JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. 2018, 83, 5104−5113
Article
pubs.acs.org/joc

One-Pot Synthesis of Trifluoromethylated Quinazolin-4(3*H*)-ones with Trifluoroacetic Acid as CF_3 Source

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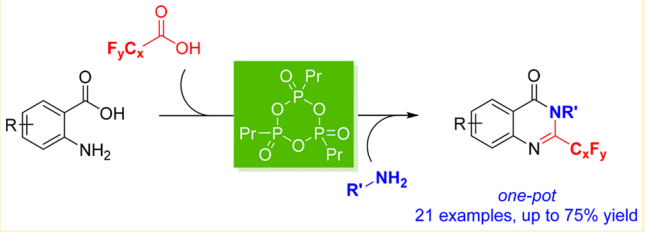
Supporting Information

ABSTRACT: A novel and convenient one-pot sequential cascade method for the preparation of 2-trifluoromethylquinazolin-4(3*H*)-ones is described. Trifluoroacetic acid (TFA) was employed as inexpensive and readily available CF_3 source, which in the presence of T3P was condensed with a variety of anthranilic acids and amines to provide the products in up to 75% yield. The protocol was proved to be robust on 80 g scale, and the synthetic versatility of the prepared quinazolinon-4-ones was demonstrated by derivatization to further useful building blocks.



INTRODUCTION

The pivotal role of fluorine as substituent in shaping physicochemical and pharmacological properties of organic molecules, especially of heterocycles, is widely recognized.[1] As a consequence, the number of methods for fluorination and trifluoromethylation has significantly increased in recent years.[2] Despite such enormous progress, the quest for synthetic methods that would allow to explore new chemical spaces in the domain of fluorinated and trifluoromethylated heterocycles remains very high and in some circumstances, still unmet.

In the context of trifluoromethylations, TFA represents an ideal source of the CF_3-group. In terms of price and availability on bulk scale, TFA competes well against hydrogen fluoride and sulfur tetrafluoride.[3] The major differences, however, is that TFA does not bear the same handling concerns calling for special dedicated laboratory, equipment and plants.[3b,c] TFA is highly chemically stable toward decarboxylation and this represents the major limiting factor for its use, for example, in late-stage trifluoromethylation methods. Even derivatives such as methyl trifluoroacetate (low boiling point liquid) and trifluoroacetate salts (toxic and hygroscopic solids) possess high decarboxylation temperatures (>120 °C) that make their use in trifluoromethylation chemistry challenging and only scarce applications were reported.[4]

On the other hand, the incorporation of TFA into molecular frameworks by condensation/dehydration is attractive and well documented mostly for the preparation of 5-membered heterocycles such as indoles, benzo-1,3-azoles and triazoles.[5] To a much lower extent, preparation of 6 membered rings was mainly performed with methyl- or ethyl trifluoroacetate and with trifluoroacetic anhydride,[6] while TFA itself has been employed only to prepare respectively fluorinated 4-hydroxypyridines,[7a,b] pyrimidine derivatives,[7c] β-carbolines[7d] and 2-(trifluoromethyl)quinazolin-4-(3*H*)-one (**11**).[7e]

Quinazolin-4(3*H*)-ones are a class of compounds present in naturally occurring alkaloids as well as in commercial drugs and displaying a broad spectrum of biological activities.[8]

Surprisingly, among the vast literature around quinazolinones and their synthetic accesses,[8e] a survey on the available methods for the corresponding 2-trifluoromethyl substituted scaffolds **4** revealed a much more limited number of possibilities (Scheme 1). Anthranilic amides (**I**) are among the substrates preferentially employed using ethyl trifluoroacetate in sodium ethoxide,[9a] trifluoroacetic anhydride,[6c] or in one specific example, with TFA under microwave heating as CF_3-reagent.[7e] Anthranilic esters (**II**) have also been condensed with unstable trifluoroacetamidine,[9b,c] while nitrile derivatives (**III**) have been reported to cyclize with trifluoroacetic anhydride.[9d] One specific example is reported in which 2-(trifluoromethyl)-quinazolines were obtained in few steps from alkyne (**IV**) via hydroamination,[9e] while the last approach relied on first reacting isatoic anhydride (**V**) with trifluoroacetic anhydride to generate 2-trifluoromethylbenzoxazin-4-ones **2**, followed by displacement with amines.[9f]

At the beginning of our study, we aimed to have a more general and straightforward access to 2-trifluoromethylquinazolinones **4** that offers opportunities for diversification by using the commodity chemical TFA as trifluoromethyl source. Anthranilic acids **1** being simpler and more available raw material as compared to amides, esters, anhydrides and cyanides, are the substrates of choice. For this purpose, we envisioned to use T3P as both coupling and condensation

Received: February 16, 2018
Published: April 12, 2018

DOI: 10.1021/acs.joc.8b00389
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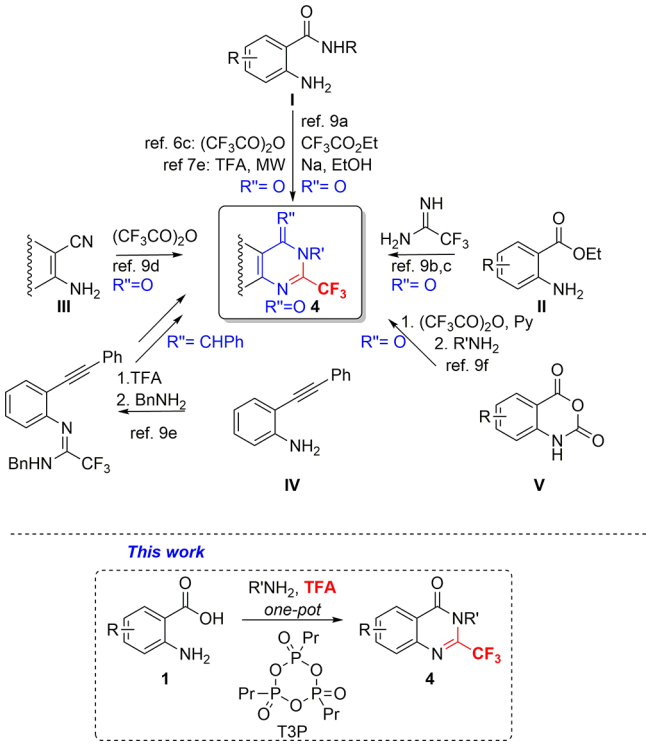
Scheme 1. Strategies for the Synthesis of 2-Trifluoromethylquinazolin-4(3*H*)-ones Derivatives

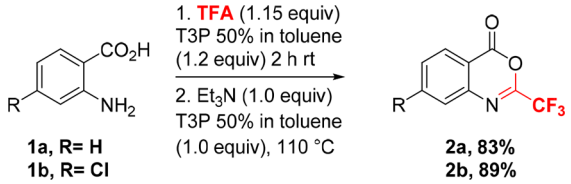


reagent. While *n*-propanephosphonic anhydride (T3P)[10] has been already used to prepare nonfluorinated quinazolinones by condensation of anthranilic amides with aldehydes,[11a] or anthranilic acids **1** with aldehydes, amines and DDQ as oxidant,[11b] the direct condensation of anthranilic acids with TFA and amines to prepare 2-trifluoromethylquinazolin-4-ones is to the best of our knowledge unprecedented. In this communication, we wish to report our results on the development of this novel practical synthetic strategy. The utility of quinazolinone products as building blocks is also being demonstrated with several trifluoromethyl-derivatives prepared.

RESULTS AND DISCUSSION

To prove the ability of T3P to perform the condensation step, we first tested the reaction of anthranilic acids **1** with TFA to provide CF_3-benzoxazin-4-ones **2** (Scheme 2).

Scheme 2. T3P-Mediated Synthesis of 2-Trifluoromethylbenzoxazin-4-ones 2



1a, R= H
1b, R= Cl

2a, 83%
2b, 89%

After heating to reflux mixtures of acids **1a,b**, TFA, base and T3P in toluene the corresponding products **2a,b** were obtained in good to excellent yields and without requiring chromatographic purification (>95% area purity by LC–MS.). These results confirmed our initial hypothesis that once *N*-trifluoroacetylation of **1** has occurred, T3P can act as dehydrating/condensation agent, comparing well with the more classical protocol that uses trifluoroacetic anhydride as both CF_3 source and condensation partner.[12,9f]

To prepare CF_3-quinazolin-4-(3*H*)-ones **4** with the same precursors and similar one-pot strategy, we could first transform the acid moiety into an amide **3**, followed by *N*-trifluoroacetylation and dehydration (strategy I, Scheme 3) or alternatively, *N*-trifloroacetylation could be followed by amide formation and cyclization (strategy II, Scheme 3). With trifluoroacetic anhydride leading to the corresponding benzoxazinones **2** (Scheme 2),[9f,12] we envisaged to use T3P as alternative and afford the synthesis of CF_3-quinazolinones either with strategy I or II.

