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The "Off-Shore" Construction of Optionally Substituted 4-Trifluoromethyl-2-quinolinones

Frédéric Leroux,[a] Olivier Lefebvre,[b] and Manfred Schlosser*[b]

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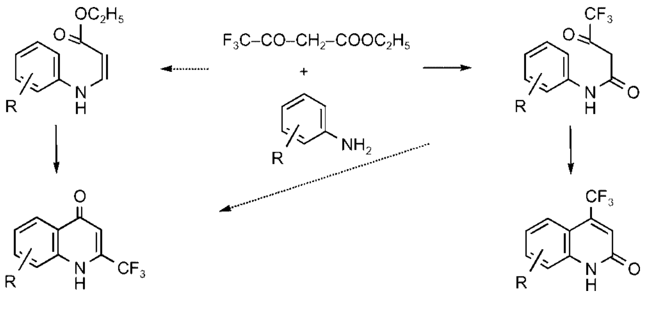
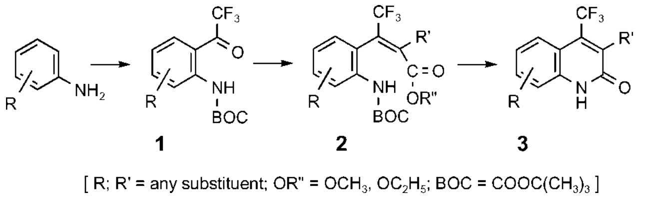
Treatment of *ortho*-lithiated *tert*-butyl *N*-arylcarbamates (i.e., BOC-protected anilines) with *N*-(trifluoroacetyl)piperidine provides 2-(*N*-BOC-amino)aryl trifluoromethyl ketones which, upon consecutive reaction with an α-alkoxycarbonyl-substituted phosphorus ylide and acid (or base) yields 4-trifluoromethyl-2-quinolinones which may bear additional substituents at any available position. The method is convenient and expedient.

The common access to the pharmaceutically attractive 4-trifluoromethyl-2-quinolinones[1,2] consists of two reaction steps which have to be controlled carefully (Scheme 1). The preparation of the prerequisite *N*-(4,4,4-trifluoroacetoacetyl)anilides poses the first problem. In particular anilines carrying electron-withdrawing substituents tend to produce concomitantly or exclusively the isomeric "anils"[3] (or β-anilinocrotonate tautomers thereof), the precursors to 2-trifluoromethyl-4-quinolinones.[4] Even if this stumbling block can be circumvented by applying the "watering protocol"[2] or another suitable regiodiscriminating method,[5] one has to be aware of another pitfall. The cyclization of the acetoacetanilide may go astray providing still 2-trifluoromethyl-4-quinolinones rather than the targeted 2-quinolinone isomers if the reaction is not carried out in a most effective manner using hot concentrated sulfuric acid.[2]



Scheme 1. Known condensation of anilines with ethyl 4,4,4-trifluoroacetoacetate giving 4-trifluoromethyl-2-quinolinones.

Such uncertainties encouraged us to develop a new method that would open a regiochemically unbiased, though structurally flexible entry to 4-trifluoromethyl-2-quinolinones. We opted for an "off-shore"[6] cyclization approach, that is the construction of the heterocyclic part without the active participation of the aromatic ring. In this way, electronegative substituents would not compromise the electrophilic attachment of a heterofunctional side chain, the crucial feature of any "on-shore" process. This design concretized in an *ortho*-trifluoroacetylation of the aniline starting material bearing an *N*-*tert*-butoxycarbonyl ("BOC") protective group at the nitrogen atom, a C_2 chain extension by a suitable condensation reaction and an ultimate closure of the lactam unit (affording products **1**, **2** and **3**, respectively) (Scheme 2).



Scheme 2. Projected new reaction sequence leading to 4-trifluoromethyl-2-quinolinones: *ortho*-lithiation, trifluoroacetylation, reaction with an α-(alkoxycarbonyl)-bearing phosphorus ylide and ring closure.

