Green Chemistry

Cite this: DOI: 10.1039/c2gc36095k

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PAPER

# Ultrasound-promoted sterically congested Passerini reactions under solvent-free conditions†

**Can Cui, Cong Zhu, Xiu-Jiang Du, Zhi-Peng Wang, Zheng-Ming Li and Wei-Guang Zhao***

***Received 15th July 2012, Accepted 31st August 2012***
**DOI: 10.1039/c2gc36095k**



A facile, efficient and environmentally-friendly protocol for the synthesis of α-acyloxy amides has been developed by ultrasound-promoted sterically congested Passerini reactions under solvent-free conditions. This method provides several advantages over current reaction methodologies including a simpler work-up procedure, shorter reaction times and higher yields.

## Introduction

Multicomponent reactions have become increasingly popular as powerful tools for drug discovery[1–4] because of their high atom economy and chemical efficiency, and because they provide ideal scaffolds for parallel synthesis and combinatorial chemistry. The Passerini reaction is one of the most used and oldest multicomponent reactions to use isocyanides, and is the best method for producing α-acyloxy amides, depsides, and depsipeptides.[5–8] For example, mandipropamid, a novel fungicide against foliar diseases caused by *Oomycetes*, was rapidly discovered using isocyanide-based multicomponent reactions of the Passerini type,[9] and bicalutamide, the leading antiandrogen used for the treatment of prostate cancer, can be synthesized *via* a Passerini reaction.[10] Both aromatic and aliphatic aldehydes are usually good substrates for Passerini reactions. However, with ketones, the reactions are generally slower or even fail to proceed. An interesting empirical phenomenon is that the use of high pressure significantly increases the yields in sterically congested Passerini reactions.[11] Although the synthesis is efficient, the reaction times are usually long (16.5 h), and it is difficult to achieve sufficiently high compaction pressures in practice.

Ultrasound techniques have increasingly been used in organic synthesis during the last few years. Compared with traditional methods, this method can give higher yields in shorter reaction times and under milder conditions.[12] As is well known, high-power ultrasound can generate cavitations within a liquid. Cavitation induces temperatures of several thousand degrees and pressures in excess of 1000 atm inside bubbles, and enhances mass transfer and turbulent flow in the liquid.[13,14]

Promotion of Passerini reactions at high pressure provides further support for this idea and suggests that these reactions could be accelerated by ultrasound. However, the influence of ultrasound on Passerini reactions has not yet been reported. Accordingly, this attracted us to investigate whether ultrasound can accelerate hindered Passerini reactions.

## Results and discussion

According to the literature, at ambient pressure, hindered Passerini reactions give poor yields; when performed at 300 MPa, the NMR yield (Table 1, entry 4) increases from 6 to 28% (reaction time 16.5 h). To determine the effects of ultrasound irradiation on this reaction, experiments were carried out using a sonic horn as an ultrasound source, with other conditions the same as those in the literature.[11] The reaction mixture was irradiated at 25 kHz/1200 W (pulse-on time = 2 s, pulse-off time = 2 s) for 1 h. We found that the use of ultrasound did indeed accelerate the reaction. The yield (Table 1, entry 4) increased from 6 (NMR yield) to 41% (isolated yield), and the reaction time was shortened from 16.5 to 1 h (the reaction time was not monitored closely). We also investigated the effects of the sizes of $R_1$ (acid), $R_2$ (ketone), and $R_3$ (isocyanide). As expected, most ultrasonic reactions provided higher yields than high-pressure reactions (Table 1). The Passerini reaction shown in entry 3 was reported to require 16.5 h at 300 MPa with 3-methyl-2-butanone as solvent (38% NMR yield). Under ultrasound irradiation, the product was isolated in 44% yield after only 1 h. The lower product yields for entries 1 and 2 may be the result of losses during silica gel column chromatography. Obviously, performing a reaction under ultrasound irradiation is much more convenient than performing it at high pressure.

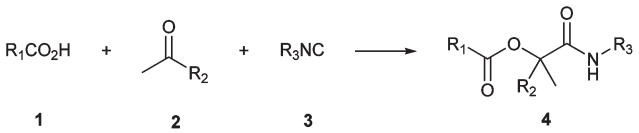
To achieve more suitable conditions for the synthesis of Passerini products (**4**), different reaction conditions were investigated in the reaction of acetic acid, 2,2,2-trifluoro-1-phenylethanone, and 1-isocyanato-4-methoxy-2-nitrobenzene, because the progress of the reaction could be easily monitored using TLC.

