Chemoselectivity in the Reactions Between Ethyl 4,4,4-Trifluoro-3-oxobutanoate and Anilines: Improved Synthesis of 2-Trifluoromethyl-4- and 4-Trifluoromethyl-2-quinolinones

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Abstract: Chemoselectivity in the reactions between ethyl 4,4,4-trifluoroacetoacetate (ethyl 4,4,4-trifluoro-3-oxobutanoate) and various anilines was systematically studied as a function of the reaction conditions used (solvent/temperature, catalyst). The results obtained allowed chemoselective (>90%) synthesis of the corresponding ethyl 3-arylamino-4,4,4-trifluorobut-2-enoates and N-aryl-4,4,4-trifluoro-3-oxobutyramides, which were cyclized to afford 2-trifluoromethyl-4-quinolinones and 4-trifluoromethyl-2-quinolinones, respectively.

Key words: chemoselectivity, enamino esters, keto amides, quinolines, fluorine

Recently Schlosser’s group reported a series of publications on synthetically useful elaboration of 2- and 4-(trifluoromethyl)quinolinones 1 and 2 into various polyfunctional trifluoromethyl-containing quinoline derivatives.1–4 While the chemistry developed by the authors’ features high regioselectivity and chemical yields, the synthetic usefulness of the method as a whole is nullified by the poor availability of the starting quinoliones 1 and 2.1–4 In our own experience we faced the same logistic problems of relatively low chemical yields of the corresponding α-fluoroalkyl-containing imines/enamines, starting materials for preparing fluorinated amines and amino acids by the biomimetic transamination methodology developed by us.5–8 To solve the problem of low chemo/regioselectivity and unsatisfactory chemical yields in the reactions between highly electrophilic and/or polyfunctional trifluoromethyl-containing carbonyl compounds (e.g. ethyl 4,4,4-trifluoroacetoacetate, ethyl 3,3,3-trifluoropyruvate, and 1,1,1,5,5,5-hexafluoropentane-2,4-dione) with benzylamine derivatives, we conducted a systematic study of these reactions and found proper conditions and reagents allowing for highly regio/chemoselective and efficient preparation of the target fluorinated imines/enamines. Drawing inspiration from our recent results9 and taking into account the obvious similarity in the nature of the problems faced by Schlosser’s1,2 and our groups, we decided to apply our approach to study the regioselectivity in the reactions between ethyl 4,4,4-trifluoroacetoacetate (3) and anilines 4.

Here we report synthetically useful procedures for chemoselective (>90%) preparation of the corresponding ethyl 4,4,4-trifluoro-3-phenylaminobut-2-enoates 5 and 4,4,4-trifluoro-3-oxo-N-phenylbutyramides 6, which were cyclized, using the literature methods, to afford 2-trifluoromethyl-4-quinolinones 1 and 4-trifluoromethyl-2-quinolinones 2, respectively.

The reaction dichotomy or chemodivergence can be an irritating synthetic obstacle or a pleasant synthetic bonus provided by the chemistry of polyfunctional organic compounds. However, search for reaction conditions allowing, at will, selective synthesis of either of two or more different target products, using the same starting compounds, is not an ordinary task. For instance, ethyl trifluoroacetoacetate (3) react with aniline 4 (Scheme 1) to afford 2-trifluoromethyl-4-quinoline (1) or 4-trifluoromethyl-2-quinoline (2), depending on the reaction conditions used. While these methods feature attractive

Scheme 1

Yields: 46-79%
operationally convenient conditions, their practical use is plagued by the chemical yields. Thus, 2-trifluoromethyl-4-quinolinones 11 are available in moderate-to-low yields by heating the starting compounds 3 and 4 in polyphosphoric acid. On the other hand, preparation of 4-trifluoromethyl-2-quinolinones 22 by the direct condensation of keto ester 3 with anilines 4, followed by heating of the resulting mixture in 75% sulfuric acid, gives disappointingly low yields of the target products 2.

