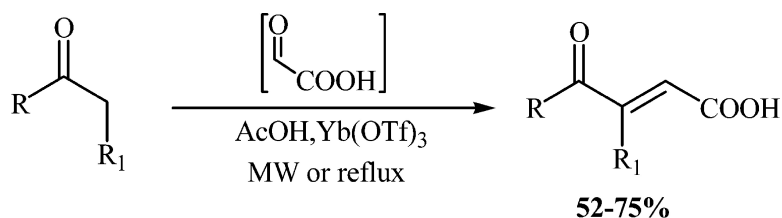## Article

Efficient Ytterbium Triflate Catalyzed Microwave-Assisted Synthesis of 3-Acylacrylic Acid Building Blocks

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Efficient Ytterbium Triflate Catalyzed Microwave-Assisted Synthesis of 3-Acylacrylic Acid Building Blocks

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The derivatives of 4-(hetero)aryl-4-oxobut-2-enoic acid are useful as building blocks in the synthesis of biologically active compounds. An efficient general protocol for the synthesis of these building blocks was developed. This method combines microwave assistance and ytterbium triflate catalyst and allows the fast preparation of the target acids starting from different (hetero)aromatic ketones and glyoxylic acid monohydrate giving pure products in 52–75% isolated yields.

Introduction

The derivatives of 3-acylacrylic acids possess a high synthetic potential that allows them to be applied as polyfunctional building blocks in the diversity orientated synthesis.[1] Moreover these compounds are known to be of great biological and pharmaceutical importance, for example, 4-(2-aminophenyl)-4-oxobutanoic acid **1** has recently been identified as a tryptophan metabolite and it plays role of UF-filter in human lenses.[2] Other derivatives are frequently reported as different enzyme inhibitors[3] probably because of their ability to react with the sulfhydryl of cysteine.[4] The simple Michael-type addition of mercaptoacetic acid to 3-benzoylacrylic acid derivatives leads to compounds **2** that efficiently suppressed proliferation of human cervix carcinoma.[5] Interestingly that combination of 4-aryl-4-oxobutanoic acid fragment with the known scaffold improves significantly its antibacterial activity (Chart 1, compounds **3**).[6]

One of the first and the most commonly used methods for synthesis of the 3-acylacrylic acids is the Friedel–Crafts reaction of substituted aromatic or heteroaromatic hydrocarbons with maleic anhydride and AlCl₃. However, this method involves environmentally hazardous substrates, and it does not allow to synthesize target molecules with variable substituents.[7] Another method is acid-catalyzed aldol condensation of aromatic ketones with glyoxylic acid monohydrate in acetic acid.[8] The advantage of this reaction is the synthesis of a wide range of the aromatic and heteroaromatic 3-acylacrylic acids starting from the corresponding aromatic ketones that are available with different substituents. However this method supposes either long-term refluxing in acetic acid (8–24 h) or two step synthesis: synthesis of an aldol

intermediate and its dehydration that usually allows the target compounds in low or moderate yields. There are also few new methods described for synthesis of 3-acylacrylic acid esters using Nineham–Raphael Reaction[9] or oxidation–Wittig reaction;[10] however they require laborious preparation of starting materials.

Chart 1
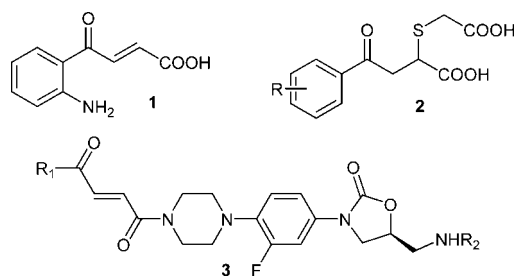
Result and Discussion

Herein, we describe a new facile protocol for the synthesis of a range of the aromatic and heteroaromatic 3-acylacrylic acid derivatives **6a–o** directly from aromatic ketones **4a–o** and glyoxylic acid monohydrate **5** combining microwave activation and water-tolerant Lewis acid as catalyst (Scheme 1).

To find acceptable conditions for microwave-assisted synthesis we chose 4-methoxyacetophenone **4a** as a model. The reaction with equimolar amounts of glyoxylic acid

Scheme 1[a]
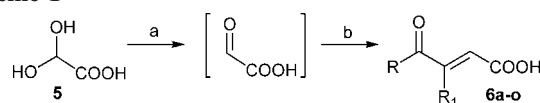
[a] Reagents and conditions: (a) Ac₂O, Yb(OTf)₃ (2.5 mol %) rt, 10 min; (b) aromatic or heteroaromatic ketones **4a–o**, MW 130 – 150 °C, 10–35 min (see Table 1).