The classical Passerini reaction is generally performed in a low-polarity medium such as dichloromethane (DCM), EtOAc, diethyl ether, or tetrahydrofuran.[15] Although compound **4h** could be obtained in DCM by conventional methods (Table 2, entry 12), the required reaction time is too long (more than 2

*State Key Laboratory of Elemento-Organic Chemistry, National Pesticide Engineering Research Center (Tianjin), Nankai University, Tianjin 300071, China. E-mail: zwg@nankai.edu.cn; Fax: +862223505948; Tel: +862223498368*

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2gc36095k

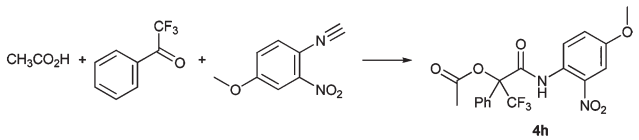
**Table 1** Effect of ultrasound on Passerini reactions[a]




| Entry | Product | $R_1$ | $R_2$ | $R_3$ | Yield (%) 0.1 MPa[b] | 300 MPa[b] | Sonic horn[c] |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | $CH_3$ | Me | Cyclohexyl | 41 | 89 | 68 |
| 2 | **4b** | *n*-Bu | Me | Cyclohexyl | 16 | 51 | 43 |
| 3 | **4c** | *i*-Bu | Me | Cyclohexyl | 9 | 38 | 44 |
| 4 | **4d** | *t*-Bu | Me | Cyclohexyl | 6 | 28 | 41 |
| 5 | **4e** | *t*-Bu | Et | Cyclohexyl | —[d] | — | 50 |
| 6 | **4f** | 4-MePh | Me | Cyclohexyl | 17 | 40 | 49 |
| 7 | **4g** | 4-MePh | Et | Cyclohexyl | 15 | 36 | 45 |

[a] General reaction conditions: acid (0.4 mmol), isocyanide (0.5 mmol), ketone (reactant and solvent), 25 °C. [b] The yield determined from relative intensities of characteristic protons *versus* methylene protons of the internal standard; reaction time = 16.5 h. [c] Isolated yield after silica gel column chromatography; reaction time = 1 h. [d] Not tested.

**Table 2** Effects of solvent and temperature on ultrasound-promoted Passerini reactions[a]




| Entry | Solvent | Condition | Time | Temp. (°C) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | DCM | Sonic horn[c] | 3 h | RT | 0 |
| 2 | EtOAc | Sonic horn[c] | 3 h | RT | 0 |
| 3 | THF | Sonic horn[c] | 3 h | RT | 0 |
| 4 | $H_2O$ | Sonic horn[c] | 3 h | RT | 0 |
| 5 | LiCl aq. | Sonic horn[c] | 3 h | RT | 0 |
| 6 | Petroleum ether | Sonic horn[c] | 3 h | RT | 0 |
| 7 | Solvent-free | Sonic horn[c] | 50 min | RT | 49 |
| 8 | Solvent-free | Sonic horn[c] | 40 min | 40 | 58 |
| 9 | Solvent-free | Sonic horn[c] | 40 min | 60 | 50 |
| 10 | Solvent-free | Stir | 24 h | RT | 52 |
| 11 | DCM | Stir | 2 weeks | RT | 39 |

[a] General reaction conditions: acid (1.5 mmol), isocyanide (1.0 mmol), ketone (1.5 mmol). [b] Isolated yield after silica gel column chromatography. [c] Sonic horn power = 1200 W, irradiation frequency = 25 kHz.

weeks). To address questions concerning solvent effects, this reaction was examined in DCM, EtOAc, and tetrahydrofuran; however, ultrasound did not significantly accelerate the reactions (Table 2, entries 1–3). It has also been reported[16] that performing a Passerini reaction in water or aqueous LiCl is much more convenient than performing it at high pressure. However, no reactions occurred in water or aqueous LiCl whether ultrasound was used or not (Table 2, entries 4 and 5). Under these conditions, isonitrile was quickly degraded to the corresponding *N*-substituted formamide.

Solvent-free reactions have proven to be efficient and environmentally friendly procedures for organic synthesis.[17–19] We decided to change to solvent-free procedures to get rid of organic solvents or water, which always decrease the chances of collisions between reactant molecules. For ultrasound irradiation conditions, at the same temperature and with the power set at 1200 W (pulse-on time = 2 s, pulse-off time = 2 s), compound **4h** is obtained in 50 min at a 49% yield (Table 2, entry 7). Because a self-curing mixture hinders the reaction, the reactions were carried out in excess phenylethanone as solvent at acid : ketone : isonitrile ratios of 1.5 : 1 : 1.5. For comparison, we also examined the same reaction under solvent-free conditions and conventional conditions; the reaction was completed in 24 h under solvent-free conditions (52% isolated yield; Table 2, entry 10) and in 2 weeks under conventional conditions (39% isolated yield; Table 2, entry 11).

