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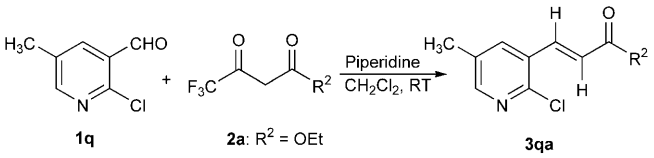
New and Facile Approach for the Synthesis of (*E*)-α,β-Unsaturated Esters and Ketones

Bhimapaka China Raju* and Pathi Suman[a]

Preparation of (*E*)-α,β-unsaturated esters and ketones is an important task in organic synthesis.[1] Such esters and ketones are excellent building blocks for the synthesis of a plethora of synthetic and natural products.[2] The most versatile and widely used methods are the Wittig reaction[3] with aldehydes by using alkoxycarbonylmethylene(triphenyl)phosphoranes and the Horner–Wadsworth–Emmons[4] procedure using trialkyl phosphonoacetates with stronger bases. These methods generate stoichiometric amounts of byproducts, namely triphenylphosphine oxide and phosphate salts. Decarboxylative Knoevenagel-type reactions employing malonic acid half esters[5] and the olefination of aldehydes with ethyl diazoacetate[6] (EDA) are alternative methods reported for the synthesis of (*E*)-α,β-unsaturated esters. The synthesis of (*E*)-α,β-unsaturated ketones involves the reaction of aromatic aldehydes with aromatic ketones, alkynes and the Grignard reaction of unsaturated aromatic nitriles.[7] The Knoevenagel condensation is an important reaction for the synthesis of α,β-unsaturated compounds; aromatic aldehydes afforded (*E*)-α,β-unsaturated esters and salicylaldehydes afforded 3-substituted coumarins[8] with β-ketoesters in the presence of base. Generally, the condensation of carbonyl compounds with active methylene substrates containing trifluoroacetoacetate substituents seldom gives the condensation product; however, it has been reported that the reaction of benzaldehyde with ethyl-4,4,4-trifluoroacetoacetate in the presence of piperidine in toluene under reflux conditions afforded ethyl (*E*)-3-phenyl-2-(2,2,2-trifluoroacetyl)-2-propenoate in low yields.[9]

As part of our ongoing efforts in developing approaches for the synthesis of various heterocyclic compounds with potential biological applications,[10] we recently reported the synthesis of methyl (*E*)-3-(2-chloro-5-methyl-3-pyridyl)-2-propenoate[11] by adopting Horner–Wadsworth–Emmons (HWE) reaction conditions and synthesized new Knoevenagel products. Herein, we report a new, general, and practical method for the synthesis of (*E*)-α,β-unsaturated esters and ketones by Aldol-adduct elimination under basic conditions. Treatment of 2-chloro-5-methylnicotinaldehyde (**1q**) with ethyl-4,4,4-trifluoroacetoacetate (**2a**) in CH_2Cl_2 in the presence of piperidine at room temperature for 4–6 h gave the geometrically selective *E* product **3qa** instead of the condensation product (Scheme 1).



Scheme 1. Synthesis of (*E*)-α,β-unsaturated esters.

The result surprised and encouraged us to search for the best reaction conditions. The optimization of the reaction conditions was first examined with the use of mostly basic catalysts, namely 1,4-diazabicyclo[2.2.2]octane (DABCO), 4-dimethylaminopyridine (DMAP), imidazole, triethylamine, NaOMe, pyridine, and picoline, and we found that the reaction did not take place under these basic conditions. However, when we studied the use of piperidine with various solvents we found that CH_2Cl_2 was the solvent of choice in terms of yield, reaction time, and selectivity for the synthesis of (*E*)-α,β-unsaturated esters (Table 1). Regarding the optimum quantity of catalyst, one equivalent of piperidine is necessary to promote the reaction in an efficient manner.

