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A novel synthesis of polysubstituted naphthalenes

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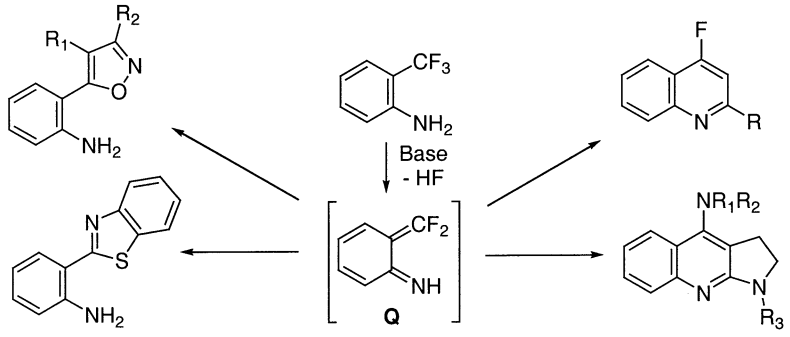
Abstract—The reaction of (2-trifluoromethyl)phenyl acetic acid derivatives with anions derived from aromatic acetonitriles furnishes polysubstituted naphthalenes in good yields (30–68%). A solid-phase version of this reaction is reported as well. The transformation is proposed to proceed via the intermediate formation of the quinone methide intermediate.

The anionically activated trifluoromethyl group has great utility in the synthesis of various aromatic, and hetero-aromatic compounds.[1] Representative examples of this chemistry featuring *ortho*-trifluoromethyl aniline are summarized in Scheme 1.[2–11] It has been suggested that these transformations are initiated by the proton abstraction from the anilinic nitrogen to afford the quinone methide intermediate **Q** (Scheme 1). The subsequent reaction of this intermediate with various nucleophiles may lead to the observed array of products. The utility of the CF_3-group in heterocyclic synthesis was further confirmed by a facile synthesis of arylbenzimidazoles,[12] and cinnolines.[13] The corresponding base-induced reactions of the *ortho*-trifluorotoluene derivatives are studied to a lesser extent.[10]

In this paper, I report the facile synthesis of 1,2,3,4-tetra-substituted naphthalenes via the condensation of derivatives of (2-trifluoromethylphenyl)acetic acid with aromatic aceto-nitriles under basic conditions. In the initial experiment, I found that the ethyl ester derivative **1** undergoes a facile self-condensation reaction under basic conditions to afford naphthalene derivatives (**2**). The yields of **2** varied dramatically depending on the reaction conditions (Scheme 2). In order to optimize the yield of **2**, I studied the effects of several factors on the outcome of this reaction, including: (i) reaction temperature; (ii) ratio of substrate (**1**) to base; (iii) reaction time; (iv) type of solvent, and (v) nature of base. Some of these studies are summarized in Scheme 2.

The temperature was shown to have a profound effect on the reaction course. For example, treatment of **1** with 1 equiv. of LDA in THF at −78°C for 24 h followed by aqueous quench of the reaction mixture with water afforded only the starting material in quantitative yield. A similar treatment of **1** at −30°C (MeCN/ethylene glycol/dry ice mixture) for 12 h allowed for the isolation of **2** in 13% yield along with the starting material **1** (55%). A further increase in the reaction temperature to 0°C did not improve the yield of **2** (22%) significantly. A decrease in the yield of **2** (11%), as well as the formation of unidentified high-molecular weight products was observed when the reaction was conducted at ambient temperature.



Scheme 1.

Keywords: naphthalenes; fluorine and compounds; condensations; supported reagents/reactions.