There are several alternative approaches available in the literature for preparing quinolinones (quinolinols) 2. In one of them,11 quinoline-4-carboxylic acid was first fluorinated with SF₅ to give the corresponding trifluoromethyl derivative (69%) which was oxidized with 30% H₂O₂ to afford 4-(trifluoromethyl)quinoline 1-oxide (68.5%). Thermal isomerization of the N-oxide, thus prepared, in a solution of Ac₂O afforded the target 2 in 74% yield. Another method12 focused on preparation of amides 6 (Scheme 1), used as a starting material for further Knorr–Conrad–Limpach cyclization to prepare quinolinones (quinolinols) 2. In this method α,α-dihydroperfluorolakanoic acid, α,α-dihydroperfluorobutanoic acid in particular, was converted to the corresponding N-arylamide (PCC, >95%), which was dehydrofluorinated (Et₃N, NaHCO₃, >95%) to give N-aryl-3-fluoro-3-fluoroalkyl-prop-2-enamides. These α,β-unsaturated amides were converted to the target N-aryl-3-oxoamides 6 using a two-step procedure including Michael addition reaction with pyrrolidine and hydrolysis of the corresponding addition products.

Considering these methods, one may agree that despite the synthetically useful chemical yields they have in common one significant drawback, which is the methodological deficiency of a multi-step procedure. From this point of view, the direct condensation between the keto ester 3 and anilines 4 (Scheme 1) holds an apparent advantage of a straightforward procedure, provided of course, that the target products can be obtained in chemical yields comparable with the literature methods. Therefore, we decided to study the reactions between keto ester 3 and anilines 4 in detail to realize the methodological potential of this approach for preparing trifluoromethyl-containing quinolinones (quinolinols) 1 and 2. Assuming that the Knorr–Conrad–Limpach cyclization of enamino esters 5 and amides 6 do not pose any synthetic problem, we focused on searching for reaction conditions that would lead to the chemoselective preparation of key intermediates 5 and 6.

Brief analysis of the reaction conditions for the condensations of 3 and 4 (Scheme 1) allowed us to notice that the reactions conducted under the acidic conditions give a preference for the formation of the intermediate enamino ester 5, while under the neutral, or slightly basic (aniline) conditions amide 6 is the favored product. This conclusion is in good agreement with the trend of chemoselectivity we had observed before in the reactions of keto ester 3 with benzylamines.9 Therefore, we decided to try the reaction between 3 and acetic acid salt of aniline 4a (Scheme 2) using chloroform as a solvent, the conditions that allowed us to prepare N-benzylanilino ester 8 with virtually complete chemoselectivity.9 Under these conditions the reaction proceeded at a low rate and, quite surprisingly, with the formation of noticeable amounts of enamino amide 7a (Table 1, entry 1). Application of the trifluoroacetic acid salt of 4a in the reaction with 3 resulted in an improved ratio of enamino ester 5a which was isolated in 90% yield (entry 2). To briefly assess the generality of the reaction, we conducted condensations of keto ester 3 with the trifluoroacetates of p-methyl-4b, p-methoxy-4c and p-fluoroanilines 4d (entries 3–5). In all cases the target compounds 5b–d were isolated with more than 90% chemical yields rendering the reaction conditions described here synthetically useful for chemoselective synthesis of enamino esters 5, key intermediates for preparation of various derivatives of 2-trifluoromethyl-4-quinolinones 1.

As mentioned above, formation of enamino amide 7a was rather unexpected since in the reaction between keto ester 3 and the acetate of benzylamine, conducted under the same conditions, the enamino ester 8 was obtained as the sole product.9 Therefore we decided to study this intriguing difference in reactivity in detail. Thus, use of benzene as a solvent (higher reaction temperature) for the reaction of 3 with trifluoroacetate of 4a resulted in a substantially increased formation of enamino amide 7a (entry 6 vs 2). Further increase in the reaction temperature (toluene as a solvent) and application of 4a salt with the weaker acetic acid allowed the preparation of amide 7a in synthetically useful chemical yield (entry 7 vs 6 and 2).