The *ortho*-acylation of *ortho*-lithiated[7–9] BOC-protected anilines was accomplished with *N*-(trifluoroacetyl)piperidine as the reagent. Trifluoroacetic anhydride, previously successfully employed in the reaction with *N*,3-dilithiated *N*-pivaloyl-3,4-dimethoxyaniline[10] gave only poor results. The oxacarbamates **1a** (71%), **1b** (68%), and **1c** (51%) thus obtained were transformed into the cinnamic ester derivatives **2a** (79%), **2b** (76%), and **2c** (74%) by simple Wittig reaction using 1-methoxy-2-(triphenylphosphonio)ethene

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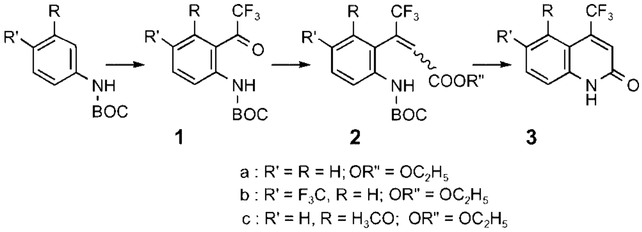
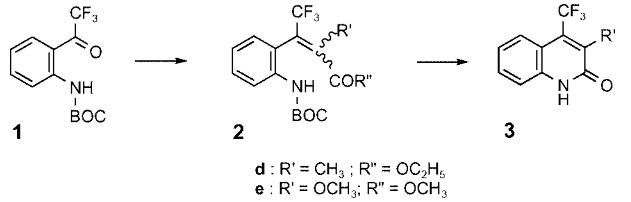
[a] Laboratoire de Stéréochimie (UMR CNRS 7509), Université Louis Pasteur (ECPM),
25 rue Becquerel, 67087 Strasbourg, France
[b] Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale, BCh
1015 Lausanne, Switzerland
Fax: +41-21-6939365
E-mail: manfred.schlosser@epfl.ch

oxide[11] [triphenylphosphonio-α-(methoxycarbonyl)methanide, (methoxycarbonylmethylene)triphenylphosphorane,[12] methyl (triphenylphosphoranylidene)acetate]. Treatment with acid or base afforded eventually the 4-trifluoromethyl-2(1*H*)-quinolinones **3a** (73%), **3b** (74%), and **3c** (69%) (Scheme 3).



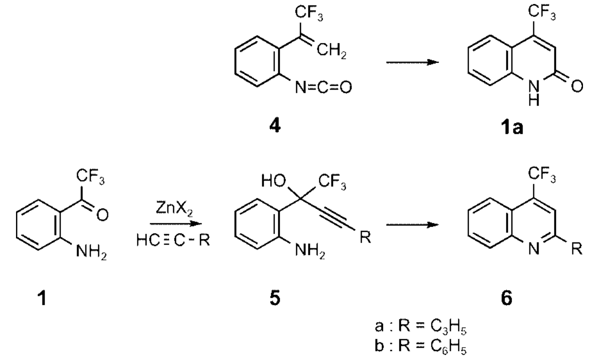
Scheme 3. Condensation of ring-substituted *tert*-butyl *N*-[2-(trifluoroacetyl)aryl]carbamates with triphenylphosphonio-α-(methoxycarbonyl)methanide and subsequent cyclization.

Air-insensitive resonance-stabilized ester ylides such as the α-methyl-,[13,14] α-phenyl-,[15] α-cyano-,[16] α-formyl-,[17] and α-methoxy-substituted[18,19] (methoxycarbonylmethylene)triphenylphosphoranes and the α-fluoro-,[20] α-chloro-,[21] α-bromo-,[22,23] and α-iodo-substituted[24,25] (ethoxycarbonylmethylene)triphenylphosphoranes can be readily prepared and stored. Employed in the reaction sequence outlined above, they enable the introduction of a variety of substituents into the 3-position of the final quinolinone. This was exemplified by the conversion of *tert*-butyl *N*-[2-(trifluoroacetyl)phenyl]carbamate (**1a**) into the intermediate esters **2d** (78%) and **2e** (81%) and thereafter into the quinolinones **3d** (76%) and **3e** (83%) (Scheme 4).



Scheme 4. Condensation of *tert*-butyl *N*-[2-(trifluoroacetyl)phenyl]carbamate with α-alkyl- or α-hetero-substituted triphenylphosphonio-α-(methoxycarbonyl)methanides and subsequent cyclization.