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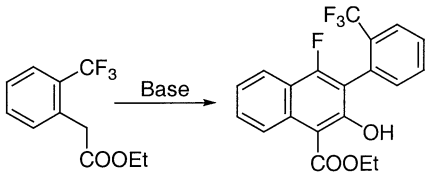


1 2

Reaction conditions:

Base	Ratio 1/base	Solvent	Temperature, °C	Rxn time, h	Yield of 2, %[a]
LDA	1	THF	-78 to -60	24	no rxn
LDA	1	THF	-30	12	13
LDA	1	THF	-10 to 0	12	22
LDA	1	THF	RT	10	15
LDA	2	THF	-30	12	36
LDA	2	THF	-10 to 0	12	35
LDA	**4**	**THF**	**-30**	**12**	**62**
LDA	6	THF	-30	12	58
LiTMP[b]	4	THF	-30	12	57
LiHMDS[c]	4	THF	-30	12	55
NaHMDS	4	THF	-30	12	52
EtMgBr	4	THF	-30	8	14
EtO^-	6	EtOH	RT to reflux	14	22

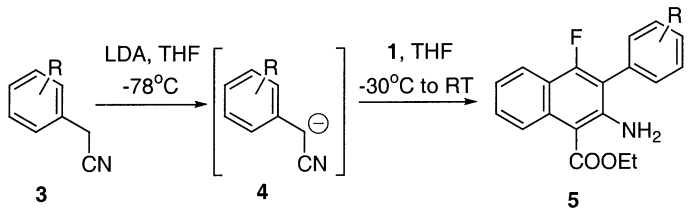
[a]Yield refers to isolated **2**; [b]TMP = 2,2,6,6-tetramethylpiperidiene; [c]HMDS = 1,1,1,3,3,3-hexamethyldisilazane

Scheme 2.

The optimal ratio of **1** to base was found to be 1:4. Lower ratios resulted in lower yields of **2**. Higher ratios (6–8) did not significantly affect the reaction outcome. THF as well as dimethoxyethane (DME) were the best solvents for the reaction (57–62% yields of **2**), whereas reactions conducted in diethyl ether afforded only 12–18% isolated yield of **2**. Several amide bases, including LDA, LiTMP (2,2,6,6-tetramethylpiperidide), and LiHMDS (1,1,1,3,3,3-hexamethyldisilazide) furnished essentially similar yields of **2** (52–62%). Reaction times of 12–13 h were essential to assure the complete conversion of **1** to **2** at −30–0°C. The optimized reaction conditions are indicated in Scheme 2 (bold captions).

The nature of the cation did not affect the yield of **2**. Notably, this reaction was also promoted by EtMgBr, although a number of side products were detected in the reaction mixture along with **2** (14% isolated yield). Application of NaOEt in refluxing EtOH (6 equiv.) also allowed for the isolation of **2** albeit in lower yields (22%) when compared with lithium amides. In this case, the starting material **1** was the major component of the reaction mixtures. Longer reaction time did not improve the outcome of this conversion in EtOH.

The development of the reaction protocol for the self-condensation reaction of **1** prompted me to attempt a similar transformation involving **1** and anions derived from aromatic acetonitriles (**4**). To my satisfaction, addition of **1** to a solution of **4** (2 M equiv.) and LDA (2 M equiv.) at −30°C followed by stirring at rt for 4 h allowed for a smooth condensation reaction to afford **5** in 37–68% isolated yields (Scheme 3).

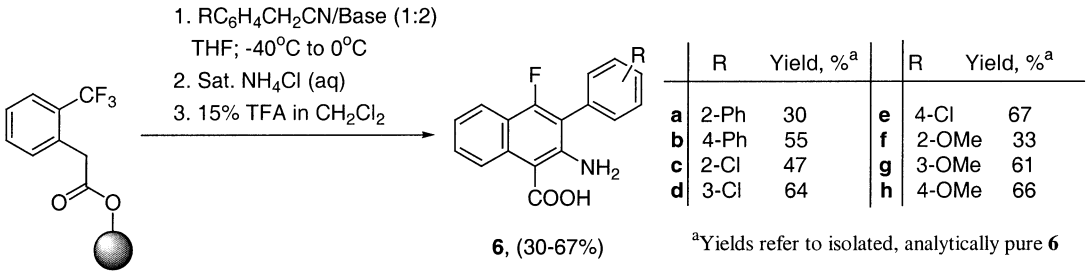


3 4 5

	R	Yield, %[a]		R	Yield, %[a]
a	2-Ph	37	**e**	4-Cl	64
b	4-Ph	63	**f**	2-OMe	41
c	2-Cl	53	**g**	3-OMe	63
d	3-Cl	68	**h**	4-OMe	65