The classical Passerini reaction is typically carried out at room temperature.[15] The effects of temperature on Passerini reactions have not often been studied. We carried out experiments at different temperatures; the results show that temperature plays a

role in this process (Table 2). When the reaction was carried out at 40 °C, after 40 min, the yield had increased to 58% (Table 2, entry 8). This result shows that an ultrasound-assisted solvent-free procedure provides an approximately 36-fold acceleration compared with the solvent-free procedure. However, when the reaction was carried out at 60 °C, after 40 min, the yield had decreased to 50%, apparently because of isonitrile decomposition. Motivated by this fact, we carried out the experiments using petroleum ether, which does not dissolve the raw materials, as a dispersant. The reaction was still unaffected by ultrasound irradiation (Table 2, entry 6). We think that the most significant reason why these reactions could not be accelerated by ultrasound irradiation in solution is that ultrasound bubbles may be generated mainly in the solvent because of the low vaporization temperature of the solvent; thus, it is difficult for the three components to exist simultaneously in the same cavitation bubble.

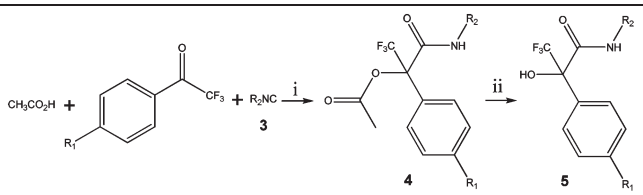
After optimizing the conditions, the generality of this method was examined using the reactions of several trifluorophenylethanones, isocyanides, and acetic acid under ultrasound irradiation; the results are shown in Table 3.

Under the optimized conditions, the reactions proceeded smoothly, and good-to-excellent conversions were observed regardless of whether the isocyanide or the trifluorophenylethanone bore electron-withdrawing or electron-donating substituents (Table 3, entries 1–4). Higher yields and shorter reaction times were obtained for the benzyl isocyanide (Table 3, entries 3 and 4). Excellent conversions were observed for **4e** (Table 3, entry 4); compound **4e** was obtained in 15 min in 85% yield.

With a view to evaluate the bio-activities of α-hydroxyl amides, the generality of this method was examined using a convenient one-pot Passerini-hydrolysis reaction. After completion of the Passerini reaction, the reaction mixture was hydrolyzed by directly adding aqueous sodium hydroxide solution and methanol under ultrasound irradiation for 15 min. The substituent on the isonitrile ($R_2$) had little or no effect on the reaction yield. Substituted phenylisonitriles, benzylisonitrile, or phenylethanylisonitrile were suitable for this reaction and gave α-hydroxy amides **5** in good yields (Table 3, entries 5–14). However, the yields were affected by the presence of electron-donating or electron-withdrawing substituents at the *para* positions of 2,2,2-trifluoro-1-phenylethanone. Electron-donating substituents ($R_1$) decreased the yields (Table 3, entries 15–17), whereas electron-withdrawing substituents had the opposite effect (Table 3, entry 18).

To determine the influence of ultrasonic irradiation on the development of the process, following the same work up, the reaction was developed using an ultrasonic cleaner as an ultrasound source. When the reaction flask was located in the cleaner bath (40 kHz, 100 W), compound **4h** was obtained in 3 h in 52% isolated yield. When the reaction was carried out in a cleaner bath, the reaction rate was significantly accelerated (Table 3, entries 1–4). Comparable yield of the desired product was obtained after only 2–3 h, which is approximately eight- to twelve-fold faster than the reaction performed under solvent-free conditions (Table 2, entry 10). The reaction time was increased approximately four-fold to six-fold compared with the reaction performed using a sonic horn (Table 2, entry 8).This is probably

**Table 3** Influence of ultrasonic irradiation source on process development[a]




| | | | | Sonic horn[b] | | Bath cleaner[c] | |
|---|---|---|---|---|---|---|---|
| Entry | Product | $R_1$ | $R_2$ | Time (min) | Yield[d] (%) | Time (min) | Yield[d] (%) |
| 1 | **4h** | H | 2-$NO_2$-4-MeOPh | 40 | 58 | 180 | 52 |
| 2 | **4i** | H | 2-($PhCO_2$)Ph | 30 | 61 | 180 | 61 |
| 3 | **4d** | H | 4-MeOPh$CH_2$ | 15 | 78 | 120 | 76 |
| 4 | **4e** | H | 4-FPh$CH_2$ | 15 | 85 | 120 | 82 |
| 5 | **5a** | H | Ph$CH_2$ | 15 | 65 | —[e] | — |
| 6 | **5b** | H | 4-MePh$CH_2$ | 15 | 62 | — | — |
| 7 | **5c** | H | 2-MeOPh$CH_2$ | 15 | 72 | — | — |
| 8 | **5d** | H | 4-MeOPh$CH_2$ | 15 | 73 | — | — |
| 9 | **5e** | H | 4-FPh$CH_2$ | 15 | 79 | — | — |
| 10 | **5f** | H | 2-ClPh$CH_2$ | 15 | 72 | — | — |
| 11 | **5g** | H | 3,4-MeOPh$CH_2CH_2$ | 15 | 68 | — | — |
| 12 | **5h** | H | 4-MePh | 40 | 68 | — | — |
| 13 | **5i** | H | 4-MeOPh | 40 | 80 | — | — |
| 14 | **5j** | H | 4-ClPh | 40 | 75 | — | — |
| 15 | **5k** | Et | 4-MeOPh | 40 | 60 | — | — |
| 16 | **5l** | 4-MeO | 4-MeOPh | 40 | 47 | — | — |
| 17 | **5m** | 4-PhO | 4-MeOPh | 40 | 50 | — | — |
| 18 | **5n** | 4-Ph | 4-MeOPh | 40 | 69 | — | — |