Using 2-aminobenzoic acid (**1a**) as substrate for the initial screening of reaction conditions and simple ammonia or NH_4Cl as the amine counterpart, no primary amide was detected with strategy I even after prolonged stirring and heating in toluene.[13] Pleasingly, by replacing ammonia with benzylamine, conversion into the corresponding benzylamide **3a** occurred, which after treatment with a mixture of T3P and TFA was transformed into the *N*-trifluoroacetyl derivative and subsequently cyclized to the desired quinazolinone in 70% isolated yield (strategy I Scheme 3, see Experimental Section for details).

Under these conditions, a wide range of substrates were prepared (Scheme 4).

Electron-rich anthranilic acids afforded quinazolinones **4b** and **4c** in good yields, as well as halogen-containing products **4d–h** that were prepared in 51–72% yields. The highly electron-withdrawing trifluoromethyl-group was also well tolerated and the corresponding product **4i** was obtained in 72% yield.

In the case of quinazolinones **4j–l,o**, dimeric amide species deriving from the attack of the nucleophilic amino moiety of an anthranilic acid **1j–l,o** to the T3P-activated acid moiety of another molecule of **1j–l,o** were prevalently formed with strategy I during the amidation step (Scheme 5).[14]

The observed higher reactivity of the aniline function for those substrates suggested that reverting the order of events (strategy II Scheme 3) would suppress the formation of this side-product. In such way products **4j–l,o** were obtained in 38–75% yields (see Experimental Section for details). Our synthetic approach bears as well some limitations and pyridine-containing bicycles **4m,n** were obtained only in modest to low yields with strategy I. In addition, 5-aminoorotic acid and 2-aminobenzensulfonic acid did not afford desired products **4p** and **4q**, most likely due to a lack of reactivity of the sulfonic acid and incompatibility of T3P with 5-aminoorotic acid, respectively.

The possibility to modify both the amine and acid counterparts offers the advantage of chemical diversification which is especially valuable in combinatorial and exploratory chemistry. Representative modified substrates were prepared according to strategy I (Scheme 6). Quinazolinone **4r** deriving from challenging hindered *o*-toluidine was obtained in 42% yield, while with *n*-pentylamine the corresponding product **4s** was prepared in 59% yield. By using L-leucine methyl ester as amine, instead of the desired product, benzo[1,4]diazepine-2,5-dione **6** was obtained in a not-optimized 32% yield.[15] This result demonstrates that anthranilic acids in combination with T3P are a practical synthetic equivalent of isatoic anhydride **V**, known to condense with α-amino acids for the preparation of benzo[1,4]diazepine-2,5-diones.[15a–f] With regards to the acid partner, variation was achieved by using commercially available

DOI: 10.1021/acs.joc.8b00389
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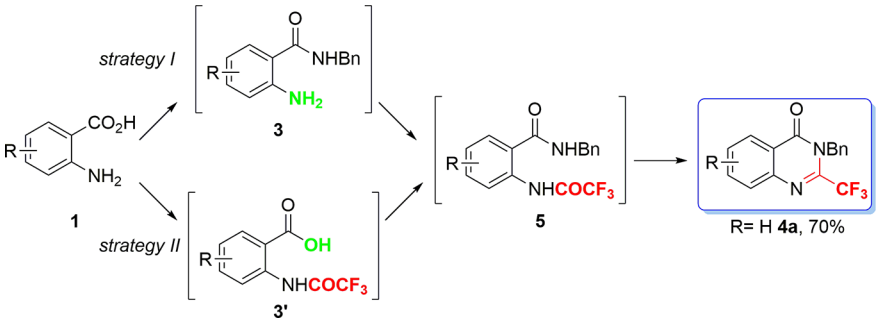
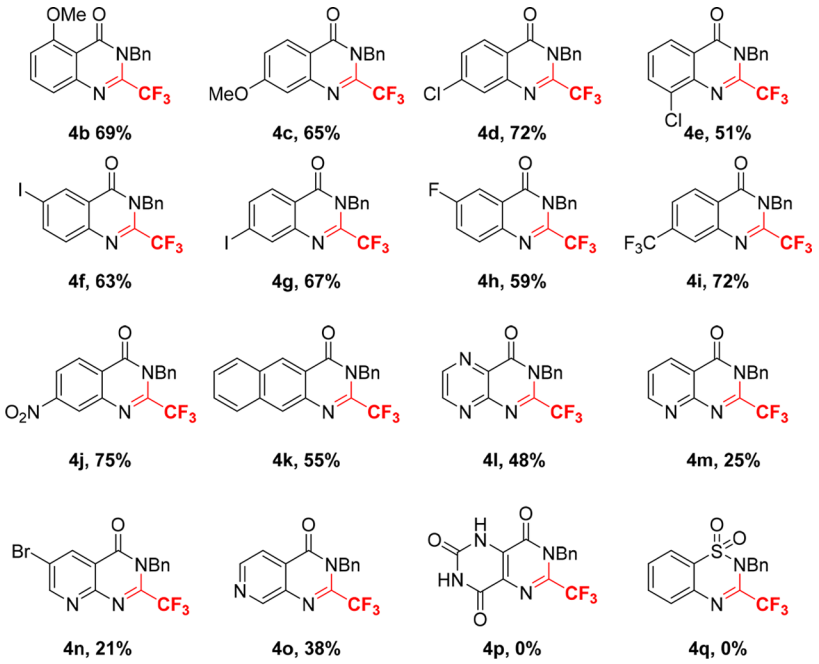
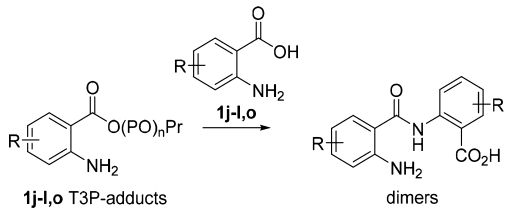
Scheme 3. T3P-Mediated Synthesis of 3-Benzyl-2-(trifluoromethyl)quinazolin-4(3*H*)-ones 4



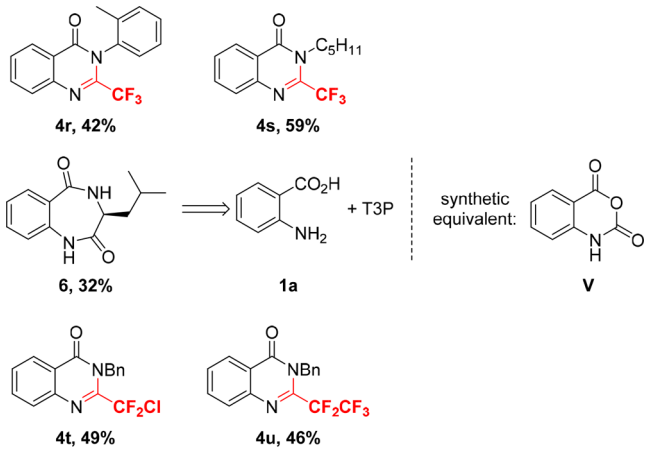
Scheme 4. CF_3-Quinazolinones 4 Prepared by Variation of Anthranilic Acid Substrates



Scheme 5. Dimeric Species Formation



Scheme 6. Amine and Fluoride Source Variation



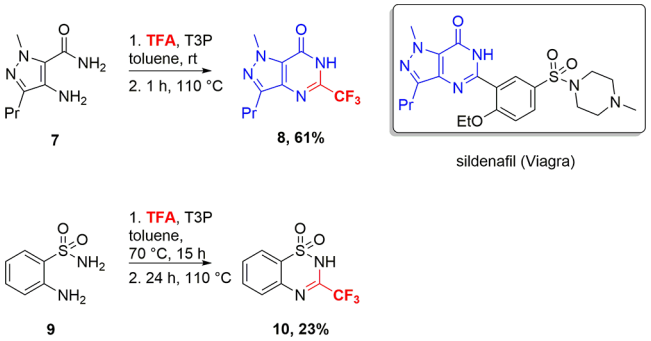
chlorodifluoroacetic acid and pentafluoropropionic acid as examples, allowing for the preparation of the corresponding quinazolinones **4t,u** in reasonable yields.