[a]Yields refer to isolated, analytically pure **5**

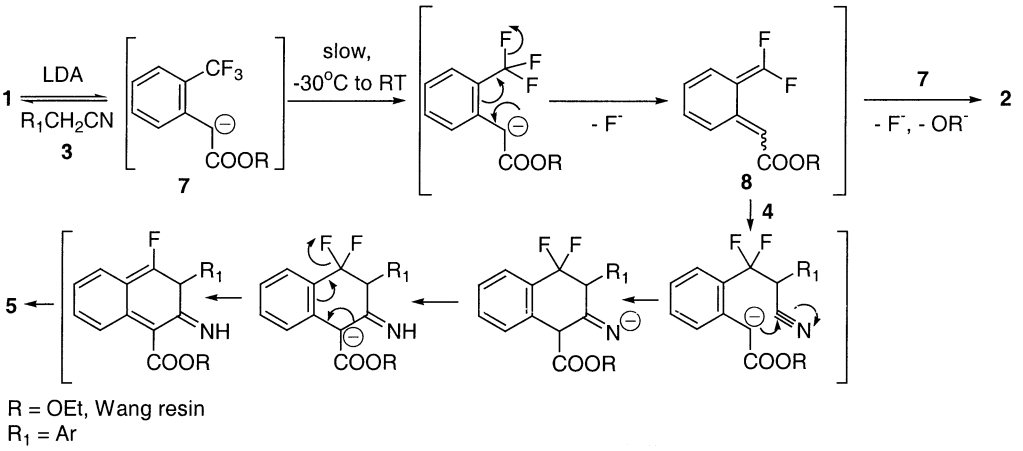
Scheme 3.



	R	Yield, %[a]		R	Yield, %[a]
a	2-Ph	30	**e**	4-Cl	67
b	4-Ph	55	**f**	2-OMe	33
c	2-Cl	47	**g**	3-OMe	61
d	3-Cl	64	**h**	4-OMe	66

[a]Yields refer to isolated, analytically pure **6**

Scheme 4.



Scheme 5.

Varying amounts of **2** (20–35%) were detected in the reaction mixtures. Separation of the desired products **5** from **2** via conventional methods including recrystallization from EtOH, column, and circular chromatography on silica gel was not efficient. Attempts to improve the ratio of **5** to **2** by changing the experimental conditions were not successful. The optimal rate of addition of **1** (0.01 M solution in THF) to **4** (0.01 M solution in THF) was 0.25–0.5 mL/min. Significant amounts of self-condensation product **2** (40–90% conversion) were observed with faster addition rates, application of a more concentrated solution of **1**, and lower reaction temperatures. When a larger excess of **4** was used to facilitate the reaction the overall yield of **5** was not affected significantly.

In order to avoid the formation of the self-condensation product **2**, I immobilized (2-trifluoromethyl)phenyl acetic acid on Wang resin using a previously reported procedure.[14] The resulting resin (250 mg, 0.85 mmol/g loading, as determined by cleavage of the immobilized acid with 15% TFA in CH_2Cl_2 (30 min)) was treated with the mixture of aromatic acetonitrile **3** (5 mmol) and LDA (10 mmol) in THF at −40°C for 1 h and at 0°C for 8 h.[15] The subsequent treatment of the reaction mixture with saturated aq. NH_4Cl, followed by a standard work up of the resin,[16] and TFA cleavage of the product afforded the crude **6**. Purities of the resultant product varied between 76 and 91% as determined by reverse-phase HPLC. The main impurity (LC MS) was the starting (2-trifluorometyl)phenyl acetic acid (5–20%). The naphthalenes **6** were further purified by reverse-phase preparative HPLC to yield analytically pure materials as summarized in Scheme 4.