Scheme 2

We believe that the difference in the outcome of the reactions of keto ester 3 with benzylamine and aniline stems from a low stability of enamino esters 5a-d and lower basicity of aniline as compared with that of benzylamine. Previously we showed that benzylamine derived compound 8 exists exclusively in enamino form stabilized by intramolecular hydrogen bond. We have also demonstrated that due to the low electrophilicity of the conjugated ester function in 8, it did not react with excess of benzylamine or its salts.\(^9\) By contrast, as it follows from NMR data, enamino esters 5a-d exist as a mixture with the corresponding ketimines 5a-d in which the ester group is relatively electrophilic to react with a nucleophile. Furthermore, taking into account the low basicity of anilines 4a-d, we can assume that their salts, in particular acetates, might be unstable at high temperatures (benzene, toluene) generating free bases (benzene, toluene) giving any improvement, probably due to noticeable solubility of product 6a in the aqueous phase. Though successful and operationally simple, as compared with the literature methods, this approach still cannot be rendered synthetically efficient, affording the target compounds 6 in moderate yields via two-step (condensation-hydrolysis) procedure. Therefore, we continued a search for convenient and efficient reaction conditions for a more efficient preparation of amides 6 and thus quinolinones 2.

### Table 1

Reactions of Keto Ester 3 with Salts 4a-d. Synthesis of Enamino Esters 5a-d and Enamino Amides 7a-d (Scheme 2)\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Acid</th>
<th>Ratio(^b)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Ratio(^c)</th>
<th>Yield of 5a-d(^c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHCl(_3)</td>
<td>AcOH</td>
<td>1:1.5</td>
<td>50</td>
<td>95</td>
<td>15 (%93:7)/%85 (%78:22)</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>CHCl(_3)</td>
<td>TFA</td>
<td>1:1.5</td>
<td>68</td>
<td>&gt;99</td>
<td>9 (%82.18)/%91 (%99:1)</td>
<td>92</td>
</tr>
<tr>
<td>3(^f)</td>
<td>CHCl(_3)</td>
<td>TFA</td>
<td>1:1.5</td>
<td>70</td>
<td>99</td>
<td>10 (%&gt;99:1)/%90 (%85:15)</td>
<td>96</td>
</tr>
<tr>
<td>4(^g)</td>
<td>CHCl(_3)</td>
<td>TFA</td>
<td>1:1.5</td>
<td>69</td>
<td>99</td>
<td>1/&gt;99 (%90:10)</td>
<td>90</td>
</tr>
<tr>
<td>5(^h)</td>
<td>CHCl(_3)</td>
<td>TFA</td>
<td>1:1.5</td>
<td>75</td>
<td>98</td>
<td>4 (%100:0)/%96 (%86:14)</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>benzene</td>
<td>TFA</td>
<td>1:1.5</td>
<td>45</td>
<td>66</td>
<td>60 (%96:4)/%40 (%89:11)</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>toluene</td>
<td>AcOH</td>
<td>1:2</td>
<td>35</td>
<td>&gt;99</td>
<td>87 (%90:11)/%13 (%76:24)</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>toluene</td>
<td>–</td>
<td>1:3.5</td>
<td>1.5</td>
<td>63</td>
<td>88 (%89:11)/%12 (%74:26)</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were conducted under reflux in the indicated solvent.
\(^b\) Ratio between keto ester 3 and the corresponding aniline 4a-d (Scheme 2).
\(^c\) Determined by \(^{19}\)F NMR (300 MHz) analysis of the crude reaction mixtures.
\(^d\) The enamino ester 5b was isolated as the major reaction product.
\(^e\) Ratio of enamino amide 7a-d to imino amide 7a-d respectively (Scheme 2).
\(^f\) Ratio of enamino ester 5a-d to imino ester 5a-d respectively (Scheme 2).
\(^g\) Entry corresponding to \(p\)-toluidine 4h.
\(^h\) Entry corresponding to \(p\)-anisidine 4c.
\(^i\) Entry corresponding to \(p\)-fluoroaniline 4d.