[a] General reaction conditions: acid (1.5 mmol), isocyanide (1.0 mmol), ketone (1.5 mmol), 40 °C. [b] Sonic horn power = 1200 W, irradiation frequency = 25 kHz. [c] Bath cleaner power = 100 W, irradiation frequency = 40 kHz. [d] Isolated yield after silica gel column chromatography. [e] Not tested.

because the mixture is exposed to weaker ultrasonic energy. Nevertheless, both methodologies were more efficient, less time consuming, and more environmentally friendly than the conventional method, particularly when considering basic green chemistry concepts.

All the synthesized compounds were characterized using spectral data (HRMS, and $^{1}H$ and $^{13}C$ NMR).

## Conclusions

In conclusion, we present an eco-friendly and high-yielding procedure for sterically congested Passerini reactions under ultrasound irradiation at 40 °C in solvent-free conditions. This mild and time-saving procedure leads to the simple α-acyloxy amides **4** or α-hydroxy amides **5**. To the best of our knowledge, this new procedure provides the first example of an efficient and ultrasound-promoted sterically congested Passerini reaction under solvent-free conditions. This method for the acceleration of Passerini reactions could also be applied to the parallel synthesis of Passerini reaction products using a non-contact ultrasonic cell crusher or cleaner bath.

## Experimental

### General remarks

$^{1}H$ and $^{13}C$ NMR spectra were measured on a Bruker AC-P500 instrument using TMS as the internal standard and $CDCl_3$ as solvent. Melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments, Beijing, China) and were uncorrected. HRMS were recorded on an Ionspec 7.0 T Fourier-transform ion-cyclotron resonance (FTICR) mass spectrometer.

The ultrasonic irradiation experiments were carried out in (a) a Nanjing SL2010-N ultrasonic processor equipped with a 2 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture; the operating frequency was 25 kHz and the output power was manually adjusted to 1200 W; and (b) a Kunshang KQ-100 ultrasonic cleaner with a frequency of 40 kHz and a nominal power of 100 W. All chemicals and reagents were purchased from standard commercial suppliers.

### Classical method

Acetic acid (0.07 g, 1.1 mmol), 1-isocyano-4-methoxy-2-nitrobenzene (0.2 g, 1.1 mmol), and 2,2,2-trifluoro-1-phenylethanone (0.74 g, 1 mmol) were dissolved in DCM (10 mL). The solution was stirred at room temperature for 14 d. After completion of the reaction, the solvent was removed under vacuum. The resulting crude product was purified by column chromatography with silica gel and a mixture of EtOAc–petroleum ether (1 : 25) as the eluent to give **4h** as a yellow solid; yield 39%.

### Solvent-free method

A dry 10 mL flask was charged with 2,2,2-trifluoro-1-phenylethanone (1.5 mmol), acetic acid (1.5 mmol), and isonitrile (1.0 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was purified by column chromatography with silica gel and a mixture of EtOAc–petroleum ether (1 : 25) as the eluent to give **4h** as a yellow solid; yield 52%.

### Ultrasonic irradiation

Method A: A dry 10 mL flask was charged with a 2,2,2-trifluoro-1-phenylethanone derivative (1.5 mmol), acetic acid (1.5 mmol), and isonitrile (1.0 mmol). The reaction mixture was then sonicated using an ultrasonic probe (ultrasonic power = 1200 W, frequency = 25 kHz, pulse-on time = 2 s, pulse-off time = 2 s) with a frequency of 25 kHz at 25 or 40 °C for a specified period of time (see Table 1 or 2, monitored by TLC). The resulting crude products were purified by column chromatography using a mixture of petroleum ether–EtOAc (25 : 1) as the eluent. The corresponding products (**4**) were obtained.