Two methods reported in the literature are reminiscent of ours to some extent (Scheme 5). Their practical value is difficult to assess as they were tested so far only on an analytical scale (≤ 1 mmol). When heated to 150 °C, 2-[(1-trifluoromethyl)vinyl]phenyl isocyanate (**4**) underwent an intramolecular C–H bond addition to an activated (ketene-like) double bond, thus giving 4-trifluoromethyl-2-quinolinone (**1a**).[26] A new route to 2-alkyl- or 2-aryl-4-trifluoromethylquinolines started from 2-aminophenyl trifluoromethyl ketone and a few congeners thereof. After treatment with cyclopropylacetylene or phenylacetylene in the presence of zinc(II) chloride or trifluoromethanesulfonate ("triflate") and triethylamine, the adduct **5** or the quinoline **6** were isolated depending on whether the reaction was executed at +25 °C or +50 °C, respectively.[27] Replacing the hydrocarbon alkynes so far used by ethoxyacetylene[28] might open still another entry to 4-trifluoromethyl-2(1*H*)-quinolinones, although obviously without any reasonable chance to introduce a substituent at the 3-position in this way.



Scheme 5. Thermolysis of 2-[(1-trifluoromethyl)vinyl]phenyl isocyanate (**4**) and Lewis acid catalyzed addition of alkynes to 2-aminophenyl trifluoromethyl ketone followed by cyclization of the intermediate **5**.

Experimental Section

General Remarks: Starting materials, if commercial, were purchased from Aldrich-Fluka (9479 Buchs, Switzerland) or Apollo Scientific (Stockport SK6 2QR, UK) and used as such, provided that adequate checks (melting ranges, refractive indices, and gas chromatography) had confirmed the claimed purity. Solutions of *tert*-butyllithium in pentanes were supplied by Chemetall (60487 Frankfurt, Germany). When known compounds were prepared according to literature procedures, pertinent references are given. Air- and moisture-sensitive materials were stored in Schlenk tubes or Schlenk burettes. They were protected by and handled under 99.995% pure nitrogen, using appropriate glassware (Glasgerätebau Pfeifer, 98711 Frauenwald, Germany). Diethyl ether and tetrahydrofuran were dried by distillation from sodium wire after the characteristic blue color of sodium diphenyl ketyl (benzophenone–sodium "radical anion") had been found to persist.[29,30] Ethereal or other organic extracts were dried by washing with brine and then by storage over sodium sulfate. Prior to distillation, a spatula tip of hydroquinone or potassium carbonate was added to compounds prone to radical polymerization or sensitive to acids. If no reduced pressure is specified, boiling ranges (b.p.) refer to ordinary atmospheric conditions (725 ± 25 Torr). Melting ranges (m.p.) given were found to be reproducible after resolidification, unless stated otherwise ("decomp."), and were corrected using a calibration curve established with authentic standards. If melting points are missing, it means that all attempts to crystallize the liquid at temperatures down to –75 °C failed. The temperature of dry ice/methanol baths is consistently indicated as –75 °C and "room temperature" (22–26 °C) as 25 °C. Silica gel (Merck Kieselgel 60) of 70–230 mesh (0.06–0.20 mm) particle size was used for column chromatography. The solid support was suspended in hexanes and, when all air bubbles had escaped, was washed into the column. When the level of the liquid was still 3–5 cm above the support layer, the dry powder, obtained by adsorption of the crude mixture to some 25 mL of silica and subsequent evaporation of the solvent, was poured on top of the column. Whenever possible and appropriate, yields of products were determined, prior to isolation, by gas chromatographic comparison of their peak areas with those of known amounts of reference substances ("internal standards"), the ratios thus obtained being corrected by means of separately established calibration factors. The purity of distilled compounds was checked on at least two columns loaded with stationary phases of contrasting polarity. Chromosorb G-AW of 80–100 and 60–80 mesh particle size was used as the support for packed columns on the analytical and preparative scales (2 or 3 m long, 2 mm inner diameter and 3 or 6 m long, 1 cm inner diameter, respectively). Packed columns were made of glass, while quartz was the material selected for capillary columns (> 10 m long). For programmed temperature increase, a constant rate of 10 °C/min was applied. The stationary phases employed are encoded as DB-23 (of the silicon type) and DB-WAX (belonging to the polyethylene glycol family). ^{1}H and (^{1}H-decoupled) ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 400 and 101 MHz, respectively. The samples were dissolved in deuteriochloroform or, if marked by an asterisk (*), in [^{2}H$_6$]dimethyl sulfoxide. Chemical shifts δ refer to the signal of tetramethylsilane (δ = 0.00 ppm) and coupling constants J are given in Hz. Coupling patterns are abbreviated as, for example, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), oct (octet), non (nonet), td (triplet of doublets), and m (multiplet). The carbamate NH signals were frequently too broad to be unambiguously identified. Mass spectra were taken by electron impact fragmentation at 70 eV ionization potential and 200 °C source temperature. Whenever no molecular peak was observed under such standard conditions, chemical ionization ("c.i.") in an ammonia atmosphere was applied. Elementary analyses were performed by the laboratories of I. Beetz (96301 Kronach, Germany) or Solvias (4002 Basle, Switzerland). The expected percentages were calculated using the atomic weight numbers listed in the 1999 IUPAC recommendations.

