An Efficient Solvent-Free Synthesis of 2-Hydroxy-2-(trifluoromethyl)-2H-chromenes Using Silica-Immobilized L-Proline

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Abstract: An efficient synthesis of 2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylates was carried out under solvent-free conditions in an oven or microwave oven via the Knoevenagel condensation of salicylaldehydes with ethyl trifluoroacetacetate followed by intramolecular cyclization in the presence of silica-immobilized L-proline. The structures of the title compounds were characterized by IR, 1H-NMR, 13C-NMR, HRMS and X-ray single crystal diffraction. The improved method described herein is economical, easily-operated and environmentally friendly. Furthermore, the catalyst can be recovered conveniently and reused without obvious loss of activity.

Keywords: solvent-free; 2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylates; synthesis; Knoevenagel condensation; silica-immobilized L-proline

1. Introduction

The chromene ring moiety has been identified as one of the privileged scaffolds for drug discovery due to its broad spectrum of biological activity [1–3]. Among various chromene isomers, 2H-chromenes are attracting much more interest from chemists because compounds that possess this group show a variety
of activities, including antiviral [4,5], anti-tumor [6,7], anti-bacterial/antimicrobial [8,9], fungicidal [10], antioxidative [11], insecticidal agents [12], and activator of potassium channels effects [13,14].

On the other hand, although introduction of fluorine atoms into organic compounds has been known as one of the best strategies for the enhancement or modification of their original biological activities [15–19], up to now there are limited reports on the preparation of 2-fluoroalkylated 2H-chromenes. Laurent et al. reported the synthesis of 2-(trifluoromethyl)- and 2-(perfluoroalkyl)-2-hydroxy-2H-chromenes by intramolecular cyclization of 3-(perfluoroalkyl)-3-phenoxypropenals in the presence of aluminum chloride [20]. Wang et al. reported the synthesis of 2-trifluoromethyl-2H-benzopyran-3-carboxylic acids from the reaction of substituted salicylaldehydes with ethyl trifluorocrotonate and found these potential as novel potent and selective cyclooxygenase-2 inhibitors [21–23]. Recently Chizhov et al. prepared ethyl 6-substituted 2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylates via the Knoevenagel condensation of salicylaldehydes with ethyl trifluoroacetoacetate in the presence of piperidinium acetate [24]. Li synthesized novel coumarin dyes bearing trifluoromethyl substituents by the condensation of 3-(trifluoroacetyl)coumarins with various arylhydrazines and studied their fluorescence activities [25]. Zhu’s group reported a Lewis acid-promoted reaction of 2-(trifluoromethyl)-2-hydroxy-2H-chromenes with indoles and thiophenols, and obtained both 2-functionalized-2-trifluoromethyl-3-ethoxycarbonyl-2H-chromenes and 4-functionalized-2-trifluoromethyl-3-ethoxycarbonyl-4H-chromenes [26,27]. To the best of our knowledge, however, there are no reports on the synthesis of 2-hydroxy-2-(trifluoromethyl)-2H-chromenes under solvent-free conditions.

Recently the progress in the field of solvent-free reactions has provided organic chemists with an efficient synthetic method of great promise [28–30]. Particularly this technique has been coupled with microwave-assisted organic synthesis (MAO), resulting in clean, easy-to-perform, cheap, safe and environmentally friendly conditions which are widely used as synthetic tools under “Green Chemistry” conditions [31,32]. Difficult recycling of homogeneous catalysts, such as piperidinium acetate, prompted us to find a suitable heterogeneous catalyst. L-Proline and its analogues have been extensively investigated as catalysts for many reactions; much effort has been dedicated to the immobilization and recycling of L-proline and its analogues with the assistance of organic and inorganic supports [33–35].

In continuation of our work on green synthetic strategies for the preparation of heterocyclic compounds [36,37], we were prompted to use a solvent-free methodology for the synthesis of 2-hydroxy-2-(trifluoromethyl)-2H-chromenes from salicylaldehydes and ethyl trifluoroacetoacetate under solvent-free conditions in the presence of silica-immobilized L-proline (L-proline/SiO2).