Our developed protocol is also amenable to the use of amides (Scheme 7). Pyrazole carboxamide **7** was smoothly converted into quinazolinone **8**, a trifluoromethylated variant of the core structure of sildenafil. Additionally, 2-aminobenzenesulfonamide **9** was converted into 3-(trifluoromethyl)-benzothiadiazine-1,1-dioxide **10**, albeit in low isolated yield due to instability of the product during the aqueous workup hydrolyzing back to the starting material.

To prove the practicality and robustness of our T3P-mediated method, we performed a scale-up of the reaction to 80 g of anthranilic acid **1a** affording 86.5 g of pure quinazolinone **4a** corresponding to 50% yield. The lower yield compared to the small scale result (70%, Scheme 3) is caused by the different isolation procedure (see Experimental Section for details). On 80 g scale, classical flash chromatography was replaced by trituration with TBME and a significant amount of product was lost into the mother liquors after

DOI: 10.1021/acs.joc.8b00389
J. Org. Chem. 2018, 83, 5104−5113

Scheme 7. Synthesis of 5-Trifluoromethylpyrimidin-7-ones 8 and 3-(Trifluoromethyl)benzothiadiazine-1,1-dioxide 10 from Corresponding Amides



filtration, indicating room for improvement in the final recovery by fine-tuning of the trituration conditions.

Finally, the synthetic versatility of the obtained CF_3-quinazolinones prepared was demonstrated (Scheme 8). Debenzylation with $AlCl_3$ followed by chlorination-aromatization with $POCl_3$ transformed **4a** into 4-chloro-2-trifluoromethylquinazine **12** in high yield. This versatile intermediate was successfully converted into different derivatives through functionalization at the highly reactive 4-position. For instance, C−C bond formation was achieved by treatment with *i*PrMgCl resulting in the formation of alkylated product **13** in high yield. S_NAr with aniline **14** smoothly produced derivative **15** in 71% yield and methoxylation with NaOMe afforded derivative **16** in quantitative yields.

The highly reactive nature of TFA combined with T3P prompted us to investigate the thermal stability of the mixture—information that becomes of vital importance for preparation and handling on scale. Differential scanning calorimetry (DSC) is a diagnostic and very effective measurement that is usually performed for this purpose, and the result of the nonisothermal DSC of the mixture TFA-T3P in toluene is shown in Figure 1.

Fortunately, only minor exothermic events appeared at lower temperatures (left limits of 118 and 196 °C), and due to the low amount of energy involved they can be regarded as no safety concern. Above 254 °C, larger decompositions are detected with release of moderate to high energies, confirming that this mixture is stable and can be handled and safely used at temperatures below 100 °C. This finding is well in line with the known high thermal stability of T3P itself.[16]

CONCLUSIONS

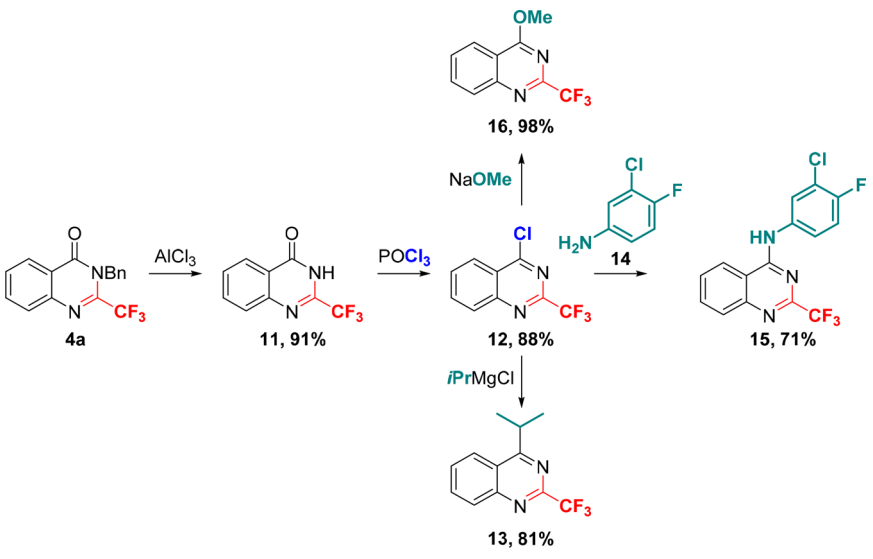
In summary, we have developed a novel and practical one-pot sequential cascade method for the preparation of 2-trifluoromethylquinazolin-4(3*H*)-ones **4**. Our approach uses inexpensive TFA as CF_3 source in combination with commercially available T3P as coupling and dehydrating agent. Chemical diversification was achieved by varying the amine and the acid partners and represents an additional strength of the current method. Most of the compounds that have been prepared are novel (with the exception of **2a**,**b**, **4a**, **6**, **11** and **12**). The potential interest for this specific class of quinazolinones does not only rely on the similarity to the corresponding biologically active nonfluorinated analogs, but also on the fact that such building blocks can be easily derivatized providing access to a wide range of trifluoromethylated derivatives that might be difficult to access with other methods.

EXPERIMENTAL SECTION

General Methods. All the chemicals employed are commercially available and were used as such with no further purification. Solution of T3P in toluene was purchased from Euticals.

Infrared spectra were recorded on a PerkinElmer SPECTRUM ONE-Spectrophotometer and are reported as cm^{-1} (w = weak, m = medium, s = strong). High resolution mass spectrometric measurements were performed with SYNAPT G2MS (Waters) Q-Tof instrument that can provide up to 40 000 fwhm resolution, data-acquisition rate of 20 spectra/second, exact mass (1 ppm RMS) information and a dynamic range of up to 5 orders of magnitude (conditions for analysis in the Supporting Information). LC−MS analyses were performed using Aquity Waters system equipped with an Agilent G4220A binary pump coupled with Thermo Finnigan MSQ Plus MS (Ionization: ESI+), Agilent DAD-G4212A and Column oven Dionex TCC-3200. (conditions for analysis in the Supporting Information). Melting points were measured with DSC analyses. ^1H and ^{13}C (proton decoupled) spectra were recorded on a Bruker NMR 500 MHz spectrometer Avance HD equipped with DCH-Cryoprobe (500 and 125 MHz respectively) and with a Bruker NMR 400 MHz

Scheme 8. Derivatization of 3-Benzyl-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4a)



DOI: 10.1021/acs.joc.8b00389
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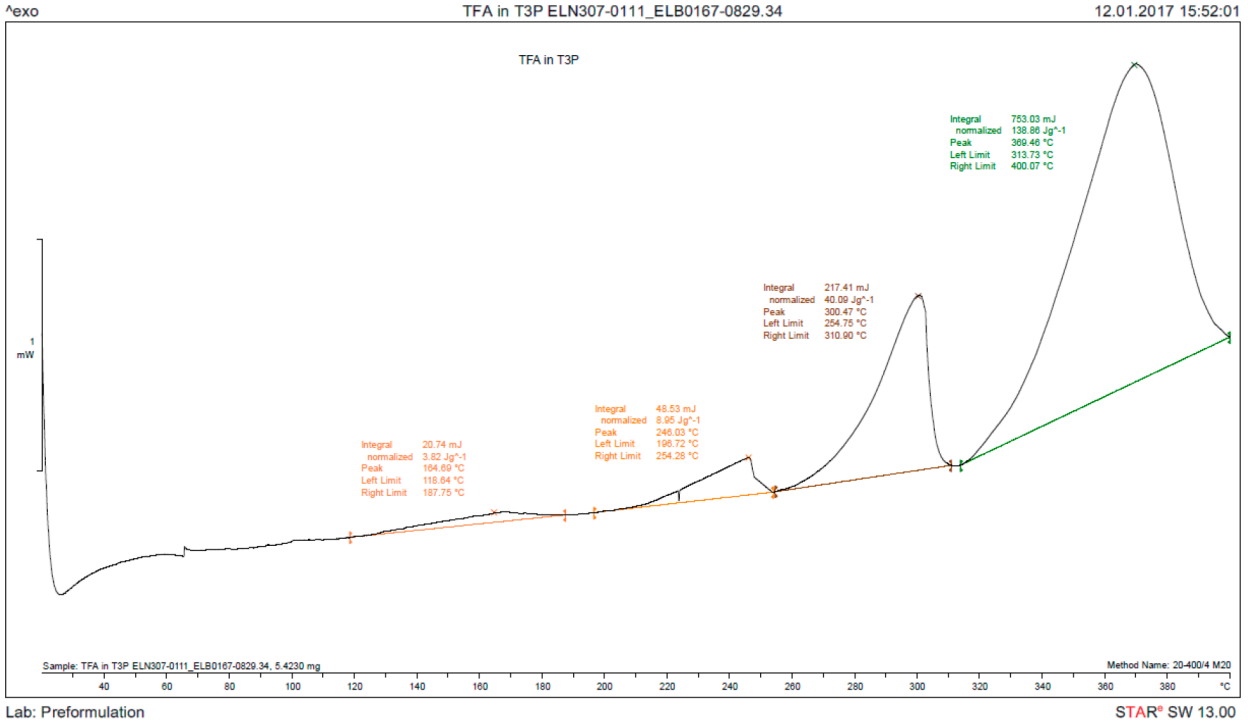

Figure 1. DSC of TFA-T3P mixture in toluene (heat ramp 4 °C/min).