tert-Butyl *N*-[2-(Trifluoroacetyl)phenyl]carbamates (1)

***tert*-Butyl *N*-[2-(Trifluoroacetyl)phenyl]carbamate (1a):** At –30 °C, *tert*-butyllithium (0.33 mol) in pentanes (0.22 L) was added dropwise in the course of 45 min to a solution of *tert*-butyl *N*-phenylcarbamate[7,8] (29 g, 0.15 mol) in dry diethyl ether (0.45 L). After 4 h at –10 °C, the mixture was treated at +25 °C with 1-(trifluoroacetyl)piperidine[31,32] (29 mL, 36 g, 0.20 mol) in diethyl ether (50 mL). The mixture was washed with brine (0.15 L) and the solvents were evaporated. The residue was extracted with pentanes (3 × 0.10 L) and the combined organic layers were filtered through a pad of silica (50 mL). Upon concentration of the solution and cooling, yellowish needles were obtained; m.p. 60–61 °C; yield 30.8 g (71 %). ^{1}H NMR: δ = 10.45 (s, 1 H), 8.59 (dd, J = 8.8, 1.2 Hz, 1 H), 7.92 (dt, J = 8.2, 2.0 Hz, 1 H), 7.65 (t, J = 8.0 Hz, 1 H), 7.09 (t, J = 7.2 Hz, 1 H), 1.54 (s, 9 H) ppm. ^{13}C NMR: δ = 181.9 (q, J = 32 Hz), 152.4, 144.5, 137.3, 131.6 (q, J = 4 Hz), 121.1, 119.6, 116.5 (q, J = 292 Hz), 114.6, 81.4, 28.2 (3 C) ppm. MS (c.i.): m/z (%) = 289 (3) [M$^+$], 233 (20), 216 (5), 189 (10), 146 (32). $C_{13}H_{14}F_3NO_3$ (289.25): calcd. C 53.98, H 4.88; found C 54.11, H 4.71.

***tert*-Butyl *N*-[2-(Trifluoroacetyl)-4-(trifluoromethyl)phenyl]carbamate (1b):** Analogously as described for the preparation and isolation of ketone **1a** but starting from *tert*-butyl *N*-[4-(trifluoromethyl)phenyl]carbamate[33] (13 g, 50 mmol) and replacing diethyl ether by tetrahydrofuran (0.15 L) as the solvent; colorless needles; m.p. 95–96 °C; yield 12.1 g (68 %). ^{1}H NMR: δ = 10.45 (br. s, 1 H), 8.78 (d, J = 9.2 Hz, 1 H), 8.16 (s, 1 H), 7.86 (dd, J = 9.1, 2.0 Hz, 1 H), 1.55 (s, 9 H) ppm. ^{13}C NMR: δ = 182.1 (q, J = 35 Hz), 152.0, 147.3, 133.6 (q, J = 3 Hz), 128.8 (q, J = 4 Hz), 123.5 (q, J = 35 Hz), 123.2 (q, J = 272 Hz), 120.0, 114.9 (q, J = 292 Hz), 118.9, 82.4, 28.2 (3 C) ppm. MS (c.i.): m/z (%) = 358 (11) [M$^+$ + 1], 357 (9) [M$^+$], 319 (27), 257 (100), 214 (38). $C_{14}H_{13}F_6NO_3$ (357.25): calcd. C 47.07, H 3.67; found C 47.35, H 3.44.