Method B: A dry 10 mL flask was charged with a 2,2,2-trifluoro-1-phenylethanone derivative (1.5 mmol), acetic acid (1.5 mmol), and isonitrile (1.0 mmol). The mixture was sonicated in the water bath of an ultrasonic cleaner (ultrasonic power = 100 W, frequency = 40 kHz) at 40 °C for a specified period of time (see Table 3, monitored by TLC). The resulting crude products were purified by column chromatography using a mixture of petroleum ether–EtOAc (25 : 1) as the eluent to give the corresponding products **4**.

### 1,1,1-Trifluoro-3-((4-methoxy-2-nitrophenyl)amino)-3-oxo-2-phenylpropan-2-yl acetate (4h)

White solid; m.p.: 115 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 10.51 (s, 1H, CONH), 8.56 (d, $J$ = 12.4 Hz, 1H, Ar-H), 7.71–7.54 (m, 3H, Ar-H), 7.46–7.33 (m, 3H, Ar-H), 7.17 (dd, $J$ = 12.4 Hz, $J$ = 4.4 Hz, 1H, Ar-H), 3.76 (s, 3H, $OCH_3$), 2.31 (s, 3H, $COCH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 165.75, 160.88, 153.68, 135.39, 128.50, 127.96, 126.66, 125.24, 124.98, 122.28, 121.76, 121.34, 118.48, 106.97, 53.94, 19.14; $^{19}F$ NMR (376 MHz, $CDCl_3$) $\delta$ −72.33; HRMS (ESI) $m/z$ Calcd for $C_{18}H_{13}F_3N_2O_6^-$ $[M - H]^-$ 411.0809, found 411.0818.

### 2-(2-Acetoxy-3,3,3-trifluoro-2-phenylpropanamido)phenyl benzoate (4i)

White solid; m.p.: 122–123 °C; $^{1}H$ NMR ($CDCl_3$) 400 MHz: $\delta$ 9.51 (s, 1H, CONH), 8.20–8.04 (m, 2H, Ar-H), 7.68 (t, $J$ = 7.6 Hz, 1H, Ar-H), 7.63–7.40 (m, 6H, Ar-H), 7.32 (dd, $J$ = 7.6 Hz, $J$ = 1.2 Hz, 2H, Ar-H), 7.22 (d, $J$ = 7.6 Hz, 1H, Ar-H), 2.12 (s, 3H, $CH_3$); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 172.99, 164.33, 161.59, 147.22, 134.26, 130.94, 130.32, 129.95, 128.85, 128.28, 127.16, 124.15, 29.72; $^{19}F$ NMR (376 MHz, $CDCl_3$) $\delta$ −73.21; HRMS (ESI) $m/z$ Calcd for $C_{24}H_{18}F_3NO_5Na$ $(M + Na)^+$ 480.1029, found 480.1030.

### 1,1,1-Trifluoro-3-((4-methoxybenzyl)amino)-3-oxo-2-phenylpropan-2-yl acetate (4d)

White solid; m.p.: 105–106 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.54 (d, $J$ = 7.2 Hz, 2H, Ar-H), 7.40 (d, $J$ = 5.6 Hz, 3H,

Ar-H), 7.17 (d, $J$ = 8.0 Hz, 2H, Ar-H), 6.85 (d, $J$ = 8.0 Hz, 2H, Ar-H), 6.33 (br, 1H, NH), 4.46 (qd, $J$ = 14.8 Hz, $J$ = 5.2 Hz, 2H, ArCH$_2$), 3.79 (s, 3H, CH$_3$O), 2.29 (s, 3H, CH$_3$); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ −72.84. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.05, 163.79, 159.19, 130.90, 129.74, 129.23, 128.50, 127.25, 114.13, 77.36, 77.04, 76.72, 55.31, 43.61, 21.41; HRMS (ESI) $m/z$ Calcd for $C_{19}H_{18}F_3NO_4H^+$ $[M + H]^+$ 382.1261, found 382.1262.

**1,1,1-Trifluoro-3-((4-fluorobenzyl)amino)-3-oxo-2-phenylpropan-2-yl acetate (4e)**

White solid; M.p.: 101–102 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.53 (d, $J$ = 7.2 Hz, 2H, Ar-H), 7.41 (d, $J$ = 6.2 Hz, 3H, Ar-H), 7.25–7.14 (m, 2H, Ar-H), 7.01 (t, $J$ = 8.4 Hz, 2H, Ar-H), 6.42 (br, 1H, CONH), 4.48 (qd, $J$ = 14.8 Hz, $J$ = 5.6 Hz, 2H, CH$_2$NH), 2.29 (s, 3H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.04, 163.99, 129.82, 129.60, 129.52, 128.54, 127.20, 115.75, 115.53, 43.35, 21.39; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ −72.88, −114.52; HRMS (ESI) $m/z$ Calcd for $C_{18}H_{16}F_4NO_3H$ $(M + H)^+$ 370.1064, found 370.1063.