We believe that the difference in the outcome of the reactions of keto ester 3 with benzylamine and aniline stems from a low stability of enamino esters 5a-d and lower basicity of aniline as compared with that of benzylamine. Previously we showed that benzylamine derived compound 8 exists exclusively in enamino form stabilized by intramolecular hydrogen bond. We have also demonstrated that due to the low electrophilicity of the conjugated ester function in 8, it did not react with excess of benzylamine or its salts.\(^9\) By contrast, as it follows from NMR data, enamino esters 5a-d exist as a mixture with the corresponding ketimines 5a-d in which the ester group is relatively electrophilic to react with a nucleophile. Furthermore, taking into account the low basicity of anilines 4a-d, we can assume that their salts, in particular acetates, might be unstable at high temperatures (benzene, toluene) generating free bases (benzene, toluene) giving any improvement, probably due to noticeable solubility of product 6a in the aqueous phase. Though successful and operationally simple, as compared with the literature methods, this approach still cannot be rendered synthetically efficient, affording the target compounds 6 in moderate yields via two-step (condensation-hydrolysis) procedure. Therefore, we continued a search for convenient and efficient reaction conditions for a more efficient preparation of amides 6 and thus quinolinones 2.

![Scheme 3](image-url)
As discussed above, the target amides 6 are assumed to be favored products in the direct condensation between keto ester 3 and anilines 4 conducted under neutral or slightly basic conditions. Therefore, we focused our efforts on using various amines as additives to influence the chemoselectivity of the reaction. After numerous attempts, we found that the condensation between keto ester 3 and aniline 4a conducted in the presence of triethylamine gave rise to amide 6a with virtually complete (>99%) chemoselectivity (Scheme 3). Thus, heating a mixture of 3/4a/ Et3N in a ratio of 1:3.5:3 in toluene under reflux resulted in relatively fast (2.5 h) and complete (>98%) conversion of the starting compounds to afford amide 6a as the sole product (Table 2, entry 1). A decrease in the ratio of both 4a and Et3N resulted in lower reaction rates but did not influence the chemical outcome (entries 2, 3). The reactions conducted in benzene and chloroform showed the same excellent chemoselectivity but proceeded at substantially slower rates (entries 4, 5). Therefore, in our opinion, the optimum reaction conditions presented in entry 3 were used to check the generality of this procedure. The condensations of keto ester 3 with p-methyl-4b, p-methoxy-4c and p-fluoroanilines 4d (entries 6–8) proceeded at similar reaction rates and regardless of the nature of the substituent on the phenyl ring of 4, affording the target amides 6b–d as individual reaction products. On the other hand, isolation of 6a–d posed some problems due to solubility of the hydrates of amides 6a–d in aqueous solutions. The highest isolated yields of 6a–d we obtained were in the range of 55–65%. Therefore, taking into account that under the Knorr–Conrad–Limpach conditions, the 20% excess of aniline 4a–d and Et3N might not interfere with the cyclization forming the corresponding water-soluble salts, we tried the cyclization of 6a without prior isolation. Thus, crude 6a, obtained by evaporation of the toluene solution, was treated with 75% sulfuric acid according to the literature procedures. The result was rather satisfactory as the target 4-trifluoromethyl-2-quinolinone (2a) was isolated in 73% (based on 3) chemical yield. Accordingly, the condensation of keto ester 3 with anilines 4, conducted in the presence of Et3N, and further cyclization of the intermediate 6 could be recommended as a general, convenient, economical and operationally simple method for preparing 4-trifluoromethyl-2-quinolinones 2 in reasonable chemical yields.

In summary, a systematic study of the reactions between keto ester 3 and anilines 4 allowed us to find suitable reaction conditions for highly chemoselective synthesis of either enamino esters 5 (Table 1) or amides 6 (Table 2), key intermediates for preparation of 2-trifluoromethyl-4-quinolinones 1 and 4-trifluoromethyl-2-quinolinones 2. Simplicity and operational convenience of the experimental procedures as well as reasonable chemical yields and ratios of the starting compounds, compared to the literature methods, render the procedures developed in this study synthetically useful.