2. Results and Discussion

2.1. Synthesis

Initially, the reaction of salicylaldehyde (1a) and ethyl trifluoroacetoacetate (2) was tested without any catalyst under neat conditions, but almost no product was obtained without or with microwave irradiation (Scheme 1 and Table 1, entries 1–2). After adding 20 mol% of L-proline/SiO2, the reaction afforded the product 3a in 80% (entry 5) and 69% (entry 3) yield, respectively, with or without MW irradiation (MWI), under solvent-free conditions. Thus, the reaction could be catalyzed by
L-proline/SiO₂ and the reaction rate could be increased by MWI. Increasing the loading of catalyst improved the yield and shortened the reaction time (entries 4–7), however, the yield did not increase when the amount of the catalyst was more than 30 mol% of substrate 1a (entry 7). Next, the reaction with different ratios of 1a to 2 was examined under 30 mol% L-proline/SiO₂ catalysis. It was observed that the variation of this ratio had a great influence on the yield. The yield of 3a reached a maximum at the molar ratio of 1:1.5 and 1:2. When the quantity of compound 2 continued to increase, yield was reduced and more side-products were observed according to HPLC (entries 10–11). Therefore, the ratio of 1a to 2 was optimized as 1:1.5. After the product was extracted thoroughly with dichloromethane, the separated catalyst was subjected to another cycle with fresh reactants under similar conditions. It was observed that the yield was nearly the same. The above procedure was repeated for three cycles, and no substantial loss in the catalytic activity of the immobilized catalyst was observed (entries 12–13).

**Scheme 1.** Solvent-free synthesis of compound 3a.

![Scheme 1](image)

**Table 1.** Optimization for the synthesis of 2H-chromene 3a.

| Entry | Mol ratio of 1a and 2 | Loading of catalyst (mol%) | Time | Yield (%)
|-------|----------------------|-----------------------------|------|--------|
| 1     | 1:1.5                | 0                           | 6 h  | 0.5    |
| 2     | 1:1.5                | 0                           | 20 min | 0.7   |
| 3     | 1:1.5                | 20                          | 6 h  | 69     |
| 4     | 1:1.5                | 10                          | 15 min | 38    |
| 5     | 1:1.5                | 20                          | 18 min | 80    |
| 6     | 1:1.5                | 30                          | 14 min | 82    |
| 7     | 1:1.5                | 40                          | 9 min | 82     |
| 8     | 1:1                  | 30                          | 17 min | 43    |
| 9     | 1:2                  | 30                          | 14 min | 82    |
| 10    | 1:2.5                | 30                          | 15 min | 56    |
| 11    | 1:3                  | 30                          | 15 min | 38    |
| 12    | 1:1.5                | 30                          | 14 min | 82    |
| 13    | 1:1.5                | 30                          | 14 min | 80    |

| Reaction conditions: 1a (7 mmol), L-proline/SiO₂ (4.5 g), MWI (126 W). | Isolated yield based on 1. All yields are the average of two runs based on fresh catalyst. | Heating in the oven at 80 °C under solvent-free condition. | Catalyst was reused in the second run. | Catalyst was reused in the third run. |

To evaluate the efficiency of this methodology, various substituted salicylaldehydes 1b–1l were next reacted with ethyl trifluoroacetoacetate under optimal conditions (Scheme 2). The results are shown in Table 2.
Scheme 2. Solvent-free synthesis of compound 3a–l.

\[
\begin{array}{c}
\text{1a-1l} + 2 \rightarrow 3a-3l
\end{array}
\]

Table 2. Synthesis of 2-hydroxy-2-(trifluoromethyl)-2H-chromenes 3a–l under optimum conditions.