**One-pot Passerini-hydrolysis method**

A dry 10 mL flask was charged with a 2,2,2-trifluoro-1-phenylethanone derivative (1.5 mmol), acetic acid (1.5 mmol), and isonitrile (1.0 mmol). The reaction mixture was then sonicated using an ultrasonic probe (ultrasonic power, 1200 W; frequency, 25 kHz; pulse-on time, 2 s; pulse-off time, 2 s) with a frequency of 25 kHz at 25 °C or 40 °C for a specified period of time. After completion of the reaction, 4 mL of methanol and 2 mL of 10% sodium hydroxide were added to the reaction mixture to hydrolyze the α-acyloxy amides **4** to α-hydroxyl amides **5** under ultrasound irradiation. After irradiation of the mixture for 30 min, the solvent was evaporated and the residue was extracted several times with EtOAc. The combined organic phases were washed with brine, dried over MgSO$_4$, evaporated, and recrystallized from EtOH to give **5**.

***N*-Benzyl-3,3,3-trifluoro-2-hydroxy-2-phenylpropanamide (5a)**

White solid; m.p.: 138 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.64 (d, $J$ = 3.8 Hz, 2H, Ar-H), 7.55–7.37 (m, 3H, Ar-H), 7.37–7.27 (m, 3H, Ar-H), 7.15 (d, $J$ = 6.8 Hz, 2H, Ar-H), 6.41 (br, 1H, CONH), 4.85 (s, 1H, OH), 4.51 (ddd, $J$ = 33.6 Hz, $J$ = 15.2 Hz, $J$ = 6.0 Hz, 2H, CH$_2$NH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.24, 136.69, 134.33, 129.62, 129.00, 128.87, 127.90, 127.37, 126.31, 44.47; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ −74.01; HRMS (ESI) $m/z$ Calcd for $C_{16}H_{14}F_3NO_2H^+$ $[M + H]^+$ 310.1049, found 310.1055.

**3,3,3-Trifluoro-2-hydroxy-*N*-(4-methylbenzyl)-2-phenylpropanamide (5b)**

White solid; m.p.: 122 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (d, $J$ = 4.5 Hz, 2H, Ar-H), 7.49–7.37 (m, 3H, Ar-H), 7.12 (d, $J$ = 7.8 Hz, 2H, Ar-H), 7.03 (d, $J$ = 8.0 Hz, 2H, Ar-H), 6.37 (br, 1H, CONH), 4.88 (s, 1H, OH), 4.45 (ddd, $J$ = 32 Hz, $J$ = 16.0 Hz, $J$ = 4.0 Hz, 2H, CH$_2$NH), 2.33 (s, 3H, Ar-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.16, 137.69, 134.38, 133.62, 129.59, 129.53, 128.98, 127.39, 126.33, 122.40, 44.30, 21.11; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ −73.99, −74.01; HRMS (ESI) $m/z$ Calcd for $C_{17}H_{16}F_3NO_2H^+$ $[M + H]^+$ 324.1206, found 324.1210.

**3,3,3-Trifluoro-2-hydroxy-*N*-(2-methoxybenzyl)-2-phenylpropanamide (5c)**

White solid; m.p.: 146–147 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.69–7. 55 (m, 2H, Ar-H), 7.50–7.38 (m, 3H, Ar-H), 7.36–7.26 (m, 1H, Ar-H), 7.19 (dd, $J$ = 7.2 Hz, $J$ = 1.2 Hz, 1H, Ar-H), 6.92 (td, $J$ = 7.2 Hz, $J$ = 0.8 Hz, 1H, Ar-H), 6.86 (d, $J$ = 8.0 Hz, 1H, Ar-H), 6.70 (br, 1H, CONH), 5.04 (s, 1H, OH), 4.61–4.41 (m, 2H, CH$_2$NH), 3.75 (s, 3H, Ar-OCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.89, 157.43, 134.64, 129.61, 129.37, 128.81, 126.39, 125.31, 124.55, 122.47, 120.71, 110.30, 55.12, 41.23; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ −74.14; HRMS (ESI) $m/z$ Calcd for $C_{17}H_{16}F_3NO_3H^+$ $[M + H]^+$ 340.1155, found 340.1158.

**3,3,3-Trifluoro-2-hydroxy-*N*-(4-methoxybenzyl)-2-phenylpropanamide (5d)**

White solid; m.p.: 138 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71–7.56 (m, 2H, Ar-H), 7.50–7.34 (m, 3H, Ar-H), 7.08 (d, $J$ = 8.0 Hz, 2H, Ar-H), 6.83 (d, $J$ = 8.0 Hz, 2H, Ar-H), 6.36 (br, 1H, CONH), 4.89 (s, 1H, OH), 4.42 (ddd, $J$ = 34.8 Hz, $J$ = 14.4 Hz, $J$ = 5.6 Hz, 2H, CH$_2$NH), 3.78 (s, 3H, Ar-OCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.10, 159.26, 134.37, 129.58, 128.98, 128.83, 128.71, 126.32, 125.24, 122.39, 114.21, 55.31, 44.02; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ −74.02; HRMS (ESI) $m/z$ Calcd for $C_{17}H_{16}F_3NO_3H^+$ $[M + H]^+$ 340.1155, found 340.1158.