### Table 2: Synthesis of Amides 6a–d by the Reactions of Keto Ester 3 with Anilines 4a–d in the Presence of Triethylamine (Scheme 3)*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Ratio</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Yield of 6a–d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>1:3.5:3</td>
<td>2.5</td>
<td>98</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>1:2:1.5</td>
<td>3</td>
<td>96</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>1:1.2:2</td>
<td>7</td>
<td>96</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>benzene</td>
<td>1:1.2:2</td>
<td>5 days</td>
<td>92</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>CHCl3</td>
<td>1:1.2:2</td>
<td>14 days</td>
<td>90</td>
<td>–</td>
</tr>
<tr>
<td>6d</td>
<td>toluene</td>
<td>1:1.2:2</td>
<td>7</td>
<td>96</td>
<td>69</td>
</tr>
<tr>
<td>7e</td>
<td>toluene</td>
<td>1:1:2:2</td>
<td>7</td>
<td>95</td>
<td>55</td>
</tr>
<tr>
<td>8f</td>
<td>toluene</td>
<td>1:1:2:2</td>
<td>7</td>
<td>92</td>
<td>66</td>
</tr>
</tbody>
</table>

* All reactions were conducted under reflux in the indicated solvent using designated ratio of 3, 4a–d and Et3N.


Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. All the reactions were carried out without any special caution to exclude air. Unless indicated, 1H, 19F and 13C NMR spectra were taken in CDCl3 solutions at 299.95, 282.24 and 75.42 MHz, respectively, on the NMR instrument in the University of Oklahoma NMR Spectroscopy Laboratory. Chemical shifts refer to TMS and CFCl3 as the internal standards.

Yields refer to isolated yields of products of greater than 95% purity as estimated by 1H and 19F NMR spectroscopy. All new compounds were characterized by 1H, 19F, 13C NMR and mass spectroscopy.

### 4,4,4-Trifluoro-3-(phenylamino)but-2-enoic Acid Ethyl Ester (5a): Typical Procedure

(Scheme 2, Table 1, entry 2)

To a solution of aniline 4a (0.381 g, 4.07 mmol) and trifluoroacetic acid (0.465 g, 4.07 mmol) in CHCl3 (2 mL) was added a solution of keto ester 3 (0.505 g, 2.75 mmol) in CHCl3 (3 mL) at r.t. The resulting mixture was refluxed until the reaction was completed (68 h, monitored by 19F NMR spectroscopy). The CHCl3 solution was washed with H2O (3 × 10 mL), dried (MgSO4) and evaporated to afford the enamino ester 5a as a viscous oil (0.651 g, 92%); Rf 0.84 (hexanes–EtOAc, 5:1); exists as a mixture of enamino ester 5a and imino ester 5a in a ratio of 4:1.

5a

1H NMR (CDCl3): δ = 9.83 (s, 1 H), 7.15–7.35 (m, 5 H), 5.33 (s, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 3.41 (s, 2 H), 1.30 (t, J = 7.2 Hz, 3 H).

13C NMR (CDCl3): δ = 169.8, 147.3 (q, J = 131.7 Hz), 138.6, 129.1, 126.8, 126.2, 126.0 (q, J = 276.7 Hz), 88.8 (q, J = 5.5 Hz), 60.4, 14.6.

19F NMR (CDCl3): δ = –63.39 (s).
4.4.4-Trifluoro-3-(4'-methylphenylamino)but-2-enoic Acid Ethyl Ester (5b)

(Scheme 2, Table 1, entry 3); yield: 96%; R₂: 0.86 (hexanes–EtOAc, 5:1); exists as a mixture of enamino ester 5b and imino ester 5c in a ratio of 4:1.2.