| Entry | R₁ | R₂ | R₃ | Product | MWI (126 W) | Without MWI b |
|-------|----|----|----|---------|-------------|---------------|
|       |    |    |    |         | Time (min)  | Time (h)      | Yield a (%)   | Yield a (%)   |
| 1     | H  | H  | H  | 3a      | 12          | 6             | 75            |               |
| 2     | Cl | H  | H  | 3b      | 17          | 6             | 81            |               |
| 3     | Br | H  | H  | 3c      | 16          | 8             | 77            |               |
| 4     | Cl | H  | Cl | 3d      | 12          | 8             | 80            |               |
| 5     | Br | H  | Br | 3e      | 16          | 6             | 81            |               |
| 6     | H  | H  | OMe| 3f      | 12          | 6             | 69            |               |
| 7     | H  | OMe| H  | 3g      | 8           | 8             | 65            |               |
| 8     | H  | H  | OEt| 3h      | 16          | 8             | 66            |               |
| 9     | Me | H  | H  | 3i      | 18          | 6             | 65            |               |
| 10    | H  | OH | H  | 3j      | 17          | 8             | 67            |               |
| 11    | NO₂| H  | H  | 3k      | 6           | 2             | 83            |               |
| 12    | H  | -CH=CH- | H | 3l      | 18          | 8             | 68            |               |

a Isolated yield based on 1. b Heating in the oven at 80 °C under solvent-free conditions.

As can be seen from Table 2, electron-withdrawing (entries 2–5, entry 11) and electron-donating groups (entries 7–10, entry 12) at various positions of the benzene rings are well tolerated. The aromatic aldehydes with electron-donating groups afforded lower yields in comparison with those with electron-withdrawing groups. For instance, 4-methoxy-2-hydroxybenzaldehyde (1g) and 4-hydroxy-2-hydroxybenzaldehyde (1j) gave products 3g and 3j with yields of 68% and 66% under MWI, respectively (entries 7 and 10), but compounds 1b and 1k afforded the products 3b and 3k with yields of 89% and 92% (entries 2 and 11), respectively. On the other hand, the reactions required longer times and gave relatively lower yields by the alternative method employing heating in the oven at 80 °C. In most cases the microwave-assisted conditions were found to be superior to those without MWI, and the chromenes 3a–3l were obtained in better yields (66%–92%), compared with yields of 65%–83% in the same reaction without MWI.

The proposed catalytic cycle is shown in Scheme 3. The L-proline-catalyzed reaction proceeds via an enamine intermediate A. Intermediate A reacts with salicylaldehyde via transition state B to give intermediate C, which produced the Knoevenagel product E through hydrolysis and dehydration. The subsequent cyclization occurs to yield 3a by addition of phenoxide ion to the more electrophilic carbonyl group rather than to the ester group forming intermediate G.
2.2. Structural Characterization of Chromenes 3a–1

The chemical structures of chromenes 3a–1 were characterized by IR, \(^1\)H-NMR, \(^{13}\)C-NMR and HRMS. All of the data in the spectra were in good accordance with the structures. The IR spectra of 3a–1 displayed OH absorption in the range 3110–3443 cm\(^{-1}\), and the intensive absorption bands in the range 1671–1721 cm\(^{-1}\) attributed to the C=Os in the ester groups. The diagnostic signal for the proton H-4 in chromenes 3a–1 appeared at 7.64–8.47 ppm, which is usually in lower field than common aromatic protons are. The signal for -OH at C-2 in 3a–1, which appeared at 7.22–9.60 ppm, was shifted downfield because of the formation of intramolecular H-bonding between the OH and O atom in the carboxyl group and neighboring electron-withdrawing CF\(_3\) group. In the \(^{13}\)C-NMR spectra of 3a–1, the quartets of CF\(_3\) and C-2 atom with their corresponding coupling constants \(^1\)J\(_{C,F}\) = 289–291 Hz and \(^2\)J\(_{C,F}\) = 33.6–36.4 Hz, appeared at 122.0–123.0 ppm and 95.2–96.6 ppm respectively, similar to the related data [24,38]. Compounds 3a–1 all showed the molecular-ion peak [M+Na]\(^+\) in the high resolution mass spectrum, matching with the calculated data.