**3,3,3-Trifluoro-*N*-(4-fluorobenzyl)-2-hydroxy-2-phenylpropanamide (5e)**

White solid; m.p.: 137–138 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.73–7.55 (m, 2H, Ar-H), 7.51– 7.31 (m, 3H, Ar-H), 7.11 (dd, $J$ = 8.8 Hz, $J$ = 5.6 Hz, 2H, Ar-H), 6.98 (t, $J$ = 8.8 Hz, 2H, Ar-H), 6.50 (br, 1H, CONH), 4.82 (s, 1H, OH), 4.44 (qd, $J$ = 14.8 Hz, $J$ = 6.0 Hz, 2H, CH$_2$NH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.27, 163.57, 161.12, 134.24, 132.59, 132.56, 129.65, 129.16, 129.08, 128.98, 126.28, 126.27, 125.19, 122.35, 115.84, 115.62, 43.65; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ −74.10, −114.29; HRMS (ESI) $m/z$ Calcd for $C_{16}H_{13}F_4NO_2H^+$ $[M + H]^+$ 328.0955, found 328.0957.

***N*-(2-Chlorobenzyl)-3,3,3-trifluoro-2-hydroxy-2-phenylpropanamide (5f)**

White solid; m.p.: 132–133 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62 (d, $J$ = 2.8 Hz, 2H, Ar-H), 7.50–7.37 (m, 2H, Ar-H), 7.35 (d, $J$ = 6.8 Hz, 2H, Ar-H), 7.26–7.11 (m, 2H, Ar-H), 6.62 (br, 1H, CONH), 4.80 (s, 1H, OH), 4.64–4.50 (m, 2H, CH$_2$NH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.27, 134.22, 134.12, 133.50, 129.76, 129.67, 129.61, 129.36, 128.97, 127.19, 126.27, 42.55; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ −74.11; HRMS (ESI) $m/z$ Calcd for $C_{16}H_{13}ClF_3NO_2H^+$ $[M + H]^+$ 343.0660, found 343.0651.

**_N_-(3,4-Dimethoxyphenethyl)-3,3,3-trifluoro-2-hydroxy-2-phenylpropanamide (5g)**

Colourless liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.68–7.32 (m, 5H, Ar-H), 6.87–6.49 (m, 3H, Ar-H), 6.09 (br, 1H, CONH), 4.86 (s, 1H, OH), 3.87 (s, 3H, Ar-$CH_3$), 3.82 (s, 3H, Ar-$CH_3$), 3.63–3.50 (m, 2H, $CH_2CH_2$), 2.74 (t, $J$ = 6.8 Hz, 2H, $CH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.12, 149.10, 147.84, 134.38, 130.40, 129.43, 128.85, 126.21, 120.62, 111.76, 111.40, 55.92, 55.78, 41.71, 34.73; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −74.11; HRMS (ESI) $m/z$ Calcd for $C_{19}H_{20}F_3NO_4H^+$ $[M + H]^+$ 384.1417, found 384.1419.

**3,3,3-Trifluoro-2-hydroxy-_N_-(4-methoxyphenyl)-2-phenylpropanamide (5i)**

Pale yellow solid; m.p.: 165–166 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (s, 1H, CONH), 7.74–7.70 (m, 2H, Ar-H), 7.49–7.43 (m, 3H, Ar-H), 7.38 (d, $J$ = 9.0 Hz, 2H, Ar-H), 6.86 (d, $J$ = 9.0 Hz, 2H, Ar-H), 4.63 (s, 1H, OH), 3.79 (s, 3H, $OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.82, 157.29, 134.05, 129.77, 129.33, 129.07, 126.35, 125.21, 122.36, 122.05, 114.29, 55.52; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −74.04; HRMS (ESI) $m/z$ Calcd for $C_{16}H_{13}F_3NO_3^-$ $[M - H]^-$ 324.0848, found 324.0861.

**_N_-(4-Chlorophenyl)-3,3,3-trifluoro-2-hydroxy-2-phenylpropanamide (5j)**

White solid; m.p.: 146–147 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (s, 1H, CONH), 7.72 (s, 2H, Ar-H), 7.46 (d, $J$ = 7.3 Hz, 5H, Ar-H), 7.31 (d, $J$ = 7.9 Hz, 2H, Ar-H), 4.39 (s, 1H, OH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.86, 134.90, 133.60, 130.66, 129.97, 129.22, 126.26, 125.05, 121.44; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −74.27; HRMS (ESI) $m/z$ Calcd for $C_{15}H_{10}ClF_3NO_2^-$ $[M - H]^-$ 328.0352, found 328.0351.