Spectrometer Avance 2 used as well to measure ^{19}F spectra recorded with 5 mm BBO Probehead at 375 MHz. Chemical shifts (δ) values are reported in parts per million using residual solvent signal as reference and the coupling constants (J) are reported in Hz. Novel compounds were characterized with ^{1}H, ^{13}C NMR, IR and HRMS and melting point when applicable.

General Procedure for 2-Trifluoromethylbenzoxazin-4-ones 2. To a suspension of the corresponding anthranilic acids **1a,b** (1.0 g, 1.0 equiv) in toluene (4 mL) at rt was added dropwise trifluoroacetic acid (1.15 equiv) followed by T3P (50% w/w in toluene, 1.2 equiv). The reaction mixture was stirred at rt for 2 h before adding Et_3N (1.0 equiv) and T3P (50% in toluene, 1.0 equiv). The reaction mixture was then heated at reflux (110−115 °C). After completion of the reaction, the mixture was cooled to rt and quenched by slow addition of aq. sat. $NaHCO_3$ (25 mL, ***Caution!*** *Gas evolution*) followed by extraction with solvents such as EtOAc or DCM. Collected organic phases were washed with aq. sat. $NaHCO_3$ (25 mL) and brine (25 mL), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to afford desired crude benzoxazinones **2**.

*2-(Trifluoromethyl)-4H-benzo[d][1,3]oxazin-4-one (**2a**).*[11b] The reaction was performed according to the general procedure with anthranilic acid **1a** as starting material. After workup, desired compound **2a** was obtained without further purification as an off-white solid (2.59 g, 83%). mp 49 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, J_1 = 7.9 Hz, J_2 = 1.3 Hz, 1 H), 7.94−7.99 (m, 1 H), 7.82 (d, J = 7.6 Hz, 1 H), 7.73 (td, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 147.4 (q, J = 42.0 Hz), 144.0, 137.4, 130.9, 129.3, 128.3, 117.9, 116.1 (q, J = 276.0 Hz). ^{19}F NMR (375 MHz, $CDCl_3$) δ −72.49. MS $[M - H]^+ + H_2O$ 232.09. The analytical data are consistent with reported data.

*7-Chloro-2-(trifluoromethyl)-4H-benzo[d][1,3]-oxazin-4-one (**2b**).*[11] The reaction was performed according to the general procedure with 4-chlorobenzoic acid **1b** as starting material. The crude compound was purified by trituration with TBME yielding compound **2b** as a light brown solid (1.27 g, 89%). mp 50 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 8.5 Hz, 1 H), 7.81 (d, J = 2.0 Hz, 1 H), 7.69 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.72, 148.6 (q, J = 42 Hz), 145.03, 144.09, 131.56, 130.50, 128.23, 117.05, 115.87 (q, J = 166.6 Hz). ^{19}F NMR (375 MHz, $CDCl_3$) δ −72.56. MS $[M - H]^+ + H_2O$ 266.00. The analytical data are consistent with reported data.

General Procedure for 3-Benzyl-2-(trifluoromethyl)-quinazolin-4(*3H*)-ones 4a−i,m,n,r−u (Strategy I). To a suspension of the corresponding anthranilic acids **1a−i,m,n,r−u** (1 g, 1.0 equiv) in toluene (4 mL) at rt was added Et_3N (1.0 equiv) and T3P (50% w/w in toluene, 1.0 equiv). After stirring until total consumption of **1a−i,m,n,r−u** (checked by LC−MS, 3−5 h typically) benzylamine (0.98 equiv) was added dropwise at rt and then heated at 70 °C and left at this temperature for 12−15 h. Aside, a solution of the fluorinated acid (1.0 equiv) in T3P (50% w/w in toluene, 1.0 equiv) was prepared and added dropwise to the reaction mixture cooled to rt. The resulting mixture was stirred until total consumption of the amide (2−3 h typically), and then heated at reflux for 16−20 h until full conversion was achieved. The cooled reaction mixture was quenched by dropwise addition of aq. sat. $NaHCO_3$ (25 mL, ***Caution!*** *Gas evolution*) followed by extraction with solvents such as EtOAc/*i*PrOAc or DCM (1× 25 mL). Collected organic phases were washed with 25 mL of aq. sat. $NaHCO_3$ and brine (25 mL) respectively, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to afford desired crude quinazolino-4-ones **4a−i,m,n,r−u**.

*3-Benzyl-2-(trifluoromethyl)quinazolin-4(3H)-one (**4a**).*[9e] The reaction was performed according to the general procedure with anthranilic acid **1a** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4a** as a white solid (1.54 g, 70%). mp 95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.0 Hz, 1 H), 7.89 (d, J = 3.8 Hz, 2 H), 7.63−7.70 (m, 1 H), 7.33 (m, 3 H), 7.20 (d, J = 7.4 Hz, 2 H), 5.47 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 145.1, 142.4 (q, J = 35.9 Hz), 135.5, 135.2, 129.5, 128.7, 128.6, 127.7, 127.4, 126.3, 121.9, 118.18 (q, J = 277.2 Hz), 47.90. ^{19}F NMR (375 MHz, $CDCl_3$) δ −65.30. MS $[M + H]^+$ 305.20 m/z. The analytical data are consistent with reported data.

Scale-up Experiment. The reaction was performed in a 4 L double-jacketed reactor with 80 g of anthranilic acid as starting material according to the general procedure. After workup, crude product (207 g) was taken up in TBME (160 mL) and the mixture heated to 45 °C and then cooled to 0 °C for 30 min. The resulting suspension was filtered off and the cake washed with TBME (100 mL).

DOI: 10.1021/acs.joc.8b00389
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Pure quinazolinone **4a** (86.5 g, 50%) was obtained as a white crystalline solid.

*3-Benzyl-5-methoxy-2-(trifluoromethyl)quinazolin-4-(3H)-one (**4b**).* The reaction was performed according to the general procedure with anthranilic acid **1b** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4b** as a yellow solid (1.38 g, 69%). mp 117 °C. ^{1}H NMR (500 MHz, DMSO) δ 7.87 (t, J = 8.3 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 7.24−7.34 (m, 4 H), 7.16 (d, J = 7.4 Hz, 2 H), 5.27 (s, 2 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, DMSO) δ 160.2, 158.5, 147.3, 142.7 (q, J = 34.8 Hz), 136.8, 136.4, 128.9, 127.5, 126.1, 120.4, 118.4 (q, J = 277.4 Hz), 111.9, 111.3, 56.7, 47.3. ^{19}F NMR (375 MHz, DMSO) δ −64.99. MS $[M + H]^+$ 335.16 m/z. IR 1694 (s), 1099 (s), 970 (s), 817(s), 738 (s) cm^{-1}. HRMS (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{17}H_{14}F_3N_2O_2$ 335.1002, found 335.1010.

*3-Benzyl-7-methoxy-2-(trifluoromethyl)quinazolin-4-(3H)-one (**4c**).* The reaction was performed according to the general procedure with anthranilic acid **1c** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4c** as a yellow solid (0.64 g, 65%, contaminated with ca. 20 mol % of *N*-benzyl-2,2,2-trifluoroacetamide). mp 124 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.14 (d, J = 8.8 Hz, 1 H), 7.24−7.38 (m, 5 H), 7.16 (d, J = 7.2 Hz, 2 H), 5.35 (s, 2 H), 3.96 (s, 3 H). ^{13}C NMR (125 MHz, DMSO) δ 165.2, 147.3, 142.93 (q, J = 34.8 Hz), 137.9, 136.7, 128.9, 128.8, 127.8, 127.6, 126.1, 119.7, 115.8 (q, J = 34.8 Hz), 110.0, 56.7, 47.5. ^{19}F NMR (375 MHz, DMSO) δ −64.74. MS $[M + H]^+$ 335.16 m/z. IR, 1680 (s), 1610 (s), 1106 (s), 1004 (s) 770 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{17}H_{14}N_2O_2F_3$ 335.1002, found 335.1020.