To account for the reported chemistry of **1** under basic conditions, I propose the mechanism presented below (Scheme 5). It involves the initial deprotonation of **1** to form **7**, which is stable at temperatures below −30°C. At higher temperatures, **7** undergoes slow elimination of HF to form the quinone methide intermediate **8**. These active species react with **7** to afford the self-condensation product **2** after a series of addition/elimination steps. Alternatively, **8** reacts with the excess of acetonitrile anion **4** to afford **5**. The indirect support of this mechanism is provided by the facts that both the dilution of the reaction mixture, as well as the slow addition of the substrate **1** (to assure a large excess of **4** over **1**, and consequently **8**) dramatically improves the yields of **5** vs the self-condensation product **2**. Additionally, higher reaction temperatures allow for the facile elimination of F^- from **7**, shifting the overall equilibrium of the reaction towards the formation of the key reactive intermediate **8**. Formation of a similar quinone methide intermediate was suggested in several relevant transformations of (2-trifluoromethyl)aniline.[1]

In summary, I have described a protocol for the rapid assembly of 1,2,3,4-tetrasubstituted naphthalenes from the derivatives of 2-(trifluoromethyl)phenyl acetic acid and aromatic acetonitriles. The proposed reaction mechanism involves the formation of the quinone methide intermediate. Further synthetic and mechanistic studies of this reaction are under investigation in my lab.

1. Experimental

1.1. Typical experimental procedure for the synthesis of naphthalenes 5 in solution

A solution of ethyl 2-(trifluoromethyl)phenyl acetate (**1**) (232 mg, 1 mmol, prepared by refluxing the corresponding commercially available acid in EtOH with a couple of drops of concentrated H_2SO_4 for 5 h) in 100 mL of dry THF was added via funnel at the rate of 0.25 mL/min to a vigorously stirred mixture of arylacetonitrile (2 mmol), and LDA (4 mmol, freshly prepared from diisopropylamine and *n*-BuLi) in 200 mL of dry THF at −30°C under Ar. After the addition was finished (6–7 h), the dark yellow reaction mixture was warmed up to room temperature and stirred for an additional 4 h. The resulting solution was concentrated in vacuo, and the residue was partitioned between EtOAc and concentrated aqueous NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (Silica gel, hexane/EtOAc=2:1) to afford the analytically pure naphthalene **5**.

1.1.1. Analytical data for 2. Oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95 (t, J=8.0 Hz, 3H), 3.65 (q, J=8.0 Hz, 2H), 7.02 (s, 1H, exch. D_2O, OH), 7.29 (t, J=8.0 Hz, 1H), 7.41 (d, J=8.0 Hz, 1H), 7.50–7.66 (m, 2H), 7.69–7.75 (m, 2H), 7.78–7.90 (m, 2H); ^{19}F NMR (400 MHz, DMSO-d_6): δ −115.8, −63.3. ESI MS: (M+1) 379, (M−1) 377. Elemental analysis, calcd for $C_{20}H_{14}F_4O_3$: C, 65.30; H, 3.73. Found: C, 65.18; H, 3.82.

1.1.2. Analytical data for 5a. 37% yield, oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (t, J=8.0 Hz, 3H), 3.69 (q, J=8.0 Hz, 2H), 6.01 (br. S, 2H, exch. D_2O, NH_2), 7.02 (t, J=8.0 Hz, 1H), 7.12–7.21 (m, 6H) 7.29 (d, J=8.0 Hz, 1H), 7.43 (t, J=8.0 Hz, 1H), 7.59 (t, J=8.0 Hz, 1H), 7.68 (t, J=8.0 Hz, 1H), 7.75 (d, J=8.0 Hz, 1H), 7.94 (d, J=8.0 Hz, 1H); ^{19}F NMR (400 MHz, DMSO-d_6): δ −113.2; ESI MS: (M+1) 386, (M−1) 384. Elemental analysis, calcd for $C_{25}H_{20}FNO_2$: C, 77.90; H, 5.23; N, 3.63. Found: C, 77.81; H, 5.29; N, 3.52.