We propose a possible mechanism for the formation of the product, which is in line with the Aldol condensation reaction. The sequence of the reaction was monitored by LCMS and the formation of the primary Aldol product (A) was observed. Further attack of piperidine on the trifluoroacetyl carbon followed by in situ stereoselective elimination

[a] Dr. B. China Raju, P. Suman
Organic Chemistry Division-1
Indian Institute of Chemical Technology
Hyderabad 500 607 (India)
Fax: (+91) 40-27160512
E-mail: chinarajuiict@yahoo.co.in

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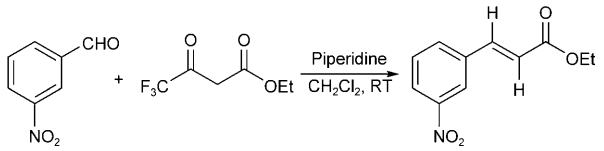
Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst [equiv]	Solvent	t [h]	Yield [%][b,c]
1	0.1	CH_2Cl_2	6	20
2	0.1	CH_2Cl_2	24	42
3	0.3	CH_2Cl_2	6	45
4	1	CH_2Cl_2	6	95
5	1.2	CH_2Cl_2	8	95
6	0.1	MeCN	6	12
7	0.1	MeOH	6	10
8	0.3	MeCN	6	25
9	0.3	MeOH	6	20
10	1	MeCN	6	60
11	1	MeOH	6	55
12	1	EtOH	6	40
13	1	THF	6	45
14	1	Benzene	24	40

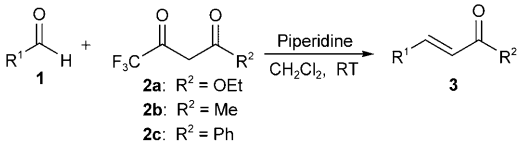
[a] Reaction conditions: **1i** (0.2 mmol), **2a** (0.2 mmol). [b] Yield of the isolated product. [c] Reaction was carried out at RT.

of piperidinium trifluoroacetate gives the (*E*)-α,β-unsaturated ester (Scheme 2).

To evaluate the efficiency of this methodology, various substituted carbonyl compounds, such as aromatic, aliphatic and heteroaromatic carbonyl compounds, were subjected to the reaction conditions and a series of (*E*)-α,β-unsaturated esters were obtained in high yields (Table 2). Having succeeded in the synthesis of a series of (*E*)-α,β-unsaturated esters, we extended this protocol for the synthesis of (*E*)-α,β-unsaturated ketones and obtained **3aa**–**3va** in very good yields. Under these conditions the use of acetophenones is futile. All the products were characterized by their spectral data (^{1}H NMR and ^{13}C NMR spectroscopy, IR, Mass, and HRMS), known compounds **3aa**, **3ab**, **3db**, **3cb**, **3ia**,[3e] **3ea**, **3ba**, **3ca**, **3la**,[12a] **3bb**, **3eb**,[12b] **3dc**,[12c] **3fa**, **3ga**, **3ka**, **3ja**,[12d] **3ha**,[12e] **3pa**, **3na**,[12f] **3oa**,[12g] **3pc**,[12h] and **3va**[12i] were compared to literature data and the unknown compounds **3qa**–**3uc** are documented in the Supporting Information.

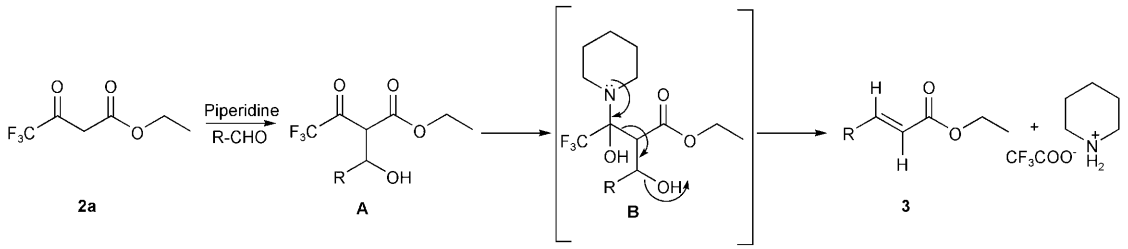
In summary, we have established a new, general, and practical method for the synthesis of (*E*)-α,β-unsaturated esters and ketones with high stereoselectivity. The present new protocol offers several advantages, such as high selectivity and yields, the use of environmentally benign conditions and an inexpensive catalyst, shorter reaction times, and a simple workup procedure, which makes it a useful and alternative procedure from the existing methods reported.

Table 2. Piperidine catalyzed synthesis of (*E*)-α,β-unsaturated esters and ketones.