***tert*-Butyl *N*-[3-Methoxy-2-(trifluoroacetyl)phenyl]carbamate (1c):** Analogously as described for the preparation and isolation of ketone **1a** but starting from *tert*-butyl *N*-(2-methoxyphenyl)carbamate[34–36] (34 g, 0.15 mol); yellowish needles; m.p. 84–85 °C; yield 24.4 g (51 %). ^{1}H NMR: δ = 8.50 (br. s, 1 H), 7.83 (d, J = 8.5 Hz, 1 H), 7.49 (t, J = 8.6 Hz, 1 H), 6.64 (d, J = 8.2 Hz, 1 H), 3.89 (s, 3 H), 1.51 (s, 9 H) ppm. ^{13}C NMR: δ = 186.1 (q, J = 37 Hz), 160.5, 152.4, 141.0, 135.9, 129.6, 116.4 (q, J = 290 Hz), 112.8, 105.2, 81.4, 56.0, 28.2 (3 C) ppm. MS (c.i.): m/z (%) = 319 (20) [M$^+$], 318 (70), 317 (58), 286 (100). $C_{14}H_{16}F_3NO_4$ (319.28): calcd. C 52.67, H 5.05; found C 53.02, H 4.86.

Phenylbutenoates (2)

Ethyl 3-{2-[(*tert*-Butoxycarbonyl)amino]phenyl}-4,4,4-trifluorobut-2-enoate (2a): A solution containing the carbamate **1a** (8.7 g, 30 mmol) and ethyl (triphenylphosphoranylidene)acetate (10.5 g, 30 mmol) in toluene (60 mL) was heated at 100 °C for 2 h. After evaporation of the solvent, the residue was dissolved in hexanes. The insoluble triphenylphosphane oxide was removed by filtration. Elution from silica gel using a 1:4 (v/v) mixture of ethyl acetate/hexanes afforded the (*Z*) and (*E*) isomers in a ratio of 5:95; yield 8.5 g (79 %). MS (c.i.): m/z (%) = 360 (14) [M$^+$ + 1], 359 (3) [M$^+$], 304 (100), 260 (47), 259 (31), 214 (79). $C_{17}H_{20}F_3NO_4$ (359.34): calcd. C 56.82, H 5.61; found C 56.79, H 5.46. (*E*) isomer: ^{1}H NMR: δ = 7.90 (d, J = 9.0 Hz, 1 H), 7.41 (ddd, J = 8.4, 5.6, 3.4 Hz, 1 H), 7.11 (t, J = 1.0 Hz, 1 H), 7.10 (s, 1 H), 6.80 (q, J = 1.3 Hz, 1 H), 6.29 (s, 1 H), 4.04 (qq, J = 7.0, 5.5 Hz, 2 H), 1.50 (s, 9 H), 1.03 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR: δ = 163.6, 152.8, 138.9 (q, J = 32 Hz), 136.3, 130.0, 128.9, 127.7, 127.6 (q, J = 5 Hz), 123.4, 122.3 (q, J = 276 Hz), 114.6, 80.6, 61.5, 28.3 (3 C), 13.6 ppm.

Ethyl 3-{2-[(*tert*-Butoxycarbonyl)amino]-5-(trifluoromethyl)phenyl}-4,4,4-trifluorobut-2-enoate (2b): Analogously as described for the preparation and isolation of butenoate **2a** but starting from carbamate **1b** (11 g, 30 mmol); (*Z*)/(*E*) = 13:87; yield 9.7 g (76 %). MS: m/z (%) = 427 (4) [M$^+$], 371 (6), 327 (12), 282 (69), 254 (18), 57 (100). $C_{18}H_{19}F_6NO_4$ (427.34): calcd. C 50.59, H 4.48; found C 50.84, H 4.43. (*Z*) isomer: ^{1}H NMR: δ = 8.24 (d, J = 8.7 Hz, 1 H), 7.87 (d, J = 8.9 Hz, 1 H), 7.48 (s, 1 H), 7.14 (s, 1 H), 6.40 (s, 1 H), 4.37 (q, J = 7.3 Hz, 2 H), 1.55 (s, 9 H), 1.39 (t, J = 7.1 Hz, 3 H) ppm. (*E*) isomer: ^{1}H NMR: δ = 8.19 (d, J = 8.9 Hz, 1 H), 7.68 (d, J = 8.7 Hz, 1 H), 7.37 (s, 1 H), 6.89 (s, 1 H), 6.44 (s, 1 H), 4.08 (qq, J = 7.1, 5.4 Hz, 2 H), 1.52 (s, 9 H), 1.06 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR: δ = 163.1, 152.3, 139.9, 137.4 (q, J = 32 Hz), 129.6 (q, J = 6 Hz), 127.3 (q, J = 4 Hz), 127.0, 126.3 (q, J = 4 Hz), 120.9, 120.1, 117.9, 115.3, 81.7, 61.8, 28.2 (3 C), 13.6 ppm.