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Table 1. Microwave-Assisted Synthesis of 3-Acylacrylic Acid Building Blocks
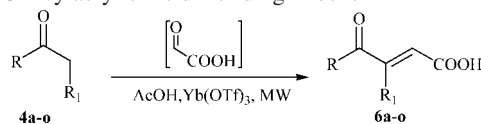
Entry	Reaction	R	R_1	T (°C)	Time (min)	Workup method	Yield (%)[a]	mp (°C)
1	**4a → 6a**	4-MeOC$_6$H$_4$	H	140	10	B	61	135-136[8a]
2	**4b → 6b**	4-NO$_2$C$_6$H$_4$	H	140	15	A	52	173-175[8a]
3	**4c → 6c**	2-FC$_6$H$_4$	H	140	13	A	54	109-111
4	**4d → 6d**	4-FC$_6$H$_4$	H	140	10	A	65	131-133[8a]
5	**4e → 6e**	2-MeC$_6$H$_4$	H	140	15	A	58	105-106[14]
6	**4f → 6f**	4-MeC$_6$H$_4$	H	140	15	A	75	134-136[8a]
7	**4g → 6g**	2.4-di-Me-C$_6$H$_3$	H	140	15	A	75	112-114[16]
8	**4h → 6h**	3-F-4-MeOC$_6$H$_3$	H	140	35	A	68	154-156
9	**4i → 6i**	3-F-4-MeOC$_6$H$_3$	Me	150	20	C	65	176-178
10	**4j → 6j**	4-HO-C$_6$H$_4$	H	140	10	D	50	192-193[8a]
11	**4k → 6k**	C$_6$H$_5$	Me	140	30	C	58	101-102[15]
12	**4l → 6l**	C$_6$H$_5$	H	140	15	A	75	93-95[8a]
13	**4m → 6m**	3-BrC$_6$H$_4$	H	140	15	A	72	148-150[14]
14	**4n → 6n**		H	140	15	A	61	143-145
15	**4o → 6o**		H	130	35[b]	C	60	199-201

[a] Yields refer to isolated yields of compounds >95% purity (^{1}H NMR and HPLC). [b] 0.5 mol % of Yb(OTf)$_3$ was used as catalyst.

Table 2. Optimization of the Microwave-Assisted Synthesis of the Acid **6a** (R = 4-MeOC$_6$H$_4$, R_1 = H), T = 140 °C

entry	catalyst (mol %)	time (min)	HPLC yield (%)	yield (%)
1	aq. HCl, (5.0)[a]	70	79	52
2	Yb(OTf)$_3$, (2.5)[a]	10	80	52
3	Yb(OTf)$_3$, (2.5)[b]	10	91	61
4	Yb(OTf)$_3$, (0.5)[b]	15	91	61
5	FeCl$_3$, (2.5)[b]	10	75	41

[a] Without acetic anhydride. [b] Pretreatment with acetic anhydride (1.0 equiv).

monohydrate **5** in acetic acid using aqueous HCl as catalyst (Table 2) accomplished only after 70 min of microwave irradiation at 140 °C giving 79% conversion (determined by HPLC). We therefore considered the use of water-tolerant Lewis acid such as a renewable[11] Yb(OTf)$_3$ and a chipper FeCl$_3$,[12] which recently have been reported as very effective catalysts for C—C bond formation. Thus, the same conversion was reached in seven times faster with the use of ytterbium triflate (2.5 mol %) as the catalyst. An application of higher reaction temperature led to the significant increase of the internal pressure in the sealed vial and the formation of undesired byproducts probably because of a side decarboxylation process. Prolonging the microwave heating did not lead to the improvement of the conversion in both cases; this might be an evidence of the achievement an equilibrium point. Then we used the acetic anhydride to decrease the amount of water in the reaction mixture and to shift the equilibrium to the side of the reaction product. The pretreat-

ment of the glyoxylic acid monohydrate **5** with acetic anhydride was done either by microwave irradiation of equimolar amounts of both components or by simple addition of ytterbium triflate to the mixture and stirring for 10 min (the latter was used in the general procedure).