The structures of 2\(H\)-chromenes were further confirmed by the X-ray diffraction determination of single crystals of compounds 3a and 3c (single crystal X-ray diffraction data of compounds 3a and 3c are deposited with CCDC Nos. 845964 and 845962, respectively). The perspective and packing views are shown in Figures 1a,b and 2a,b respectively. The crystal data and refinement details are given in Table 3. It is seen that compounds 3a and 3c are isomorphous, and they crystallize in the monoclinic space P2\(1\)/c with four molecules in the unit cell. The value of O1-C8 bond length is 1.374 (5) Å in 3c, which is slightly shorter, compared with 1.396(4) Å in 3a. This is probably due to the inductive negative effect of the halogen atom on the lactone O atom (O1) lone pair of electrons. In 3a and 3c molecules, the carboxylate carbonyl groups (O3) are out of the plane defined by atoms C2-C9 by 3.6 and 6.6°, respectively. The 2-hydroxy groups (O2) are out of the plane defined by atoms O1-C9 by 2.5
and 3.4°, respectively. The above mentioned hydroxyl deviations from planarity seem to attribute to sp³ hybridization of C1. It is interesting to note that the replacement of H by Br does not alter the space group. In the crystal structures of chromenes 3a and 3c, no intermolecular hydrogen-bonds are formed because compounds 3a and 3c present an anti conformation between the ethoxy (O4) and the hydroxy (O2). Thereby, the carboxylate carbonyl O atom (O3) acts as a hydrogen-bond acceptor allowing the formation of intramolecular hydrogen-bond, and the detailed data for intramolecular hydrogen bond are shown in Table 4. Molecules of 3a and 3c are packed in an offset face-to-face arrangement and form a layered stack.

**Figure 1.** The molecular structures of 3a and 3c, showing the atomic numbering scheme and displacement ellipsoids draw at the 30% probability level.

**Figure 2.** View of the molecular packing in 3a and 3c.
Table 3. Crystal data and structure refinement for 3a and 3c.

|        | 3a                          | 3c                          |
|--------|-----------------------------|-----------------------------|
| formula| $\text{C}_{13}\text{H}_{11}\text{F}_{3}\text{O}_{4}$ | $\text{C}_{13}\text{H}_{10}\text{BrF}_{3}\text{O}_{4}$ |
| $F_w$  | 288.22                      | 367.12                      |
| crystal system | monoclinic                  | monoclinic                  |
| space group   | $P2(1)/c$                   | $P2(1)/c$                   |
| $a$ (Å)       | 8.415 (1)                   | 7.085 (2)                   |
| $b$ (Å)       | 16.604 (3)                  | 12.831 (3)                  |
| $c$ (Å)       | 9.443 (9)                   | 15.526 (3)                  |
| $\beta$ (deg)| 97.51 (3)                   | 93.52 (3)                   |
| $V$ (Å$^3$)   | 1308.2 (5)                  | 1408.9 (5)                  |
| $Z$            | 4                           | 4                           |
| $T$ (K)       | 293 (2)                     | 293 (2)                     |
| $D_{\text{calc}}$ (Mg m$^{-3}$) | 1.463                      | 1.731                      |
| $\mu$ (mm$^{-1}$) | 0.135                      | 2.964                      |
| $R_1$ ($I>2\sigma(I)$) | 0.0792                     | 0.0492                     |
| $R_1$ (all data) | 0.0829                     | 0.0651                     |
| $wR_2$ ($I>2\sigma(I)$) | 0.2261                     | 0.1433                     |
| $wR_2$ (all data) | 0.2310                     | 0.1553                     |
| GOOF      | 1.052                       | 1.074                       |

Table 4. Hydrogen bonding distances [Å] and angles [°] for 3a and 3c.

| Crystal | D-H·  A | d(D-H) | d(D·A) | D-H·  A |
|---------|---------|--------|--------|---------|
| 3a      | O2-H2· O3 | 0.82   | 2.71 (1) | 143     |
| 3c      | O2-H2· O3 | 0.82   | 2.64 (1) | 147     |