1.1.3. Analytical data for 5b. 63% yield, oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, J=8.0 Hz, 3H), 3.68 (q, J=8.0 Hz, 2H), 5.02 (br s, 2H, exch. D_2O, NH_2), 7.08–7.34 (d, 7H), 7.37 (t, J=8.0 Hz, 1H), 7.45 (d, J=8.0 Hz, 2H), 7.72 (t, J=8.0 Hz, 1H), 7.86 (d, J=8.0 Hz, 1H), 7.97 (d, J=8.0 Hz, 1H); ^{19}F (400 MHz, DMSO-d_6): δ −114.9; ESI MS: (M+1) 386, (M−1) 384. Elemental analysis, calcd for $C_{25}H_{20}FNO_2$: C, 77.90; H, 5.23; N, 3.63. Found: C, 77.76; H, 5.34; N, 3.43.

1.1.4. Analytical data for 5c. 53% yield, oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.01 (t, J=8.0 Hz, 3H), 3.63 (q, J=8.0 Hz, 2H), 6.12 (br s, 2H, exch. D_2O, NH_2), 7.03 (t, J=8.0 Hz, 1H), 7.26 (d, J=8.0 Hz, 1H) 7.33 (d, J=8.0 Hz, 1H), 7.46 (t, J=8.0 Hz, 1H), 7.58 (t, J=8.0 Hz, 1H), 7.64 (t, J=8.0 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.92 (d, J=8.0 Hz, 1H); ^{19}F NMR (400 MHz, DMSO-d_6): δ −114.7; ESI MS: (M+1) 345, (M−1) 343. Elemental analysis, calcd for $C_{19}H_{15}ClFNO_2$: C, 66.38; H, 4.40; N, 4.07. Found: C, 66.11; H, 4.24; N, 3.92.

1.1.5. Analytical data for 5d. 68% yield, oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.99 (t, J=8.0 Hz, 3H), 3.68 (t, J=8.0 Hz, 2H), 6.14 (br s, 2H, exch. D_2O, NH_2), 7.08 (dd, J=8.0, 1.6 Hz, 1H) 7.38 (t, J=8.0 Hz, 1H), 7.42 (s, 1H), 7.46 (t, J=8.0 Hz, 1H), 7.54 (d, J=8.0 Hz, 1H), 7.60 (t, J=8.0 Hz, 1H), 7.97 (d, J=8.0 Hz, 1H), 8.05 (d, J=8.0 Hz, 1H); ^{19}F NMR (400 MHz, DMSO-d_6): δ −115.9; ESI MS: (M+1) 345, (M−1) 343. Elemental analysis, calcd for $C_{19}H_{15}ClFNO_2$: C, 66.38; H, 4.40; N, 4.07. Found: C, 66.18; H, 4.28; N, 3.86.

1.1.6. Analytical data for 5e. 64% yield, oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.03 (t, J=8.0 Hz, 3H), 3.63 (t, J=8.0 Hz, 2H), 6.11 (br s, 2H, exch. D_2O, NH_2), 7.12 (d, J=8.0 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 7.44 (t, J=8.0 Hz, 1H) 7.68 (t, J=8.0 Hz, 1H), 7.83 (d, J=8.0 Hz, 1H), 8.08 (d, J=8.0 Hz, 1H); ^{19}F (400 MHz, DMSO-d_6): δ −115.8; ESI MS: (M+1) 345, (M−1) 343. Elemental analysis, calcd for $C_{19}H_{15}ClFNO_2$: C, 66.38; H, 4.40; N, 4.07. Found: C, 66.20; H, 4.48; N, 3.95.

1.1.7. Analytical data for 5f. 41% yield, oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (t, J=8.0 Hz, 3H), 3.67 (t, J=8.0 Hz, 2H), 3.76 (s, 3H, OMe), 6.03 (br s, 2H, exch. D_2O, NH_2), 7.06 (t, J=8.0 Hz, 1H), 7.17 (d, J=8.0 Hz, 1H) 7.23 (d, J=8.0 Hz, 1H), 7.36 (t, J=8.0 Hz, 1H), 7.54 (t, J=8.0 Hz, 1H), 7.71 (t, J=8.0 Hz, 1H), 7.72 (d, J=8.0 Hz, 1H), 7.80 (d, J=8.0 Hz, 1H); ^{19}F NMR (400 MHz, DMSO-d_6): δ −114.0; ESI MS: (M+1) 340, (M−1) 338. Elemental analysis, calcd for $C_{20}H_{18}FNO_3$: C, 70.78; H, 5.35; N, 4.13. Found: C, 70.51; H, 5.08; N, 4.02.

