147.0; 148.3; 160.4; 188.9. ESI-MS: 350/352 ([*M* + H]$^+$). ESI-HR-MS: 350.0956 ([*M* + H]$^+$, $C_{21}H_{17}ClNO_2^+$; calc. 350.0948).

*(2*E*)-3-(6-Bromo-1,3-benzodioxol-5-yl)-1-phenylprop-2-en-1-one* (**3zg**). Yield: 86%. Colorless solid. M.p. 140–142°. ^{1}H-NMR: 6.04 (*s*, 2 H); 7.06 (*s*, 1 H); 7.20 (*s*, 1 H); 7.28 (*d*, *J* = 15.9, 1 olef. H); 7.44–7.59 (*m*, 3 H); 7.94–5.02 (*m*, 2 H); 8.04 (*d*, *J* = 15.1, 1 olef. H). ^{13}C-NMR: 102.2; 106.5; 113.4; 118.8; 123.0; 126.8; 128.4; 128.6; 132.7; 138.2; 143.0; 147.9; 150.2; 189.6. ESI-MS: 331/333 ([*M* + H]$^+$).

*(2*E*)-3-(6-Bromo-1,3-benzodioxol-5-yl)-1-(naphthalen-2-yl)prop-2-en-1-one* (**3zh**). Yield: 82%. Yellow solid. M.p. 146–148°. ^{1}H-NMR: 6.06 (*s*, 2 H); 7.08 (*s*, 1 H); 7.24 (*s*, 1 H); 7.40 (*d*, *J* = 15.1, 1 olef. H); 7.48–7.62 (*m*, 2 H); 7.84–7.98 (*m*, 3 H); 8.05 (*d*, *J* = 8.1, 1 olef. H); 8.12 (*d*, *J* = 15.9, 1 olef. H); 8.48 (*s*, 1 H). ^{13}C-NMR: 102.3; 106.5; 113.3; 118.8; 123.0; 124.5; 126.8; 127.8; 128.3; 128.4; 128.6; 129.5; 130.0; 132.5; 135.4; 135.5; 143.1; 148.0; 150.2; 190.1. ESI-MS: 381/383 ([*M* + H]$^+$).

tert-*Butyl 5-Bromo-3-[(1*E*)-3-(naphthalen-2-yl)-3-oxoprop-1-en-1-yl]-1*H*-indole-1-carboxylate* (**3zi**). Yield: 85%. Pale yellow solid. M.p. 130–132°. ^{1}H-NMR: 1.70 (*s*, ^{t}Bu); 7.46–7.62 (*m*, 3 H); 7.68 (*d*, *J* = 15.9, 1 olef. H); 7.88 (*d*, *J* = 15.9, 1 olef. H); 7.90–8.02 (*m*, 4 H); 8.06 (*d*, *J* = 1.9, 1 H); 8.10 (*d*, *J* = 8.7, 2 H), 8.51 (*s*, 1 H). ^{13}C-NMR: 28.3; 29.8; 116.9; 117.2; 117.4; 118.5; 121.9; 123.2; 124.7; 126.7; 127.9; 128.3; 128.3; 128.6; 129.6; 129.7; 129.8; 132.7; 135.1; 135.6; 135.7; 136.1; 161.8; 182.3. ESI-MS: 476/478 ([*M* + H]$^+$). ESI-HR-MS: 476.0856 ([*M* + H]$^+$, $C_{26}H_{23}BrNO_3^+$; calc. 476.0861).

*Synthesis of Ethyl (2*E*)-2-[(2-Chloro-5-phenylpyridin-3-yl)methylidene]-4,4,4-trifluoro-3-oxobutanoate* (**5**). *2-Chloro-5-phenylnicotinaldehyde* (**1g**; 1 mmol) and *ethyl 4,4,4-trifluoro-3-oxobutanoate* (**2a**, 1 mmol) were dissolved in dry benzene (10 ml). Piperidine (0.2 ml) and AcOEt (0.3 ml) were added, and the mixture was refluxed using *Dean–Stark* azeotropic distillation apparatus for 16–20 h. H_2O was added, the phases were separated, and the org. layer was washed with dil. HCl, followed by H_2O, org. layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The obtained oil was purified by CC (SiO_2; hexane/AcOEt). ^{1}H-NMR: 1.44 (*t*, *J* = 7.2, Me); 4.46 (*q*, *J* = 7.2, 2 H, CH_2O); 7.44–7.64 (*m*, 5 H); 8.64 (*s*, 1 H); 8.70 (*d*, *J* = 1.7, 1 H); 8.76 (*d*, *J* = 1.7, 1 H).

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