3. Experimental

3.1. General

Infrared spectra were recorded with a Nicolet IS10 Fourier Transform Infrared Spectrophotometer (4,000–400 cm$^{-1}$) (KBr pellets). $^1$H and $^{13}$C-NMR spectra of CDCl$_3$ solutions were obtained on a Bruker DPX-400 or Advance 300 Spectrometer, respectively. $^{19}$F-NMR spectra were recorded in CDCl$_3$ without an internal standard. HPLC analyses for the qualitative and quantitative analysis of the products were carried out using an Agilent 1200 pump equipped with an Agilent 1200 detector. High resolution mass spectrometry data were measured on a Waters Q-Tof micro™ instrument with an electrospray ionization source (ESIMS). X-ray diffraction data were collected on a Rigaku RAXIAS-IV type diffractometer. Melting points were determined on a X-5 digital microscopic melting-point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. A household microwave oven (Haier MM-2270MG, Qingdao, China) and electrothermal drying oven (Qin Stewart 101-2AB, Tianjin, China) were used for heating the reaction mixtures.

X-ray Crystallography parameters for data collection and refinement of the compounds are summarized in Table 1. Intensities were collected on a Rigaku Saturn 724 CCD diffractometer (Mo-Ka, $\lambda = 0.71073$ Å) at a temperature of 293 K using the SMART and SAINT programs [39]. The
structures were solved by direct method and refined on F2 by full-matrix least-squares methods with SHELXTL-97 crystallographic software package [40]. All the non-hydrogen atoms were refined with anisotropic thermal displacement coefficients. The hydrogen atoms were assigned with common isotropic displacement factors and included in the final refinement by using geometrical restraints.

All solvents and reagents were used without further purification.

3.2. Preparation of Catalyst L-Proline/SiO2

Silica (45 g, 200 mesh) was added to a solution of L-proline (22 mmol) in deionized water (50 mL). After being stirred at room temperature for 30 min, the mixture was first dried at room temperature overnight, and then heated in an oven for 6 h at 50 °C. The resulting immobilized catalyst was kept in a desiccator for use.

3.3. General Synthetic Procedures for Compounds 3a–3l

3.3.1. Oven Heating Procedure

In a typical experiment of Knoevenagel condensation reaction catalyzed by immobilized L-proline, aldehyde (7 mmol), ethyl trifluoroacetoacetate (14 mmol) and 4.5 g of L-proline/SiO2 were thoroughly ground in a mortar. The mixture was charged in a microwave tube (capacity 10 mL), then sealed with polytetrafluoroethylene film and heated in an oven at 80 °C for 6–8 h (monitored by HPLC). The mixture was allowed to cool to room temperature. Ethyl acetate was added and the resulting mixture was filtered, and the residue was sequentially washed with ethyl acetate or dichloromethane for at least three times. The combined solution was evaporated under reduced pressure, and the crude product was recrystallized from ethanol or ethyl acetate.

3.3.2. Microwave Irradiation Procedure

The same procedure and dosage was applied as above. After being mixed fully, the mixture was put into a microwave tube, sealed, irradiated in the microwave oven under 126 W power. The reaction was monitored by HPLC. After the aldehyde had consumed, the irradiation was terminated and the mixture was allowed to cool to room temperature. The same work-up was as above.