*3-Benzyl-7-chloro-2-(trifluoromethyl)quinazolin-4-(3H)-one (**4d**).* The reaction was performed according to the general procedure with anthranilic acid **1d** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4d** as an off white solid (1.40 g, 72%). mp 105 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.23 (d, J = 8.6 Hz, 1 H), 8.03 (d, J = 1.9 Hz, 1 H), 7.80 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 7.32 (m, 2 H), 7.19−7.27 (m, 3 H), 5.35 (s, 2 H). ^{13}C NMR (125 MHz, DMSO) δ 160.9, 146.2, 143.6 (q, J = 35.4 Hz), 140.5, 136.3, 130.5, 129.2, 128.9, 128.0, 127.6, 126.2, 121.1, 118.5 (q, J = 277.5 Hz), 48.0. ^{19}F NMR (375 MHz, DMSO) δ −64.83. MS $[M + H]^+$ 339.00 m/z. IR 1698 (s), 1602 (s), 1405 (s), 1199 (s), 750 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{16}H_{11}ClF_3N_2O$ 339.0507, found 339.0516.

*3-Benzyl-8-chloro-2-(trifluoromethyl)quinazolin-4-(3H)-one (**4e**).* The reaction was performed according to the general procedure with anthranilic acid **1e** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4e** as a yellow solid (0.98 g, 51%). mp 87 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.19 (dd, J_1 = 1.3 Hz, J_2 = 8.0 Hz, 1 H), 8.15 (dd, J_1 = 1.4 Hz, J_2 = 7.9 Hz, 1 H), 7.73 (t, J = 7.9 Hz, 1 H), 7.22−7.34 (m, 5 H), 5.36 (s, 2 H). ^{13}C NMR (125 MHz, DMSO) δ 161.0, 143.0 (q, J = 35.6 Hz), 141.9, 136.2, 135.9, 132.3, 130.7, 128.9, 127.6, 126.3, 126.2, 124.1, 119.1 (q, J = 277.8 Hz), 48.2. ^{19}F NMR (375 MHz, DMSO) δ −64.79. MS $[M + H]^+$ 338.98 m/z. IR 1680 (s), 1399 (s), 1205 (s), 988 (s), 765 (s). (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{16}H_{11}ClF_3N_2O$ 339.0507, found 339.0520.

*3-Benzyl-6-iodo-2-(trifluoromethyl)quinazolin-4-(3H)-one (**4f**).* The reaction was performed according to the general procedure with anthranilic acid **1f** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4f** as a yellow solid (1.0 g, 63%). mp 105 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.50 (d, J = 2.0 Hz, 1 H), 8.29 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 7.69 (d, J = 8.5 Hz, 1 H), 7.18−7.33 (m, 5 H), 5.35 (s, 2 H). ^{13}C NMR (125 MHz, DMSO) δ 160.1, 144.4, 144.3, 142.8 (q, J = 35.7 Hz), 136.3, 135.4, 130.7, 128.9, 127.6, 126.2, 123.8, 119.1 (q, J = 277.1 Hz), 96.3, 48.1. ^{19}F NMR (375 MHz, DMSO) δ −64.75. MS $[M + H]^+$ 430.98 m/z. IR 1692 (s), 1606 (m), 1202 (s), 843 (s), 722 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{16}H_{11}F_3IN_2O$ 430.9862, found 430.9870.

*3-Benzyl-7-iodo-2-(trifluoromethyl)quinazolin-4-(3H)-one (**4g**).* The reaction was performed according to the general procedure with anthranilic acid **1g** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4g** as a yellow solid (1.09 g, 67%). mp 122 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.32 (d, J = 1.5 Hz, 1 H), 8.08 (dd, J_1 = 1.6 Hz, J_2 = 8.3 Hz, 1 H), 7.95 (d, J = 8.3 Hz, 1 H), 7.18−7.33 (m, 5 H), 5.34 (s, 2 H). ^{13}C NMR (125 MHz, DMSO) δ 161.2, 145.8, 143.2 (q, J = 35.5 Hz), 138.9, 137.1, 136.3, 128.9, 128.6, 127.6, 126.2, 121.6, 117.9 (q, J = 277.4 Hz), 104.0, 47.9. ^{19}F NMR (375 MHz, DMSO) δ −64.80. MS $[M + H]^+$ 431.03 m/z. IR 1693 (s), 1588 (m), 1199 (s), 998 (m), 708 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{16}H_{11}F_3IN_2O$ 430.9862, found 430.9879.

*3-Benzyl-6-fluoro-2-(trifluoromethyl)quinazolin-4-(3H)-one (**4h**).* The reaction was performed according to the general procedure with anthranilic acid **1h** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 50/50) yielding compound **4h** as a white solid (0.59 g, 59%). mp 94 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.01 (dd, J_1 = 8.9 Hz, J_2 = 4.9 Hz, 1 H), 7.87−7.95 (m, 2 H), 7.19−7.33 (m, 5 H), 5.36 (s, 2 H). ^{13}C NMR (125 MHz, DMSO) δ 163.3, 161.3, 160.8 (d, J = 3 Hz), 142.0, 136.3, 131.9 (d, J = 9 Hz), 128.9, 127.6, 126.2, 124.4 (d, J = 24.3 Hz), 123.9 (d, J = 9.1 Hz), 118.7 (q, J = 277.1 Hz), 112.2 (d, J = 24.1 Hz), 48.0. ^{19}F NMR (375 MHz, DMSO) δ −64.63, −109.01. MS $[M + H]^+$ 323.13 m/z. IR 1694 (s), 1202 (s), 992 (m), 726 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{16}H_{11}F_4N_2O$ 323.0802, found 323.0813.

*3-Benzyl-2,7-bis(trifluoromethyl)quinazolin-4-(3H)-one (**4i**).* The reaction was performed according to the general procedure with anthranilic acid **1i** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4i** as a yellow thick oil (1.28 g, 72%). ^{1}H NMR (500 MHz, DMSO) δ 8.43 (d, J = 8.3 Hz, 1 H), 8.29 (s, 1 H), 8.06 (dd, J_1 = 8.3 Hz, J_2 = 1.3 Hz, 1 H), 7.18−7.34 (m, 5 H), 5.38 (s, 2 H). ^{13}C NMR (125 MHz, DMSO) δ 160.9, 145.3, 143.8 (q, J = 35.5 Hz), 135.3 (q, J = 32.5 Hz), 129.0, 128.9, 127.6, 126.2, 126.0 (m), 125.2, 124.9, 123.8 (q, J = 273.2 Hz), 118.46 (q, J = 277.5 Hz), 55.4, 48.2. ^{19}F NMR (375 MHz, DMSO) δ −61.69, −64.87. MS $[M + H]^+$ 373.12 m/z. IR 1701 (s), 1609 (s), 1316 (s), 1205 (s), 973 (m), 692 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{17}H_{11}F_6N_2O$ 373.0770, found 373.0775.

General Procedure for 3-Benzyl-2-(trifluoromethyl)-quinazolin-4(3*H*)-ones 4j−l,o (Strategy II). A prepared solution of the trifluoroacetic acid (1.0 equiv) in T3P (50% w/w in toluene, 1.0 equiv) was added at rt dropwise to a suspension of the corresponding anthranilic acids **1j−l,o** (1 g, 1.0 equiv) in toluene (4 mL). After stirring until total consumption of **1j−l,o** (checked by LC−MS, 3−5 h typically), Et_3N (1.0 equiv) and T3P (50% w/w in toluene, 1.0 equiv) were sequentially added followed by benzylamine (0.98 equiv). The resulting reaction mixture was heated to 70 °C and kept it for 14 h followed by 5−7 h at reflux to achieve complete cyclization. The cooled reaction mixture was quenched by dropwise addition of aq. sat. $NaHCO_3$ (25 mL, ***Caution!*** *Gas evolution*) followed by extraction with solvents such as EtOAc/*i*PrOAc or DCM (1× 25 mL). Collected organic phases were washed with 25 mL of aq. sat. $NaHCO_3$ and brine (25 mL) respectively, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to afford desired crude quinazolino-4-ones **4j−l,o**.