The following reaction with ketone **4a** was done by a one-pot method, and its conversion was increased up to 91%, which allowed isolation of the purified product in 61% isolated yield (Table 2, entry 3). Interestingly, application of only 0.5 mol % of Yb(OTf)$_3$ led to the same conversion (91%) at the same temperature during 15 min. Iron (III) chloride showed lower catalytic activity and isolated yield of the purified product **6a** (Table 2, entry 5). Thus in most cases maximal conversion was reached in 15 min of microwave irradiation at 140 °C. In the case of the starting propiophenones **4i** and **4k**, temperature was increased up to 150 °C without visible decarboxylation. As to heterocyclic ketones, the reaction proved to be suitable for preparation of acids **6n** and **6o**. In the case of more reactive ketone **4o**, the concentration of Yb(OTf)$_3$ was decreased to 0.5 mol %, and the temperature was lowered to 130 °C.

Application of the found conditions to the synthesis of the range of the 3-acylacrylic acid building blocks generally required few optimization steps (Table 1).

Finally, we investigated the efficiency of the proposed catalytic system for the aldol condensation of glyoxylic acid monohydrate **5** with aromatic and heteroaromatic ketones under conventional heating. It was shown that the reactions

Table 3. Synthesis of **6a** and **b** under Conventional Heating (Refluxing in AcOH, 2.5 mol % of Yb(OTf)$_3$)

products	time (min)	HPLC yield (%)	yield (%)^a
6a	40	89	60
6b	65	77	51

^{a} Yields refer to isolated yields of compounds >95% purity (^{1}H NMR and HPLC).

of the **4a** and **4b** derivatives were accomplished in correspondingly 40 and 65 min of refluxing in acetic acid giving almost the same conversion and the isolated yields (Table 3).

Thus this method can be efficiently used also under conventional heating without significant lost of the yield.

Conclusion

In summary, we have developed a new convenient protocol for the preparation of aromatic and heteroaromatic 3-acylacrylic acid derivatives. We have also studied its scope and limitation and concluded that this method could be used for the preparation of a wide range of the aromatic and heteroaromatic 3-acylacrylic acid derivatives both under conventional and microwave heating. We have shown that microwave activation in combination with ytterbium triflate catalyst provide the highest so far speed and yields in the synthesis of aromatic and heteroaromatic 3-acylacrylic acids building blocks. Importantly, the fast reaction conditions optimization achieved by using the controlled microwave irradiation allowed us to reach such reaction conditions that can be also efficiently applied using conventional heating, which is crucial for the synthesis of these building blocks in large scale.

Experimental Section

^{1}H NMR spectra were recorded on a Varian Mercury VX-200 (200 MHz) spectrometer. ^{13}C NMR spectra were measured on Bruker DRX-300 (75 MHz). Mass spectra were recorded on a Varian 1200 L GC-MS instrument with the use of direct exposure probe (DEP) method with EI at 70 eV. HPLC analyses were performed using a Bischoff HPLC system equipped with Prontosil 120-5-C18H reverse-phase column (70 vol% MeCN−H$_2$O mixture served as eluent). All microwave-assisted reactions were carried out in Emrys™ Creator EXP (Biotage, Sweden). Melting points were determined on a Kofler apparatus. Glyoxylic acid monohydrate **5**, aromatic ketones **4a**−**g**, **4j**−**o**, acetic acid, acetic acid anhydride, aq. HCl (37 mass %), FeCl$_3$ (anhydrous), and Yb(OTf)$_3$ are commercially available and were used without additional purification. Aromatic ketones **4h** and **4i** were synthesized by Friedel−Crafts acylation of 2-fluoroanisole by a procedure similar to that described in literature.[13] Yields refer to isolated yields of compounds estimated to be >95% pure, as determined by ^{1}H NMR and HPLC.

Microwave-Assisted Synthesis of the 3-Acylacrylic Acid Derivatives 6a−**o (General Procedure).** A mixture of glyoxylic acid monohydrate (37 mmol), acetic anhydride (39 mmol), and ytterbium triflate (0,925 mmol-0,57 g) was stirred for 10 min at room temperature in MW proceeding vial for 20 mL of the reaction mixture. Then a corresponding aromatic ketone (**4a**−**o**, 37 mmol) and glacial acetic acid (6 mL) were added. The reaction vial was sealed, and the mixture was irradiated with microwaves under conditions specified in the Table 2 (solvent absorption was chosen as "very high", which decreased the initial power to 90 W). The internal pressure was not higher than 5 bar during the experiment. After it was cooled, the product was isolated by one of the workup methods (see Table 2).