**Ethyl 2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate (3a)** [24]. White solid, yield 76%, m.p. 103.4–104.2 °C (Lit. 102.0–103.0 °C). IR cm⁻¹: 3,300, 1,695, 1,636, 1,608, 1,575, 1,489; ¹H-NMR (CDCl₃, 300 MHz) δ: 1.39 (t, J = 7.2 Hz, 3H, CH₃), 4.36 (q, J = 7.2 Hz, 2H, CH₂), 6.99–7.03 (m, 2H, H-6, H-8), 7.25 (dd, J = 7.9, 1.7 Hz, 1H, H-5), 7.36 (m, 1H, H-7), 7.54 (s, 1H, OH), 7.78 (s, 1H, H-4); ¹³C-NMR (CDCl₃, 75 MHz) δ: 13.9 (CH₃), 62.6 (CH₂), 95.2 (q, J_C,F = 34.8 Hz, CF₃), 114.6, 115.8, 117.5, 122.6 (q, J_C,F = 290 Hz, CF₃), 122.6, 129.5, 133.9, 139.3, 152.5, 166.7 (C=O); HRMS: calcd for m/z (C₁₃H₁₁F₃O₄ + Na)⁺: 311.0507; found: 311.0536.

**Ethyl 6-chloro-2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate (3b)**. White solid, m.p. 115.5–116.9 °C. IR cm⁻¹: 3,314, 1,700, 1,636, 1,565, 1,460; ¹H-NMR (CDCl₃, 300 MHz) δ: 1.40 (t, J = 7.2 Hz, 3H, CH₃), 4.37 (q, J = 7.2 Hz, 2H, CH₂), 6.98 (d, J = 8.7 Hz, 1H, H-8),
Ethyl 6-bromo-2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate (3c) [24]. Light yellow solid, m.p. 107.0–108.4 °C. IR cm$^{-1}$: 3,248, 1,684, 1,629, 1,600, 1,564, 1,478; $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$: 1.39 (t, $J = 7.2$ Hz, 3H, CH$_3$), 4.41 (q, $J = 7.2$ Hz, 2H, CH$_2$), 7.17 (d, $J = 2.4$ Hz, 1H, H-7), 7.41 (d, $J = 2.4$ Hz, 1H, H-5), 7.56 (broad, 1H, OH), 7.64 (s, 1H, H-4); $^{13}$C-NMR (CDCl$_3$, 75 MHz) $\delta$: 13.9 (CH$_3$), 62.9 (CH$_2$), 95.6 (q, $^2J_{CF} = 36.4$ Hz, CCF$_3$), 101.0, 109.7, 138.8, 148.6, 166.0 (C=O); HRMS: calcd for m/z (C$_{13}$H$_9$Br$_2$F$_3$O$_4$ + Na)$^+$: 466.8764; found: 466.8764.

Ethyl 6,8-dichloro-2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate (3d). White solid, m.p. 114.0–115.1 °C. IR cm$^{-1}$: 3,251, 1,678, 1,624, 1,554, 1,470; $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$: 1.40 (t, $J = 5.4$ Hz, 3H, CH$_3$), 4.38 (q, $J = 5.4$ Hz, 2H, CH$_2$), 7.33 (d, $J = 2.4$ Hz, 1H, H-7), 7.47 (s, 1H, OH), 7.64 (s, 1H, H-4), 7.70 (d, $J = 2.4$ Hz, 1H, H-5); $^{19}$F-NMR (CDCl$_3$, 376.5 MHz) $\delta$: -87.15 (s, 3F); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$: 14.0 (CH$_3$), 55.6 (CH$_3$O), 62.1 (CH$_2$), 95.6 (q, $^2J_{CF} = 34.8$ Hz, CCF$_3$), 110.9, 114.7, 116.9, 120.1, 122.2 (q, $^1J_{CF} = 290$ Hz, CF$_3$), 130.7, 137.3, 147.5, 166.7 (C=O); HRMS: calcd for m/z (C$_{14}$H$_{13}$F$_3$O$_5$ + Na)$^+$: 341.0623; found: 341.0692.