Ethyl 3-{2-[(*tert*-Butoxycarbonyl)amino]-6-methoxyphenyl}-4,4,4-trifluorobut-2-enoate (2c): Analogously as described for the preparation and isolation of butenoate **2a** but starting from carbamate **1c** (9.6 g, 30 mmol); (*Z*)/(*E*) = 23:77; yield 8.6 g (74 %). MS: m/z (%) = 389 (16) [M$^+$], 289 (30), 244 (44), 216 (100). $C_{18}H_{22}F_3NO_5$ (389.37): calcd. C 55.53, H 5.70; found C 55.32, H 5.49. (*Z*) isomer: ^{1}H NMR: δ = 7.60 (d, J = 8.3 Hz, 1 H), 7.17 (t, J = 8.6 Hz, 1 H), 6.84 (s, 1 H), 6.58 (dd, J = 8.0, 2.2 Hz, 1 H), 6.24 (s, 1 H), 4.32 (q, J = 7.4 Hz, 2 H), 3.80 (s, 3 H), 1.52 (s, 9 H), 1.36 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 160.0, 157.1, 152.3, 139.4, 136.7 (q, J = 32 Hz), 131.5 (q, J = 3 Hz), 130.4, 129.6, 112.7 (q, J = 275 Hz), 105.8, 103.9, 80.9, 61.7, 55.2, 28.2 (3 C), 13.8 ppm. (*E*) isomer: ^{1}H NMR: δ = 7.53 (d, J = 8.3 Hz, 1 H), 7.34 (t, J = 8.3 Hz, 1 H), 6.81 (s, 1 H), 6.66 (d, J = 8.0 Hz, 1 H), 6.22 (s, 1 H), 4.05 (qq, J = 10.9, 7.0, 2 H), 3.77 (s, 3 H), 1.48 (s, 9 H), 1.04 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 163.5, 157.1, 152.7, 137.1, 136.7 (q, J = 32 Hz), 130.5, 129.5, 128.8 (q, *J* = 5 Hz), 122.2 (q, *J* = 275 Hz), 108.6, 105.9, 80.6, 61.2, 55.9, 28.2 (3 C), 13.6 ppm.

Ethyl 3-{2-[(*tert*-Butoxycarbonyl)amino]phenyl}-2-methyl-4,4,4-trifluorobut-2-enoate (2d): Analogously as described for the preparation and isolation of butenoate **2a** but using ethyl methyl(triphenylphosphoranylidene)acetate as the reagent[13,14] (11 g, 30 mmol); (*Z*)/(*E*) ratio 33:67; yield 8.8 g (78%). MS (c.i.): *m*/*z* (%) = 374 (1) [M$^+$], 318 (6), 200 (100). $C_{18}H_{22}F_3NO_4$ (373.37): calcd. C 57.90, H 5.94; found C 57.86, H 5.86. (*Z*) isomer: ^{1}H NMR: δ = 8.03 (d, *J* = 8.1 Hz, 1 H), 7.40 (t, *J* = 8.5 Hz, 1 H), 7.11 (t, *J* = 7.9 Hz, 1 H), 7.03 (d, *J* = 4.5 Hz, 1 H), 4.37 (qq, *J* = 7.02, 5.2 Hz, 2 H), 1.78 (q, *J* = 1.8 Hz, 3 H), 1.59 (s, 9 H), 1.38 (t, *J* = 8.0 Hz, 3 H) ppm. ^{13}C NMR: δ = 168.3, 152.9, 140.9 (q, *J* = 4 Hz), 136.7, 130.2, 130.0, 129.6 (q, *J* = 32 Hz), 129.0, 123.6, 122.4 (q, *J* = 275 Hz), 121.5, 80.9, 62.1, 28.3 (3 C), 18.3, 13.9 ppm. (*E*) isomer: ^{1}H NMR: δ = 7.85 (d, *J* = 8.0 Hz, 1 H), 7.34 (td, *J* = 8.1, 4.9 Hz, 1 H), 7.15 (t, *J* = 7.2 Hz, 1 H), 7.03 (d, *J* = 4.5 Hz, 1 H), 3.89 (qq, *J* = 7.8, 6.2 Hz, 2 H), 2.30 (q, *J* = 2.5 Hz, 3 H), 1.52 (s, 9 H), 0.84 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR: δ = 168.0, 153.0, 142.4 (q, *J* = 3 Hz), 137.0, 130.1, 129.9, 129.5 (q, *J* = 32 Hz), 129.0, 123.1 (q, *J* = 276 Hz), 123.4, 121.2, 80.7, 61.5, 28.3 (3 C), 16.5 (q, *J* = 2 Hz), 13.4 ppm.