5b

1H NMR (CDCl₃): δ = 7.40 (m, 2 H), 6.77 (m, 2 H), 4.09 (q, J = 7.2 Hz, 2 H), 3.42 (s, 2 H), 2.27 (s, 3 H), 1.21 (t, J = 7.2 Hz, 3 H).

13C NMR (CDCl₃, 100 MHz): δ = 169.9, 148.1 (q, J = 30.5 Hz), 131.0, 128.6, 128.2, 120.4 (q, J = 275.4 Hz), 114.1, 87.4, (q, J = 5.3 Hz), 60.2, 55.6, 14.5.

19F NMR (CDCl₃): δ = –3.85 (s).

5c

1H NMR (CDCl₃): δ = 9.67 (s, 1 H), 7.13 (dd, J = 8.4, 2.4 Hz, 2 H), 6.83 (dd, J = 2.4, 6.75 Hz, 2 H), 5.27 (s, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 3.79 (s, 3 H), 1.30 (t, J = 7.2 Hz, 3 H).

13C NMR (CDCl₃, 100 MHz): δ = 170.0, 148.1 (q, J = 30.5 Hz), 131.0, 128.6, 128.2, 120.4 (q, J = 275.4 Hz), 114.1, 87.4, (q, J = 5.3 Hz), 60.2, 55.6, 14.5.

19F NMR (CDCl₃): δ = –3.85 (s).

5c

1H NMR (CDCl₃): δ = 4.18 (q, J = 7.2 Hz, 2 H), 3.80 (s, 3 H), 3.47 (s, 2 H), 1.26 (t, J = 7.2 Hz, 3 H), aromatic signals were obscured.

13C NMR (CDCl₃, 100 MHz): δ = 169.8, 135.3, 130.0, 123.0 (q, J = 285.9 Hz), 120.7, 94.9, 20.8.

19F NMR (CDCl₃): δ = –3.85 (s).

5c

HRMS: m/z calcd for C₁₃H₁₄F₃NO₂ (M + Cs): 272.0510. Found 272.0562. 

4.4,4-Trifluoro-3-oxo-N-(4'-methylphenylamino)butyramide (6b)

(Scheme 3, Table 2, entry 6); yield: 69%; R₂: 0.28 (hexanes–acetone, 3:1); exists as a mixture of hydrate 6'a and keto amide 6b in a ratio of 1:1.2.

6b

1H NMR (acetone-d₆): δ = 9.4–9.9 (br d, 1 H), 7.65 (m, 2 H), 7.36 (m, 2 H), 7.15 (m, 1 H), 6.90 (s, 2 H), 2.87 (s, 2 H).

13C NMR (CDCl₃): δ = 169.8, 138.2, 129.5, 125.4, 120.8, 120.0 (q, J = 285.2 Hz), 39.2.

19F NMR (CDCl₃): δ = –85.6 (s).

HRMS: m/z calcd for (M + Na) 272.0510. Found 272.0562. 

4.4,4-Trifluoro-3-oxo-N-(4'-methylphenylamino)butyramide (6c)

(Scheme 3, Table 2, entry 7); yield: 55%; R₂: 0.20 (hexanes–acetone, 3:1); exists as a mixture of hydrate 6c and keto amide 6c in a ratio of 1:4.
6c

1H NMR (acetone-d$_6$): $\delta$ = 9.61 (s, 1 H), 7.57 (m, 2 H), 6.93 (m, 2 H), 5.90 (s, 1 H), 3.79 (s, 3 H).

13C NMR (CDCl$_3$): $\delta$ = 168.9, 157.8 (q, $J$ = 36.0 Hz), 131.2, 122.5, 119.7 (q, $J$ = 272.2 Hz), 114.7, 94.9, 55.6.

$^{19}$F NMR (CDCl$_3$): $\delta$ = -74.1 (s).

HRMS: $m/z$ calcd for C$_{10}$H$_9$F$_4$NO$_3$ (M + Na): 302.0612; found: 302.0401.