*3-Benzyl-7-nitro-2-(trifluoromethyl)quinazolin-4-(3H)-one (**4j**).* The reaction was performed according to the general procedure with anthranilic acid **1j** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4j** as a light yellow solid (1.43 g, 75%). mp 110 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.62 (t, J = 1.1 Hz, 1 H), 8.46 (d, J = 1.0 Hz, 2 H), 7.24−7.36 (m, 5 H), 5.37 (s, 2 H). ^{13}C NMR (125 MHz,

DOI: 10.1021/acs.joc.8b00389
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DMSO) δ 160.7, 152.1, 145.6, 144.3 (q, J = 35.6 Hz), 138.0, 136.0, 129.5, 128.9, 127.8, 126.6, 126.3, 123.8, 118.8 (q, J = 277.8 Hz), 48.4. ^{19}F NMR (375 MHz, DMSO) δ −64.90. MS $[M + H]^+$ + NH_4^+ 366.99 m/z. IR 1698 (s), 1529 (s), 1404 (s), 1199 (s), 982 (s), 687 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{16}H_{11}F_3N_3O_3$ 350.0747, found 350.0746.

3-Benzyl-2-(trifluoromethyl)benzoquinazolin-4-(3H)-one (**4k**). The reaction was performed according to the general procedure with anthranilic acid **1k** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4k** as a white solid (1.04 g, 55%). mp 129 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.97 (s, 1 H), 8.56 (s, 1 H), 8.33 (d, J = 8.2 Hz, 1 H), 8.23 (d, J = 8.2 Hz, 1 H), 7.75 (m, 2 H), 7.21−7.34 (m, 5 H), 5.40 (s, 2 H). ^{13}C NMR (125 MHz, DMSO) δ 162.0, 141.5 (q, J = 35.1 Hz), 140.3, 136.8, 136.6, 132.8, 129.9, 129.7, 128.9, 128.8, 128.2, 127.5, 127.5, 126.1, 118.7 (q, J = 277.1 Hz), 47.6. ^{19}F NMR (375 MHz, DMSO) δ −64.60. MS $[M + H]^+$ 355.13 m/z. IR 1693 (s), 1609 (s), 1186 (s), 905 (s), 698 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{20}H_{14}F_3N_2O$ 355.1053, found 355.1061.

3-Benzyl-2-(trifluoromethyl)pteridin-4(3H)-one (**4l**). The reaction was performed according to the general procedure with anthranilic acid **1l** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (DCM/MeOH: 100/0 to 90/10) yielding compound **4l** as a yellow foam (1.05 g, 48%). ^{1}H NMR (400 MHz, DMSO) δ 9.18 (d, J = 2.1 Hz, 1 H), 9.05 (d, J = 2.1 Hz, 1 H), 7.27−7.35 (m, 5 H), 5.38 (s, 2 H). ^{13}C NMR (125 MHz, DMSO) δ 160.9, 152.1, 151.4, 147.3, 145.6 (q, J = 36 Hz), 135.9, 134.7, 128.8, 127.6, 126.3, 118.4 (q, J = 277.9 Hz), 48.6 (d, J = 3 Hz). ^{19}F NMR (375 MHz, DMSO) δ −65.11. MS $[M + H]^+$ 307.18 m/z. IR 1728 (m), 1347 (s), 1120 (s), 1125 (s), 731 (s), 695 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{14}H_{10}F_3N_4O$ $[M + H]^+$ 307.0801, found 307.0816.

3-Benzyl-2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4(3H)-one (**4m**). The reaction was performed according to the general procedure with anthranilic acid **1m** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4m** as a light yellow solid (0.55 g, 25%). mp 127 °C. ^{1}H NMR (500 MHz, DMSO) δ 9.13 (dd, J_1 = 4.5 Hz, J_2 = 1.9 Hz, 1 H), 8.63 (dd, J_1 = 7.9 Hz, J_2 = 1.9 Hz, 1 H), 7.77 (dd, J_1 = 7.9 Hz, J_2 = 4.6 Hz, 1 H), 7.23−7.34 (m, 5 H), 5.36 (s, 2 H). ^{13}C NMR (125 MHz, DMSO) δ 162.1, 157.2, 155.5, 145.3 (q, J = 35.9 Hz), 136.9, 136.2, 128.9, 127.6, 126.2, 125.5, 121.7, 120.3 (q, J = 277.4 Hz), 48.2. ^{19}F NMR (375 MHz, DMSO) δ −65.03. MS $[M + H]^+$ 305.88 m/z. IR 1698 (s), 1394 (s), 1211 (s), 731 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{15}H_{11}F_3N_3O$ 306.0849, found 306.0852.

3-Benzyl-6-bromo-2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4(3H)-one (**4n**). The reaction was performed according to the general procedure with anthranilic acid **1n** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: 100/0 to 70/30) yielding compound **4n** as a light yellow thick oil (0.37 g, 21%). ^{1}H NMR (500 MHz, DMSO) δ 9.24 (d, J = 2.6 Hz, 1 H), 8.79 (d, J = 2.6 Hz, 1 H), 7.25−7.33 (m, 5 H), 5.35 (s, 2 H). ^{13}C NMR (125 MHz, DMSO) δ 161.3, 157.9, 154.2, 145.5 (q, J = 35.8 Hz), 138.4, 135.9, 129.0, 128.9, 127.8, 127.7, 126.3, 119.1 (q, J = 276.80 Hz), 48.4. ^{19}F NMR (375 MHz, DMSO) δ −65.08. MS $[M + H]^+$ 385.75 m/z. IR 1696 (s), 1449 (s), 1308 (s), 1210 (s), 808 (s), 729, (s), 695 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{15}H_{11}BrF_3N_3O$ 383.9954, found 383.9958.

3-Benzyl-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4(3H)-one (**4o**). The reaction was performed according to the general procedure with anthranilic acid **1o** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: from 100/0 to 50/50) yielding compound **4o** as a light yellow solid (0.83 g, 38%). mp 106 °C. ^{1}H NMR (500 MHz, DMSO) δ 9.29 (s, 1 H), 8.88 (d, J = 5.2 Hz, 1 H), 8.09 (d, J = 5.2 Hz, 1 H), 7.23−7.33 (m, 5 H), 5.36 (s, 2 H). ^{13}C NMR (125 MHz, DMSO) δ 160.8, 151.7, 149.4, 144.1 (q, J = 35.7 Hz), 140.0, 136.0, 128.9, 127.7, 127.6, 126.3, 119.4 (q, J = 277.6 Hz), 119.2, 48.4. ^{19}F NMR (375 MHz, DMSO) δ −64.81. MS $[M + H]^+$ 305.92 m/z. IR 1703 (s), 1401 (s), 1202 (s), 693 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{15}H_{11}F_3N_3O$ 306.0849, found 306.0852

3-(o-Tolyl)-2-(trifluoromethyl)quinazolin-4-(3H)-one (**4r**). The reaction was performed according to the general procedure with anthranilic acid **1r** as starting material, *o*-toluidine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: from 100/0 to 70/30) yielding compound **4r** as a white solid (0.92 g, 42%). mp 144 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38−8.40 (m, 1 H), 7.91−7.96 (m, 2 H), 7.69 (m, 1 H), 7.36−7.48 (m, 3 H), 7.23 (d, J = 7.8 Hz, 1 H), 2.16 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 145.4, 142.4 (q, J = 35.5 Hz), 136.9, 135.3, 133.9, 131.0, 130.3, 129.6, 129.1, 128.8, 127.5, 126.9, 122.2, 117.8 (q, J = 277.5 Hz), 17.51. ^{19}F NMR (375 MHz, $CDCl_3$) δ −65.58. MS $[M + H]^+$ 305.21 m/z. IR 1692 (s), 1375 (s), 1202 (s), 965 (s), 693 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{16}H_{12}F_3N_2O$ 305.0896, found 305.0898.

3-Pentyl-2-(trifluoromethyl)quinazolin-4(3H)-one (**4s**). The reaction was performed according to the general procedure with anthranilic acid **1s** as starting material, *n*-pentylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: from 100/0 to 70/30) yielding compound **4s** as a transparent oil (1.23 g, 59%). ^{1}H NMR (500 MHz, DMSO) δ 8.23 (d, J = 7.7 Hz, 1 H), 7.94−7.97 (m, 1 H), 7.85 (d, J = 8.1 Hz, 1 H), 7.73 (t, J = 7.7 Hz, 1 H), 4.01 (t, J = 8.0 Hz, 2 H), 1.67−1.72 (m, 2 H), 1.35 (m, 4 H), 0.88−0.91 (m, 3 H). ^{13}C NMR (125 MHz, DMSO) δ 161.1, 145.0, 142.1 (q, J = 34.9 Hz), 135.7, 130.0, 128.6, 127.0, 122.1, 118.7 (q, J = 276.8 Hz), 45.4, 28.9, 28.0, 22.1, 14.3. ^{19}F NMR (375 MHz, DMSO) δ −64.88. MS $[M + H]^+$ 285.26. IR 2933 (m), 1690 (s), 1609 (s), 1467 (s), 1404 (s), 1321 (s), 1238 (s), 1202 (s), 1092 (s), 772 (s), 695 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{14}H_{16}F_3N_2O$ 285.1209, found 285.1216.