Methyl 3-{2-[(*tert*-Butoxycarbonyl)amino]phenyl}-2-methoxy-4,4,4-trifluorobut-2-enoate (2e): Analogously as described for the preparation and isolation of butenoate **2a** but using methyl methoxy(triphenylphosphoranylidene)acetate as the reagent (11 g, 30 mmol); (*Z*)/(*E*) = 72:28; yield 9.1 g (81%). MS: *m*/*z* (%) = 375 (2) [M$^+$], 243 (100), 211 (85). $C_{17}H_{20}F_3NO_5$ (375.34): calcd. C 54.40, H 5.37; found C 54.82, H 5.53. (*Z*) isomer: ^{1}H NMR: δ = 7.98 (d, *J* = 8.4 Hz, 1 H), 7.37 (td, *J* = 7.0, 1.7 Hz, 1 H), 7.19 (d, *J* = 7.9 Hz, 1 H), 7.08 (td, *J* = 7.6, 1.2 Hz, 1 H), 3.97 (s, 3 H), 3.62 (s, 3 H), 1.63 (s, 9 H) ppm. ^{13}C NMR: δ = 163.5, 152.7, 137.1, 136.7 (q, *J* = 32 Hz), 130.5, 129.5, 128.8 (q, *J* = 4 Hz), 122.2 (q, *J* = 275 Hz), 114.1, 108.6, 80.6, 61.2, 55.9, 28.2 (3 C), 13.6 ppm. (*E*) isomer: ^{1}H NMR: δ = 7.89 (d, *J* = 8.4 Hz, 1 H), 7.35 (td, *J* = 9.0, 2.0 Hz, 1 H), 7.09 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.02 (td, *J* = 7.5, 1.3 Hz, 1 H), 3.83 (s, 3 H), 3.49 (s, 3 H), 1.63 (s, 9 H) ppm. ^{13}C NMR: δ = 163.0, 152.6, 137.9, 136.7 (q, *J* = 32 Hz), 130.1, 129.2, 128.8 (q, *J* = 4 Hz), 120.0 (q, *J* = 273 Hz), 111.6, 111.0, 80.8, 63.0, 55.1, 29.6 (3 C), 13.6 ppm.

4-(Trifluoromethyl)quinolin-2(1*H*)-ones (3)

4-(Trifluoromethyl)quinolin-2(1*H*)-one (3a): But-2-enoate **2a** (3.6 g, 10 mmol) was heated under reflux in 5.0 M hydrochloric acid (50 mL) for 4 h. After cooling, the precipitate was collected by filtration, dried, washed with chloroform and crystallized from ethanol; colorless needles; m.p. 246–247 °C; yield 1.55 g (73%). ^{1}H NMR*: δ = 7.71 (d, *J* = 8.4 Hz, 1 H), 7.65 (td, *J* = 7.6, 1.0 Hz, 1 H), 7.43 (d, *J* = 8.5 Hz, 1 H), 7.32 (td, *J* = 7.7, 1.0 Hz, 1 H), 6.98 (s, 1 H) ppm. ^{13}C NMR*: δ = 160.0, 139.8, 136.6 (q, *J* = 31 Hz), 131.7, 124.3, 122.8, 122.6 (q, *J* = 277 Hz), 122.0 (q, *J* = 5 Hz), 116.5, 113.1 ppm. MS (c.i.): *m*/*z* (%) = 231 (27) [M$^+$ + NH$_4$], 214 (100) [M$^+$ + 1], 213 (34) [M$^+$], 185 (8), 166 (2). $C_{10}H_6F_3NO$ (213.16): calcd. C 56.35, H 2.84; found C 56.19, H 3.00. The same compound was obtained in 92% yield by starting from the but-2-enoate **2a** (1.8 g, 5.0 mmol) in ethanol (10 mL) with sodium ethanolate (0.34 g, 5.0 mmol) under reflux for 4 h.