Ethyl 2-hydroxy-8-methoxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate (3f). Light yellow solid, m.p. 99.4–99.9 °C. IR cm$^{-1}$: 3,328, 1,699, 1,637, 1,610, 1,581, 1,483; $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$: 1.40 (t, $J = 7.2$ Hz, 3H, CH$_3$), 3.89 (s, 3H, CH$_3$O), 4.37 (q, $J = 7.2$ Hz, 2H, CH$_2$), 6.86 (dd, $J = 7.2$, 1.9 Hz, 1H, H-7), 6.96–7.02 (m, 2H, H-5, H-6), 7.50 (s, 1H, OH), 7.76 (s, 1H, H-4); $^{13}$C-NMR (CDCl$_3$, 75 MHz) $\delta$: 14.0 (CH$_3$), 56.4 (OCH$_3$), 62.4 (CH$_2$), 95.4 (q, $^2J_{CF} = 34.8$ Hz, CCF$_3$), 114.8, 117.0, 118.2, 121.2, 122.4, 122.6 (q, $^1J_{CF} = 290$ Hz, CF$_3$), 139.4, 142.0, 147.5, 166.7 (C=O); HRMS: calcd for m/z (C$_{14}$H$_{13}$F$_3$O$_5$ + Na)$^+$: 341.0623; found: 341.0692.
Ethyl 8-ethoxy-2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate (3h). White solid, m.p. 112.5–113.9 °C. IR cm⁻¹: 3,301, 1,681, 1,632, 1,610, 1577, 1,486; ¹H-NMR (CDCl₃, 300 MHz) δ: 1.37–1.44 (m, 6H, 2CH₃), 4.07–4.17 (m, 2H, CH₂), 4.37 (q, J = 7.2 Hz, 2H, CH₂), 6.85–6.88 (dd, J = 7.5, 1.7 Hz, 1H, H-7), 6.91–7.03 (m, 2H, H-5, H-6), 7.46 (s, 1H, OH), 7.76 (s, 1H, H-4); ¹³C-NMR (CDCl₃, 75 MHz) δ: 13.9 (CH₃), 14.9 (CH₃), 62.3 (CH₂), 65.4 (CH₂), 95.9 (q, J CF = 34.8 Hz, CF₃), 114.7, 118.3, 119.3, 121.4, 122.3, 122.6 (q, J CF = 290 Hz, CF₃), 139.6, 142.5, 146.7, 166.7 (C=O); HRMS: calcd for m/z (C₁₄H₁₃F₃O₅ + Na)⁺: 341.0664; found: 341.0664.

Ethyl 2-hydroxy-6-methyl-2-(trifluoromethyl)-2H-chromene-3-carboxylate (3i). White solid, m.p. 81.8–82.9 °C. IR cm⁻¹: 3,315, 1,682, 1,633, 1,613, 1,582, 1,493; ¹H-NMR (CDCl₃, 400 MHz) δ: 1.37 (t, J = 7.2 Hz, 3H, CH₃), 2.28 (s, 3H, CH₃), 4.36 (q, J = 7.2 Hz, 2H, CH₂), 6.90 (d, J = 8.4 Hz, 1H, H-8), 7.04 (s, 1H, H-5), 7.11 (dd, J = 8.4, 1.6 Hz, 1H, H-7), 7.22 (s, 1H, OH), 7.73 (s, 1H, H-4); ¹³C-NMR (CDCl₃, 100 MHz) δ: 13.9 (CH₃), 20.2 (CH₃), 62.3 (CH₂), 95.3 (q, J CF = 34.7 Hz, CF₃), 114.6, 115.6, 117.3, 122.7 (q, J CF = 291 Hz, CF₃), 129.6, 132.1, 134.6, 139.5, 150.5, 166.8 (C=O); HRMS: calcd for m/z (C₁₄H₁₃F₃O₄ + Na)⁺: 325.0666; found: 325.0657.