1.1.8. Analytical data for 5g. 63% yield, oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.98 (t, J=8.0 Hz, 3H), 3.57 (t, J=8.0 Hz, 2H), 3.85 (s, 3H, OMe), 6.13 (br s, 2H, exch. D_2O, NH_2), 6.90 (s, 1H), 6.93 (d, J=8.0 Hz, 1H), 7.04 (dd, J=8.0, 1.6 Hz, 1H) 7.31 (t, J=8.0 Hz, 1H), 7.47 (t, J=8.0 Hz, 1H), 7.65 (t, J=8.0 Hz, 1H), 7.91 (d, J=8.0 Hz, 1H), 7.98 (d, J=8.0 Hz, 1H); ^{19}F NMR (400 MHz, DMSO-d_6): δ −115.7; ESI MS: (M+1) 340, (M−1) 338. Elemental analysis, calcd for $C_{20}H_{18}FNO_3$: C, 70.78; H, 5.35; N, 4.13. Found: C, 70.62; H, 5.16; N, 4.06.

1.1.9. Analytical data for 5h. 65% yield, oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.03 (t, J=8.0 Hz, 3H), 3.58 (q, J=8.0 Hz, 2H), 3.88 (s, 3H, OMe), 5.98 (br s, 2H, exch. D_2O, NH_2), 7.04 (d, J=8.0 Hz, 2H), 7.26 (d, J=8.0 Hz, 2H), 7.35 (t, J=8.0 Hz, 1H) 7.62 (t, J=8.0 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.89 (d, J=8.0 Hz, 1H); ^{19}F (400 MHz, DMSO-d_6): δ −115.9; ESI MS: (M+1) 340, (M−1) 338. Elemental analysis, calcd for $C_{20}H_{18}FNO_3$: C, 70.78; H, 5.35; N, 4.13. Found: C, 70.52; H, 5.11; N, 4.06.

1.2. Typical experimental procedure for the synthesis of naphthalenes 6 on solid support

The commercially available (2-trifluoromethyl)phenyl acetic acid was immobilized on Wang resin using the reported DIC/DMAP protocol in dry *N*-methylpiperidine.[14] The resulting resin was suspended in dry pyridine, concentrated in vacuo, washed with dry THF followed by dry Et_2O, and dried in the vacuum oven at 40°C at 0.1 Torr for 4 h. We

found that the drying procedure described above is essential to obtain good yields of the targeted naphthalenes **6a**–**h**. Loading of the resin by cleavage of the immobilized acid with 15% TFA in CH_2Cl_2 (30 min) was determined to be 0.85 mmol/g. The resulting resin (250 mg) was suspended in dry THF (10 mL) and added to a gently stirred mixture of aromatic acetonitrile **3** (5 mmol) and LDA (10 mmol, freshly prepared from diisopropylamine and *n*-BuLi) in 40 mL of dry THF at −40°C (ethyleneglycol/water/dry ice bath) under N_2. Immediately upon addition the resin turned dark yellow. The resulting mixture was stirred at −40°C for 1 h and warmed to 0°C (cold room). Stirring was continued at this temperature for an additional 8 h. The resultant mixture was treated with saturated aq. NH_4Cl (40 mL). The resin was collected and washed with with saturated aq. NH_4Cl, water, DMF, MeOH, and CH_2Cl_2. The resin was treated with 15% TFA in CH_2Cl_2 (10 mL, 30 min). The CH_2Cl_2 solution was collected, and concentrated. The crude product was purified by preparative HPLC using a Phenomenex Prodigy 5μ ODS(3) 100A 21.2×250 mm column on a Waters DeltaPrep4000 HPLC instrument. The solvent system was MeCN/H_2O (start: 20:80; finish 50:50 ratio; 8 min run; 0.1% of formic acid added) with a flow rate 20 mL/min.