(S)-3-Isobutyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**6**).[15c] To a suspension of anthranilic acid **1a** (1.0 g, 7.22 mmol, 1.0 equiv) in toluene (4 mL) at rt was added Et_3N (1.5 mL, 10.8 mmol, 1.5 equiv) followed by T3P (50% w/w in toluene, 4.38 mL, 7.22 mmol, 1.0 equiv). The resulting mixture was kept at rt for 2.5 h then heated to 70 °C and L-leucine methyl ester hydrochloride (1.3 g, 7.07 mmol, 0.98 equiv) added in one portion. After 20 h at 70 °C, the reaction mixture was cooled to rt, diluted with EtOAc (25 mL) and quenched by slow addition of aq. sat. $NaHCO_3$ (25 mL, ***Caution!*** *Gas evolution*). Aqueous phase was extracted with EtOAc (25 mL) and collected organic phases were washed with aq. sat. $NaHCO_3$ (25 mL) and brine (25 mL), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to afford desired crude **6**. After trituration with TBME (10 mL), purified benzodiazepine dione **6** was obtained as a white powder (0.53 g, 32%). mp 242 °C. ^{1}H NMR (500 MHz, DMSO) δ 10.38 (s, 1 H), 8.45 (d, J = 5.8 Hz, 1 H), 7.74 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1 H), 7.52 (m, 1 H), 7.21−7.24 (m, 1 H), 7.10 (d, J = 8.0 Hz, 1 H), 3.61 (q, J = 7.2 Hz, 1 H), 1.66−1.75 (m, 1 H), 1.56 (t, J = 7.2 Hz, 2 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.78 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (125 MHz, DMSO) δ 172.1, 168.2, 137.2, 132.7, 130.8, 126.8, 124.4, 121.4, 36.6, 24.3, 23.3, 22.0. MS $[M + H]^+$ 233.20. The analytical data are consistent with reported data.

3-Benzyl-2-(chlorodifluoromethyl)quinazolin-4-(3H)-one (**4t**). The reaction was performed according to the general procedure with anthranilic acid **1t** as starting material, benzylamine and chlorodifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: from 100/0 to 80/20) yielding compound **4t** as a transparent oil (1.13 g, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (dt, J_1 = 1.0 Hz, J_2 = 8.0 Hz, 1 H), 7.88−7.89 (m, 2 H), 7.63−7.67 (m, 1 H), 7.26−7.35 (m, 3 H), 7.17 (d, J = 7.3 Hz, 2 H), 5.57 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 145.8, 145.6 (t, J = 28.7 Hz), 145.0, 135.6, 135.1, 129.3, 128.7, 127.5, 127.4, 126.1, 121.6, 119.5 (t, J = 294.3 Hz), 48.3. ^{19}F NMR (375 MHz, $CDCl_3$) δ −53.79. MS $[M + H]^+$ 321.16. IR 1690 (s), 1602 (s), 1167 (s), 1114 (s), 924 (s), 809 (m), 772 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{16}H_{12}ClF_2N_2O$ 321.0601, found 321.0603.

DOI: 10.1021/acs.joc.8b00389
J. Org. Chem. 2018, 83, 5104−5113

*3-Benzyl-2-(perfluoroethyl)quinazolin-4-(3H)-one (**4u**).* The reaction was performed according to the general procedure with anthranilic acid **1u** as starting material, benzylamine and trifluoroacetic acid. The crude compound was purified by flash chromatography (*n*-heptane/EtOAc: from 100/0 to 70/30) yielding compound **4u** as a light brown solid (1.18 g, 46%). mp 62 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36−8.38 (m, 1 H), 7.87 (m, 2 H), 7.66 (m, 1 H), 7.30−7.36 (m, 3 H), 7.21 (d, J = 7.3 Hz, 2 H), 5.51 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 144.8, 142.1 (t, J = 27.6 Hz), 135.7, 135.0, 129.7, 128.7, 127.6, 127.3, 126.3, 122.0, 119.5 (t, J = 34.4 Hz), 117.2 (q, J = 34.2 Hz), 110.9 (m), 47.6. ^{19}F NMR (375 MHz, $CDCl_3$) δ −108.99, −79.62. MS $[M + H]^+$ 355.09 m/z. IR 1686 (s), 1608 (s), 1397 (s), 1234 (s), 1194 (s), 1134 (s), 1072 (s), 944 (s723 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{17}H_{12}F_5N_2O$ 355.0864, found 355.0870.

*1-Methyl-3-propyl-5-(trifluoromethyl)-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one (**8**).* A prepared solution of the trifluoroacetic acid (0.42 mL, 5.38 mmol, 1.0 equiv) in T3P (50% w/w in toluene, 3.3 mL, 5.38 mmol, 1.0 equiv) was added dropwise to a suspension 4-amino-1-methyl-3-*N*-propyl-1*H*-pyrazole-5-carboxamide (**7**) (1.0 g, 5.38 mmol, 1.0 equiv) in toluene (4 mL) at rt. After 4 h the mixture was heated to reflux for 1h to complete the cyclization. The cooled reaction mixture was diluted with EtOAc (45 mL), quenched by dropwise addition of aq. sat. $NaHCO_3$ (25 mL, ***Caution!*** *Gas evolution*) followed by extraction with EtOAc (25 mL). Collected organic phases were washed with 25 mL of aq. sat. $NaHCO_3$ and brine (25 mL) respectively, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to afford the crude compound as a yellow-white powder which was purified by trituration with EtOAc (20 mL) to yield **8** as a white powder (0.85 g, 61%). mp 202 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.8 (br,s, 1 H), 4.31 (s, 3 H), 2.93 (t, J = 7.5 Hz, 2 H), 1.84 (m, 2 H), 1.03 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 148.0, 139.0 (q, J = 39.1 Hz), 136.5, 125.4, 118.1 (q, J = 275.5 Hz), 38.5, 27.5, 22.3, 13.9. ^{19}F NMR (375 MHz, $CDCl_3$) δ −69.37. MS $[M + H]^+$ 261.30 m/z. IR 1690 (s), 1321 (s), 1217 (s), 877 (s), 760(s), 706 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{10}H_{12}F_3N_4O$ 261.0958, found 261.0965.

*3-(Trifluoromethyl)-2H-benzo[e][1,2,4]thiadiazine 1,1-dioxide (**10**).* A prepared solution of the trifluoroacetic acid (0.44 mL, 5.69 mmol, 1.0 equiv) in T3P (50% w/w in toluene, 3.45 mL, 5.69 mmol, 1.0 equiv) was added dropwise to a suspension of 2-amino-benzensulfonamide **9** (1.0 g, 5.69 mmol, 1.0 equiv) in toluene (4 mL) at rt. The reaction mixture was heated to 70 °C for 15 h and then additional T3P (50% w/w in toluene, 1.70 mL, 2.85 mmol, 0.5 equiv) added and further stirred at reflux for 24 h. After completion of the reaction, the cooled reaction mixture was diluted with EtOAc (20 mL), quenched by dropwise addition of aq. sat. $NaHCO_3$ (20 mL, ***Caution!*** *Gas evolution*) followed by extraction with EtOAc (20 mL). Collected organic phases were washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to afford the crude compound as a light brown solid which was purified by trituration with TBME (10 mL) to yield **10** as an off white solid (0.33 g, 23%). mp 154 °C. ^{1}H NMR (500 MHz, DMSO) δ 7.78 (d, J = 8.0 Hz, 1 H), 7.62 (t, J = 7.0 Hz, 1 H), 7.42 (d, J = 7.8 Hz, 2 H), 3.37 (br s, 1H). ^{13}C NMR (125 MHz, DMSO) δ 147.8 (m), 140.8, 132.8, 126.8, 123.9, 123.4, 123.2, 119 (m). ^{19}F NMR (375 MHz, DMSO) δ −70.70. MS $[M - H]^+$ 249.04 m/z. IR 1633 (m); 1571 (s), 1540 (s), 1471 (s), 1292 (s), 951 (s), 766 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_8H_6F_3N_2O_2S$ 251.0097, found 251.0000.