Workup method A: The solvent was evaporated. The remaining residue was washed with ice-cold water (50 mL) by decantation or on filter. The crude product was dissolved in 20 mL of 25% K$_2$CO$_3$ solution in water and washed with ethyl acetate (3 times with 15 mL). Than the mixture cooled with ice and acidified by concentrated aqueous HCl. The solid product formed was filtrated and dried for 24 h at 50 °C.

Workup method B: Cooled reaction mixture suspended in ice water (100 mL), filtered, and dried for 24 h at 50 °C.

Workup method C: Method is similar to method A but with the use of saturated aqueous NaHCO$_3$ solution (40 mL) instead of 25% K$_2$CO$_3$ solution.

Workup method D: After removal of of the solvent, the reaction mixture was washed with ice-cold water and recrystallized from water.

The identification of the previously described compounds **6a**, **6b**, **6d**, **6f**, **6j**, **6l**,[8a] **6e**, **6m**,[14] **6g**,[16] and **6k**[15] was made by comparison of their melting points or by using ^{1}H NMR spectroscopy. For all the new compounds, data confirming their structure are given below:

(*E*)-4-(2-Fluorophenyl)-4-oxobut-2-enoic Acid (6c): yield 54%; yellow solid; mp 109−111 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 13.22 (br s, 1H), 7.86−7.63 (m, 2H), 7.55 (dd, 1H, *J* = 15.6, 3.1 Hz), 7.45−7.29 (m, 2H), 6.83 (dd, 1H, *J* = 15.6, 0.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 117.1, 117.4, 125.4, 131.2, 133.2, 136.0, 136.1, 139.1, 166.6, 188.4; MS (EI) *m/z* 194 (M$^+$).

(*E*)-4-(3-Fluoro-4-methoxyphenyl)-4-oxobut-2-enoic Acid (6h): yield 68%; mp 154−156 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.96 (br s, 1H), 8.00−7.74 (m, 3H), 7.30 (t, 1H, *J* = 8.5 Hz), 6.64 (d, 1H, *J* = 15.4 Hz), 3.64 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.8, 113.8, 115.9, 116.2, 127.5, 129.5, 133.2, 136.0, 152.4, 166.7, 187.2; MS (EI) *m/z* 224 (M$^+$).

4-(3-Fluoro-4-methoxyphenyl)-3-methyl-4-oxobut-2-enoic Acid (6i): yield 65%; *E/Z* ratio 55:45 (according to HPLC analysis and literature data for analogous derivatives[15]); mp 176−178 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.89 (br s, 1H), 7.71−7.52 (m, 2H), 7.38−7.17 (m, 1H), 6.64 (d, 1H, *J* = 15.4 Hz), 3.92 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.6, 56.8, 113.7, 116.7, 116.9, 125.6, 128.2, 150.1, 151.9, 152.1, 167.1, 195.7; MS (EI) *m/z* 194 (M$^+$).

(*E*)-4-(5-Bromothiophen-2-yl)-4-oxobut-2-enoic Acid (6n): yield 61%; mp 143−145 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 13.20 (s, 1H), 8.09 (d, 1H, *J* = 4.0 Hz), 7.78 (d, 1H, *J* = 15.4 Hz), 7.45 (d, 1H, *J* = 4.0 Hz), 6.70 (d, 1H, *J* = 15.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 124.6, 133.3, 133.5, 134.9, 136.4, 145.9, 166.5, 180.7; MS (EI) *m/z* 262 (M$^+$), 260 (M$^+$).

(*E*)-4-Oxo-4-(2-oxo-2*H*-chromen-3-yl)but-2-enoic Acid (6o): yield 60%; mp 199−201 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 13.07 (s, 1H), 8.72 (s, 1H), 7.95 (dd, 1H, $J =$ 6.4, 1.3 Hz), 7.85 (d, 1H, $J =$ 15.6 Hz), 7.80−7.67 (m, 1H), 7.52−7.34 (m, 2H), 6.70 (d, 1H, $J =$ 15.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 116.6, 118.6, 124.5, 125.4, 131.3, 132.3, 135.2, 138.6, 148.8, 155.1, 158.9, 166.7, 187.3; MS (EI) *m/z* 244 (M[+]).

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