1.2.1. Analytical data for 6a. 30% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.89 (br. s, 2H, exch. D_2O, NH_2), 6.96 (t, J=8.0 Hz, 1H), 7.10–7.21 (m, 6H) 7.23 (d, J=8.0 Hz, 1H), 7.34 (t, J=8.0 Hz, 1H), 7.51 (t, J=8.0 Hz, 1H), 7.65 (t, J=8.0 Hz, 1H), 7.74 (d, J=8.0 Hz, 1H), 7.96 (d, J=8.0 Hz, 1H), 12.94 (br s. 1H, exch. D_2O, COOH); ^{19}F NMR (400 MHz, DMSO-d_6): δ −112.4; ESI MS: (M+1) 358, (M−1) 356. HRMS ESI calcd for $C_{23}H_{16}FNO_2$: 357.1165. Found: 357.1162.

1.2.2. Analytical data for 6b. 55% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.02 (br s, 2H, exch. D_2O, NH_2), 7.10–7.35 (m, 7H), 7.31 (t, J=8.0 Hz, 1H), 7.37 (d, J=8.0 Hz, 2H), 7.73 (t, J=8.0 Hz, 1H), 7.79 (d, J=8.0 Hz, 1H), 7.85 (d, J=8.0 Hz, 1H), 12.86 (br s. 1H, exch. D_2O, COOH); ^{19}F (400 MHz, DMSO-d_6): δ −114.1; ESI MS: (M+1) 358, (M−1) 356. HRMS ESI calcd for $C_{23}H_{16}FNO_2$: 357.1165. Found: 357.1163.

1.2.3. Analytical data for 6c. 47% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.04 (br s, 2H, exch. D_2O, NH_2), 7.01 (t, J=8.0 Hz, 1H), 7.21 (d, J=8.0 Hz, 1H) 7.32 (d, J=8.0 Hz, 1H), 7.46 (t, J=8.0 Hz, 1H), 7.58 (t, J=8.0 Hz, 1H), 7.64 (t, J=8.0 Hz, 1H), 7.73 (d, J=8.0 Hz, 1H), 7.92 (d, J=8.0 Hz, 1H), 12.88 (br s. 1H, exch. D_2O, COOH); ^{19}F NMR (400 MHz, DMSO-d_6): δ −114.3; ESI MS: (M+1) 317, (M−1) 315. HRMS ESI calcd for $C_{17}H_{11}ClFNO_2$: 315.0462. Found: 315.0460.

1.2.4. Analytical data for 6d. 64% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.07 (br s, 2H, exch. D_2O, NH_2), 6.98 (dd, J=8.0, 1.6 Hz, 1H) 7.29 (t, J=8.0 Hz, 1H), 7.35 (t, J=8.0 Hz, 1H), 7.40 (s, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.56 (t, J=8.0 Hz, 1H), 7.83 (d, J=8.0 Hz, 1H), 7.98 (d, J=8.0 Hz, 1H), 12.89 (br s. 1H, exch. D_2O, COOH); ^{19}F NMR (400 MHz, DMSO-d_6): δ −115.2; ESI MS: (M+1) 317, (M−1) 315. HRMS ESI calcd for $C_{17}H_{11}ClFNO_2$: 315.0462. Found: 315.0459.

1.2.5. Analytical data for 6e. 67% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.08 (br s, 2H, exch. D_2O, NH_2), 7.05 (d, J=8.0 Hz, 2H), 7.24 (d, J=8.0 Hz, 2H), 7.35 (t, J=8.0 Hz, 1H) 7.65 (t, J=8.0 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.97 (d, J=8.0 Hz, 1H), 12.98 (br s. 1H, exch. D_2O, COOH); ^{19}F (400 MHz, DMSO-d_6): δ −114.7; ESI MS: (M+1) 317, (M−1) 315. HRMS ESI calcd for $C_{17}H_{11}ClFNO_2$: 315.0462. Found: 315.0460.