Ethyl 2,7-dihydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate (3j). White solid, m.p. 152.0–153.2 °C. IR cm⁻¹: 3,110, 1,696, 1,608, 1,510, 1,460; ¹H-NMR (CDCl₃, 400 MHz) δ: 1.26 (t, J = 7.2 Hz, 3H, CH₃), 4.14–4.25 (m, 2H, CH₂), 6.38 (s, 1H, H-8), 6.49 (dd, J = 8.4, 1.6 Hz, 1H, H-6), 7.34 (d, J = 8.4 Hz, 1H, H-5), 7.87 (s, 1H, H-4) 8.83 (broad, 1H, OH), 10.37 (broad, 1H, OH); ¹³C-NMR (CDCl₃, 100 MHz) δ: 14.3 (CH₃), 60.5 (CH₂), 96.3 (q, J CF = 40.0 Hz, CF₃), 102.1, 109.6, 110.5, 114.8, 122.6 (q, J CF = 288 Hz, CF₃), 131.3, 139.4, 154.0, 162.7, 163.4 (C=O); HRMS: calcd for m/z (C₁₄H₁₁F₃O₅ + Na)⁺: 327.0456; found: 327.0455.

Ethyl 2-hydroxy-6-nitro-2-(trifluoromethyl)-2H-chromene-3-carboxylate (3k) [24]. Light yellow solid, m.p. 120.0–120.7 °C (Lit. 120–120.5 °C). IR cm⁻¹: 3,426, 1,721, 1,619, 1,517, 1,478; ¹H-NMR (CDCl₃, 400 MHz) δ: 1.32 (t, J = 7.2 Hz, 3H, CH₃), 4.29 (q, J = 7.2 Hz, 2H, CH₂), 7.28 (d, J = 9.2 Hz, 1H, H-8), 8.19 (s, 1H, H-4), 8.29 (dd, J = 9.2, 2.4 Hz, 1H, H-7), 8.61 (d, J = 2.4 Hz, 1H, H-5), 9.60 (broad, 1H, OH); ¹³C-NMR (CDCl₃, 100 MHz) δ: 14.1 (CH₃), 61.3 (CH₂), 97.1 (q, J CF = 34.5 Hz, CF₃), 116.8, 117.7, 121.5, 122.1 (q, J CF = 288 Hz, CF₃), 125.6, 128.5, 137.0, 142.4, 156.5, 162.6 (C=O). HRMS: calcd for m/z (C₁₃H₁₀F₃O₆ + Na)⁺: 356.0358; found: 356.0360.

Ethyl 2-hydroxy-2-(trifluoromethyl)-2H-benzo[h]chromene-3-carboxylate (3l). Yellow solid, m.p. 123.9–124.8 °C. IR cm⁻¹: 3,224, 1,671, 1,614, 1,592, 1,570, 1,517, 1,465; ¹H-NMR (CDCl₃, 400 MHz) δ: 1.48 (t, J = 7.2 Hz, 3H, CH₃), 4.46 (q, J = 7.2 Hz, 2H, CH₂), 7.24 (m, 1H, ArH), 7.48 (m, 1H, ArH), 7.62 (m, 1H, ArH), 7.80–7.82 (m, 2H, ArH, OH), 7.89 (m, 1H, ArH), 8.06 (m, 1H, ArH), 8.47 (d, J = 3.6 Hz, 1H, ArH); ¹³C-NMR (CDCl₃, 100 MHz) δ: 14.1 (CH₃), 62.5 (CH₂), 95.6 (q, J CF = 35.0 Hz, CF₃), 110.6, 112.3, 116.6, 120.8, 122.7 (q, J CF = 291 Hz, CF₃), 125.0, 128.3, 128.9, 129.5, 130.1, 134.9, 135.1, 152.2, 167.0 (C=O). HRMS: calcd for m/z (C₁₇H₁₃F₃O₄ + Na)⁺: 361.0664; found: 361.0663.
4. Conclusion

In summary, silica-immobilized L-proline has been employed as an efficient catalyst for the solvent-free preparation of 2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylates. The reaction proceeded via a tandem condensation-cyclization process and gave the title products in good yields. This environmentally friendly synthetic method possesses such advantages as operational simplicity, environmentally friendliness, good catalytic performance, reusability, and reduction of time when combined with MW irradiation.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/18/10/11964/s1.

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Conflicts of Interest

The authors declare no conflict of interest

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*Sample Availability*: Samples of the compounds are available from the authors.

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