**2-(4-Ethylphenyl)-3,3,3-trifluoro-2-hydroxy-_N_-(4-methoxybenzyl)-propanamide (5k)**

Colourless liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (d, $J$ = 7.6 Hz, 2H, Ar-H), 7.24 (d, $J$ = 9.4 Hz, 2H, Ar-H), 7.09 (d, $J$ = 7.6 Hz, 2H, Ar-H), 6.84 (d, $J$ = 7.5 Hz, 2H, Ar-H), 6.29 (s, 1H, CONH), 4.80 (s, 1H, OH), 4.44 (ddd, $J$ = 34.3 Hz, $J$ = 14.9 Hz, $J$ = 5.2 Hz, 2H, $CH_2$), 3.79 (s, 3H, $OCH_3$), 2.66 (q, $J$ = 7.0 Hz, 2H), 1.23 (t, $J$ = 7.6 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.31, 158.19, 144.76, 130.60, 127.86, 127.79, 127.37, 125.30, 124.28, 121.43, 113.16, 54.25, 42.83, 27.41, 14.25; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −74.18; HRMS (MALDI) $m/z$ Calcd for $C_{19}H_{20}F_3NO_3Na^+$ $[M + Na]^+$ 390.1293, found 390.1288.

**3,3,3-Trifluoro-2-hydroxy-_N_-(4-methoxybenzyl)-2-(4-methoxyphenyl)-propanamide (5l)**

White solid; m.p.: 119–121 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$7.53 (d, $J$ = 8.6 Hz, 2H, Ar-H), 7.10 (d, $J$ = 8.6 Hz, 2H, Ar-H), 6.91 (d, $J$ = 9.0 Hz, 2H, Ar-H), 6.84 (d, $J$ = 8.7 Hz, 2H, Ar-H), 6.31 (s, 1H, CONH), 4.75 (s, 1H, OH), 3.82 (s, 3H $OCH_3$), 3.79 (s, 3H $OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.40, 160.35, 159.27, 128.86, 128.81, 127.81, 126.31, 122.47, 114.26, 114.23, 55.34, 55.30, 43.98; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −74.30; HRMS (ESI) $m/z$ Calcd for $C_{18}H_{17}F_3NO_4^-$ $[M - H]^-$ 368.1110, found 368.1117.

**3,3,3-Trifluoro-2-hydroxy-_N_-(4-methoxybenzyl)-2-(4-phenoxyphenyl)propanamide (5m)**

White solid; m.p.: 113–114 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 8.6 Hz, 2H, Ar-H), 7.37 (t, $J$ = 7.9 Hz, 2H, Ar-H), 7.19–7.07 (m, 3H, Ar-H), 7.01 (t, $J$ = 7.4 Hz, 4H, Ar-H), 6.85 (d, $J$ = 8.6 Hz, 2H, Ar-H), 6.31 (s, 1H, CONH), 4.78 (s, 1H, OH), 3.79 (s, 3H, $OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.15, 159.32, 158.61, 156.16, 129.95, 128.88, 128.75, 128.62, 128.07, 124.10, 119.59, 118.42, 114.25, 55.31, 44.03; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −74.24; HRMS (MALDI) $m/z$ Calcd for $C_{23}H_{20}F_3NO_4Na^+$ $[M + Na]^+$ 454.1242, found 454.1240.

**2-([1,1′-Biphenyl]-4-yl)-3,3,3-trifluoro-2-hydroxy-_N_-(4-methoxybenzyl)propanamide (5n)**

White solid; m.p.: 158–160 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.72–7.55 (m, 6H, Ar-H), 7.50–7.35 (m, 3H, Ar-H), 7.11 (d, $J$ = 8.6 Hz, 2H, Ar-H), 6.84 (d, $J$ = 8.7 Hz, 2H, Ar-H), 6.35 (s, 1H, CONH), 4.86 (s, 1H, OH), 3.78 (s, 3H, $OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.08, 159.30, 142.44, 139.93, 133.25, 128.93, 128.87, 127.89, 127.60, 127.14, 126.82, 114.25, 55.30, 44.07; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −74.05; HRMS (MALDI) $m/z$ Calcd for $C_{23}H_{20}F_3NO_3Na^+$ $[M + Na]^+$ 438.1293, found 438.1290.

## Acknowledgements

We are grateful for financial support for this work from the National Natural Science Foundation of China (21172124), the National Basic Research Science Foundation of China (2010CB126105), and the National Key Technologies R&D Program (2011BAE06B05).

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