4,6-Bis(trifluoromethyl)quinolin-2(1*H*)-one (3b): Analogously as described for the preparation and the isolation of quinolinone **3a** but starting from the but-2-enoate **2b** (4.3 g, 10 mmol); colorless needles (from ethanol); m.p. 219–221 °C; yield 2.08 g (74%). ^{1}H NMR*: δ = 7.94 (d, *J* = 8.7 Hz, 1 H), 7.78 (s, 1 H), 7.56 (d, *J* = 9.0 Hz, 1 H), 7.09 (s, 1 H) ppm. ^{13}C NMR*: δ = 161.1, 143.1, 136.8 (q, *J* = 32 Hz), 128.9 (q, *J* = 3 Hz), 124.8 (q, *J* = 6 Hz), 123.4 (q, *J* = 276 Hz), 122.8 (q, *J* = 275 Hz), 122.6, 121.9, 118.6, 113.5 ppm. MS (c.i.): *m*/*z* (%) = 299 (14) [M$^+$ + NH$_4$], 282 (100) [M$^+$ + 1], 281 (33), 253 (7). $C_{11}H_5F_6NO$ (281.16): calcd. C 46.99, H 1.79; found C 47.21, H 1.88.

5-Methoxy-4-(trifluoromethyl)quinolin-2(1*H*)-one (3c): Prepared and isolated analogously but starting from the but-2-enoate **2c** (3.9 g, 10 mmol); colorless needles (from ethanol); m.p. 280–283 °C; yield 1.68 g (69%). ^{1}H NMR*: δ = 7.6 (m, 1 H), 7.1 (m, 1 H), 7.0 (m, 2 H); 3.92 (s, 3 H) ppm. ^{13}C NMR*: δ = 160.7, 156.4, 142.4, 136.5 (q, *J* = 32 Hz), 133.4, 123.5 (q, *J* = 274 Hz), 123.2 (q, *J* = 8 Hz), 109.8, 105.9, 105.4, 56.9 ppm. MS (c.i.): *m*/*z* (%) = 243 (100) [M$^+$], 200 (27), 172 (16). $C_{11}H_8F_3NO_2$ (243.18): calcd. C 54.33, H 3.32; found C 54.23, H 5.18.

3-Methyl-4-(trifluoromethyl)quinolin-2(1*H*)-ones (3d): Analogously as described for the preparation and isolation of quinolinone **3a** but starting from but-2-enoate **2b** (3.7 g, 10 mmol); colorless needles (from ethanol); m.p. 237–239 °C; yield 1.73 g (76%). ^{1}H NMR*: δ = 7.71 (d, *J* = 7.1 Hz, 1 H), 7.53 (t, *J* = 6.8 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.24 (t, *J* = 7.8 Hz, 1 H), 2.32 (s, 3 H) ppm. ^{13}C NMR*: δ = 161.6, 138.3, 133.3, 132.2 (q, *J* = 29 Hz), 131.0, 129.1, 129.0 (q, *J* = 4 Hz), 123.4 (q, *J* = 279 Hz), 119.1, 116.8, 13.8 ppm. MS (c.i.): *m*/*z* (%) = 228 (22) [M$^+$ + 1], 227 (100) [M$^+$], 198 (44), 130 (30). $C_{11}H_8F_3NO$ (227.19): calcd. C 58.16, H 3.55; found C 58.19, H 3.33.

3-Methoxy-4-(trifluoromethyl)quinolin-2(1*H*)-ones (3e): A solution of but-2-enoate **2e** (3.7 g, 10 mmol) in 5.0 M ethanolic hydrogen chloride (20 mL) was heated under reflux for 4 h. After evaporation of the volatiles, the residue was crystallized from acetone; colorless needles; m.p. 153–154 °C; yield 2.02 g (83%). ^{1}H NMR*: δ = 7.84 (d, *J* = 8.3 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.3 Hz, 1 H), 7.31 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1 H), 4.08 (s, 3 H) ppm. ^{13}C NMR*: δ = 171.5, 158.0, 150.0, 136.2, 129.6, 125.0, 124.1 (q, *J* = 277 Hz), 123.3, 123.0 (q, *J* = 29 Hz), 116.2, 60.6 ppm. MS (c.i.): *m*/*z* (%) = 244 (18) [M$^+$ + 1], 243 (100) [M$^+$], 215 (11). $C_{11}H_8F_3NO_2$ (243.18): calcd. C 54.33, H 3.32; found C 53.96, H 3.17.found C 53.96, H 3.17.

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