*2-(Trifluoromethyl)quinazolin-4-(3H)-one (**11**).*[17] To a suspension of $AlCl_3$ (0.35 g, 2.46 mmol, 1.5 equiv) in toluene (4 mL) was added at rt 3-benzyl-2-(trifluoromethyl)quinazolin-4-(3*H*)-one (**4a**) (0.5 g, 1.64 mmol, 1.0 equiv) in one portion. After 0.5 h the reaction mixture was diluted with EtOAc (15 mL) and carefully quenched by dropwise addition of aq. sat. $NaHCO_3$ (10 mL). After extracting with EtOAc (15 mL), collected organic phase was washed with water and brine (10 mL, respectively), dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the crude compound as a white wet solid. Pure **11** was obtained after trituration with TBME (4 mL) as a white powder (0.32 g, 91%). mp 111 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 8.9 Hz, 1 H), 7.71−7.74 (m, 2 H), 7.39 (td, J_1 = 7.7 Hz, J_2 = 1.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1 (q, J = 38.5 Hz), 137.4, 134.5, 132.8, 126.5, 121.9, 115.3, 115.3 (q, J = 288.7 Hz), 103.8. ^{19}F NMR (375 MHz, DMSO) δ −69.33. MS $[M + H]^+$ 215.15 m/z. The analytical data are consistent with reported data.

*4-Chloro-2-(trifluoromethyl)quinazoline (**12**).*[18] $POCl_3$ (1.02 mL, 11.1 mmol, 0.8 equiv) was added at 95 °C to a white suspension of **11** (2.96 g, 13.8 mmol, 1.0 equiv) in toluene (18 mL) and DMF (1.6 mL, 20.7 mmol, 1.5 equiv). After 30 min, the mixture was cooled to 0 °C with an ice−water bath and quenched with 25 mL of water. The aqueous layer was extracted with EtOAc (25 mL) and collected organic phase was washed with water (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure yielding chloroquinazoline **12** as a white solid (2.83 g, 88%) of sufficient purity to be used as such in the next steps. mp 63 °C (DSC). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (dd, J_1 = 0.8 Hz, J_2 = 8.4 Hz, 1 H), 8.26 (d, J = 8.5 Hz, 1 H), 8.14 (m, 1 H), 7.93 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 151.6 (q, J = 37.6 Hz), 150.5, 136.2, 131.1, 129.6, 126.1, 124.2, 118.2 (q, J = 275.7 Hz). ^{19}F NMR (375 MHz, $CDCl_3$) δ −69.98. MS $[M - H]^+ + H_2O$ 212.98. The analytical data are consistent with reported data.

*4-Isopropyl-2-(trifluoromethyl)quinazoline (**13**).* To a solution of **12** (0.5 g, 2.15 mmol, 1.0 equiv) in dry THF (5 mL) at −20 °C was added dropwise a solution of *i*-propylmagnesium chloride-LiCl complex 14% in THF (2.46 mL, 2.26 mmol, 1.05 equiv). The reaction mixture was stirred at this temperature for 15 min, and at 0 °C iPrOAc (10 mL) added followed by aq. 20% citric acid (5 mL). Collected organic phases were washed with water (2× 20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford compound **13** as a yellow liquid (0.42 g, 81%). ^{1}H NMR (500 MHz, DMSO) δ 8.57 (d, J = 8.4 Hz, 1 H), 8.15−8.22 (m, 2 H), 7.96 (m, 1 H), 4.12−4.20 (m, 1 H), 1.39 (d, J = 6.7 Hz, 6 H). ^{13}C NMR (125 MHz, DMSO) δ 179.1, 151.3 (q, J = 35.1 Hz), 149.3, 136.0, 130.7, 129.6, 125.8, 123.3, 119.4 (q, J = 275.6 Hz), 31.1, 22.1. ^{19}F NMR (375 MHz, DMSO) δ −68.68. MS $[M + H]^+$ 241.24. IR 2975 (m), 1617 (m), 1399 (m), 1195 (s), 1169 (s), 1112 (s), 917 (s), 766 (s), 714 (m) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{12}H_{12}F_3N_2$ 241.0947, found 241.0952.

*N-(3-Chloro-4-fluorophenyl)-2-(trifluoromethyl)quinazolin-4-amine (**15**).* A mixture of **12** (1.0 g, 4.3 mmol, 1.0 equiv), 3-chloro-4-fluoroaniline (**14**) (0.64 g, 4.3 mmol, 1.0 equiv) and DIPEA (1.12 mL, 6.45 mmol, 1.5 equiv) in toluene (10 mL) was heated at reflux for 5.5 h. The reaction mixture was cooled to rt, diluted with 10 mL of *i*PrOAc and aq. citric acid 20% (5 mL). After phase split, the aqueous phase was extracted with *i*PrOAc (10 mL) and collected organic phases dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford crude compound as a brown tick oil which was purified by trituration with MeCN (4 mL) yielding product **15** as a white powder (1.04 g, 71%). mp 127 °C. ^{1}H NMR (500 MHz, DMSO) δ 10.38 (s, 1 H), 8.66 (d, J = 8.1 Hz, 1 H), 8.25 (dd, J_1= 2.6 Hz, J_2= 6.8 Hz, 1 H), 7.97−8.04 (m, 2 H), 7.83−7.89 (m, 2 H), 7.53 (t, J = 9.1 Hz, 1 H). ^{13}C NMR (125 MHz, DMSO) δ 159.1, 155.3, 153.3, 151.4 (q, J = 34.8 Hz), 149.3, 136.2, 134.9, 129.1 (d, J = 14.4 Hz), 124.5, 123.8, 123.2 (d, J = 7.1 Hz), 119.5 (d, J = 18.4 Hz), 119.3 (m), 117.3 (d, J = 21.9 Hz), 115.6. ^{19}F NMR (375 MHz, DMSO) δ −69.68, −121.51. MS $[M + H]^+$ 342.07. IR 1920 (w), 1620 (m), 1541 (s), 1492 (s), 1180 (s), 1081 (m), 960 (s), 781 (s), cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{15}H_9ClF_4N_3$ 342.0416, found 342.0428.

*4-Methoxy-2-(trifluoromethyl)quinazoline (**16**).* NaOMe 25% w/w in MeOH (0.37 mL, 1.61 mmol, 1.5 equiv) was added at rt to a solution of **12** (0.25 g, 1.07 mmol, 1.0 equiv) in toluene (2.5 mL). After 1 h at rt, the resulting suspension was diluted with *i*PrOAc (10 mL) and aq. 20% citric acid (5 mL). Aqueous phase was extracted once with *i*PrOAc (10 mL) and collected organic phases dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford crude compound which was purified by trituration with *i*PrOH (2 mL) where the product was recovered from the mother liquors by evaporation of the solvent under vacuum to yield product **16** as a white solid (0.24 g, 98%). mp 98 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.29 (m, 1 H), 8.12 (m, 2 H), 7.88 (m, 1 H), 4.23 (s, 3 H). ^{13}C NMR

DOI: 10.1021/acs.joc.8b00389
J. Org. Chem. 2018, 83, 5104−5113

(125 MHz, DMSO) δ 168.7, 151.0 (q, J = 36 Hz), 149.9, 135.9, 130.3, 128.5, 124.1, 120.2 (q, J = 276 Hz), 116.5, 55.8. ^{19}F NMR (375 MHz, DMSO) δ −69.23. MS $[M + H]^+$ 229.19. IR 3495 (w), 1698 (m), 1571 (m), 1385 (s), 1259 (m), 1159 (s), 1135 (s), 1101 (s), 727 (s); 683 (s) cm^{-1}. (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{10}H_8F_3N_2O$ 229.0583, found 229.0589.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00389.

NMR spectra, HPLC analysis, MS and UV spectra for compound **1** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Dr. Gabriel Schäfer for proofreading the manuscript and for valuable comments. The authors would like to thank Jürgen Seifert for IR measurements, François Le Goff and Marco Caldarone for HRMS measurements, Julien Grimont for NMR support, Markus von Raumer and his team for DSC measurements. Haute école d'ingénierie et d'architecture de Fribourg is also thanked for financial support. Finally, Dr. Martin Bolli is thanked for reviewing the manuscript.

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(14) Dimers were not isolated and their structure determined on the basis of LC−MS analyses. Although increased acidity of the amino group on substrates **1j−l,o** is foreseen (pK_a: 4.64 for aniline, 4.11 for naphthalen-2-amine, 3.14 for 2-aminopyrazine and 2.45 for 3-nitroaniline, source: http://www.chem.wisc.edu/areas/reich/pkatable/pKa_compilation-1-Williams.pdf), there is no clear explanation for the occurrence of this side-reaction only with substrates **1j−l,o**.
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DOI: 10.1021/acs.joc.8b00389
J. Org. Chem. 2018, 83, 5104−5113