Entry	R^1	2	t [h]	3	Yield [%][a]	E[b]
1	C_6H_5	**2a**	6.0	**3aa**	90	100
2	C_6H_5	**2b**	5.0	**3ab**	91	100
3	4-BrC_6H_4	**2a**	5.0	**3ba**	92	100
4	4-BrC_6H_4	**2b**	4.5	**3bb**	92	100
5	4-ClC_6H_4	**2a**	5.0	**3ca**	91	100
6	4-ClC_6H_4	**2b**	4.0	**3cb**	93	100
7	4-$NO_2C_6H_4$	**2b**	4.0	**3db**	95	100
8	4-$NO_2C_6H_4$	**2c**	4.0	**3dc**	94	100
9	4-$OMeC_6H_4$	**2a**	7.0	**3ea**	84	100
10	4-$OMeC_6H_4$	**2b**	5.0	**3eb**	89	100
11	4-MeC_6H_4	**2a**	6.5	**3fa**	89	100
12	4-EtC_6H_4	**2a**	6.5	**3ga**	88	100
13	3,5-$F_2C_6H_3$	**2a**	4.5	**3ha**	90	100
14	3-$NO_2C_6H_4$	**2a**	4.0	**3ia**	95	100
15	Furyl	**2a**	6.0	**3ja**	85	100
16	2-Pyridyl	**2a**	5.0	**3ka**	90	100
17	3-Pyridyl	**2a**	5.0	**3la**	88	100
18	4-Pyridyl	**2a**	4.5	**3ma**	90	100
19[c]	$(CH_3)_2CH$	**2a**	5.0	**3na**	67	100
20[c]	n-C_5H_{11}	**2a**	7.5	**3oa**	71	100
21[c]	n-C_3H_7	**2a**	6.5	**3pa**	62	100
22[c]	n-C_3H_7	**2c**	6.5	**3pc**	74	100
23	2-Cl, 5-Me, 3-Pyridyl	**2a**	6.0	**3qa**	87	100
24	2-Cl, 5-Me, 3-Pyridyl	**2b**	4.5	**3qb**	91	100
25	2-Cl, 5-Me, 3-Pyridyl	**2c**	4.5	**3qc**	92	100
26	2-Cl, 5-Et, 3-Pyridyl	**2a**	6.5	**3ra**	90	100
27	2-Cl, 5-Pr, 3-Pyridyl	**2a**	6.5	**3sa**	89	100
28	2-Cl, 5-Ph, 3-Pyridyl	**2a**	5.5	**3ta**	90	100
29	2-Cl, 5-Ph, 3-Pyridyl	**2b**	5.0	**3tb**	90	100
30	2-Cl, 5-Ph, 3-Pyridyl	**2c**	5.0	**3tc**	92	100
31	2-Cl, 6-MeO_2C, 3-Pyridyl	**2a**	5.5	**3ua**	90	100
32	2-Cl, 6-MeO_2C, 3-Pyridyl	**2b**	5.0	**3ub**	93	100
33	2-Cl, 6-MeO_2C, 3-Pyridyl	**2c**	5.0	**3uc**	92	100
34	2-Cl, 3-Quinyl	**2a**	6.0	**3va**	85	100
35	$C_6H_5COCH_3$	**2a**	24	–	0	–

[a] Yield of the isolated product. [b] Determined by ^{1}H NMR spectroscopy analysis of the crude reaction mixture. [c] The reaction was performed under nitrogen atmosphere.



Scheme 2. The possible mechanism for tandem Aldol-adduct elimination.

Experimental Section

Typical procedure for the synthesis of (*E*)-α,β-unsaturated esters: A mixture of 2-chloro-5-methylnicotinaldehyde (**1q**, 1.0 mmol) and ethyl-4,4,4-trifluoroacetoacetate (**2a**, 1.0 mmol) in dichloromethane (2 mL) was treated with piperidine (1.0 mmol) slowly dropwise, the contents were stirred at RT (≈40 °C) for the indicated time, or until complete consumption of the starting material had occurred, as monitored by TLC. After the reaction was finished, the solvent was evaporated in a vacuum. The residue was purified by column chromatography (hexane/ethyl acetate 9:1) to afford the desired product **3qa** as a colorless solid in 87% yield.

Typical procedure for the synthesis of (*E*)-α,β-unsaturated ketones: A mixture of 2-chloro-5-methylnicotinaldehyde (**1q**, 1.0 mmol) and 1,1,1-trifluoro-2,4-pentanedione (**2b** 1.0 mmol) in dichloromethane (2 mL) was treated with piperidine (1.0 mmol) slowly dropwise, the contents were stirred at RT for the indicated time, or until complete consumption of the starting material had occurred, as monitored by TLC. After the reaction was finished, the solvent was evaporated in a vacuum. The residue was purified by column chromatography (hexane/ethyl acetate 9:1) to afford the desired product **3qb** as a colorless solid in 91% yield.

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Keywords: esters · ketones · piperidine · stereoselectivity · synthetic methods

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