1.2.6. Analytical data for 6f. 33% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.69 (s, 3H, OMe), 5.97 (br s, 2H, exch. D_2O, NH_2), 7.03 (t, J=8.0 Hz, 1H), 7.08 (d, J=8.0 Hz, 1H) 7.22 (d, J=8.0 Hz, 1H), 7.33 (t, J=8.0 Hz, 1H), 7.45 (t, J=8.0 Hz, 1H), 7.64 (t, J=8.0 Hz, 1H), 7.70 (d, J=8.0 Hz, 1H), 7.74 (d, J=8.0 Hz, 1H), 12.91 (br s. 1H, exch. D_2O, COOH); ^{19}F NMR (400 MHz, DMSO-d_6): δ −113.5; ESI MS: (M+1) 312, (M−1) 310. HRMS ESI calcd for $C_{18}H_{14}FNO_3$: 311.0958. Found: 311.0955.

1.2.7. Analytical data for 6g. 61% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.81 (s, 3H, OMe), 6.09 (br s, 2H, exch. D_2O, NH_2), 6.87 (s, 1H), 6.91 (d, J=8.0 Hz, 1H), 7.03 (dd, J=8.0, 1.6 Hz, 1H) 7.25 (t, J=8.0 Hz, 1H), 7.44 (t, J=8.0 Hz, 1H), 7.60 (t, J=8.0 Hz, 1H), 7.83 (d, J=8.0 Hz, 1H), 7.91 (d, J=8.0 Hz, 1H), 12.92 (br s. 1H, exch. D_2O, COOH); ^{19}F NMR (400 MHz, DMSO-d_6): δ −115.2; ESI MS: (M+1) 312, (M−1) 310. HRMS ESI calcd for $C_{18}H_{14}FNO_3$: 311.0958. Found: 311.0957.

1.2.8. Analytical data for 6h. 66% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.87 (s, 3H, OMe), 5.95 (br s, 2H, exch. D_2O, NH_2), 7.01 (d, J=8.0 Hz, 2H), 7.18 (d, J=8.0 Hz, 2H), 7.33 (t, J=8.0 Hz, 1H) 7.57 (t, J=8.0 Hz, 1H), 7.74 (d, J=8.0 Hz, 1H), 7.83 (d, J=8.0 Hz, 1H), 12.94 (br s. 1H, exch. D_2O, COOH); ^{19}F (400 MHz, DMSO-d_6): δ −115.5; ESI MS: (M+1) 312, (M−1) 310. HRMS ESI calcd for $C_{18}H_{14}FNO_3$: 311.0958. Found: 311.0955.

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15. When the immobilized (2-trifluoromethyl)phenyl acetic acid was treated with the same mixture of reagents at ambient temperature, followed by a standard work up and cleavage with TFA, the LC MS analysis of the resultant mixture revealed the presence of a product of the formal S_NAr of fluorine (**7**) with the anion **4** as shown in Scheme 6. The yields of this product varied from 15 to 55% depending on the reaction time. For example, **7** was the major product of this solid phase reaction at room temperature after 8 h.
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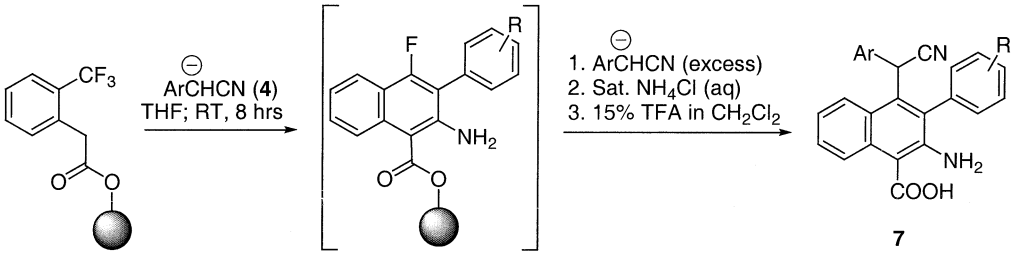

Scheme 6.