6c

HRMS: $m/z$ calcd for (M + Na): 302.0612; found: 302.0401.

4,4,4-Trifluoro-N-(4'-fluorophenyl)-3-oxobutyramide (6d) (As Hydrate 6’d)

(Scheme 3, Table 2, entry 8).

Yield: 66%; $R_f$ 0.27 (hexanes–acetone, 3:1).

1H NMR (acetone-d$_6$): $\delta$ = 9.69 (s, 1 H), 7.65 (m, 2 H), 7.08 (m, 2 H), 6.83 (s, 2 H), 2.84 (s, 2 H).

13C NMR (CDCl$_3$): $\delta$ = 170.8, 162.4, 159.2, 135.9, 124.7 (q, $J$ = 285.9 Hz), 123.4 (d, $J$ = 8.1 Hz), 116.9 (d, $J$ = 22.5 Hz), 40.1.

$^{19}$F NMR (CDCl$_3$): $\delta$ = -85.6 (s), -117.2 (m).

HRMS: $m/z$ calcd for C$_{10}$H$_9$F$_4$NO$_3$ (M + Li): 274.0679; found: 274.0679.

4,4,4-Trifluoro-3-phenaminobut-2-enoic Acid Phenylamide (7a)

(Scheme 2, Table 1, entry 8).

To a solution of keto ester 3 (0.505 g, 2.74 mmol) in toluene (2 mL) was added a solution of aniline 4a (0.893 g, 9.60 mmol) in toluene (2 mL) at r.t. The resultant mixture was refluxed until the reaction was complete (monitored by $^{19}$F NMR spectroscopy). The mixture was evaporated and the residue was purified by column chromatography using hexane–EtOAc (5:1) as an eluent, to afford an amino amide 7a (0.448 g, 53%). The prepared 7a was used for hydrolysis to 6a without additional purification; $R_f$ 0.34 (hexanes–EtOAc, 5:1).

1H NMR (acetone-d$_6$): $\delta$ = 10.54 (s, 1 H), 7.43 (d, $J$ = 8.1 Hz, 2 H), 7.29–6.98 (m, 10 H), 5.2 (s, 1 H).

$^{19}$F NMR (CDCl$_3$): $\delta$ = -63.2 (s).

Hydrolysis of 4,4,4-Trifluoro-3-phenaminobut-2-enoic Acid Phenylamide (7a)

(Scheme 3).

Enamino amide 7a (0.198 g, 0.646 mmol) was dissolved in Et$_2$O (10 mL) and stirred overnight with 3 N HCl (6 mL). The reaction was monitored by $^{19}$F NMR spectroscopy (Et$_2$O phase) and upon completion, the organic phase was separated and washed with H$_2$O (3 x 3 mL). The organic phase was evaporated after drying (MgSO$_4$) to afford 0.102 g (56%) of the hydrate 6a.

4-Trifluoromethyl-2-quinoline (2a)

To prepare the amide 6a, the procedure described above (typical procedure for preparing keto amide derivatives 6a–d) (Scheme 3, Table 2, entry 3) was followed, except that the toluene solution was evaporated, dried in high vacuum after the reaction was complete. The resulting residue was subjected to Knoe--Conrad–Limpach cyclization under the exact conditions described in Ref.12 to afford the target quinoline 2a in 73% (calculated on 3, 83% calculated on amide 7a) yield.

For general procedures for cyclization of enamines/imines 5/5 to 2-trifluoromethyl-4-quinolines 1, see Ref.14 For general procedures for cyclization of amides 6/6' to 4-trifluoromethyl-2-quinolines 2, see Ref.12.

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References

10. In the reported procedure (see Ref.2) the starting keto ester 3 and anilines 4 were used in a ratio of 2:1; accordingly, the corresponding yields of the products 2 are calculated based on 4. Despite the fact that keto ester 3 is a cheap technical bulkware, it is still more expensive than most of the anilines 4, therefore, we believe that the chemical yields, as one of the criteria of synthetic efficiency, should be calculated on 3 to make an economical sense.