JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

Synthesis of Acyl Fluorides from Carboxylic Acids Using NaF-Assisted Deoxofluorination with XtalFluor-E

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Cite This: J. Org. Chem. 2020, 85, 10253−10260 Read Online

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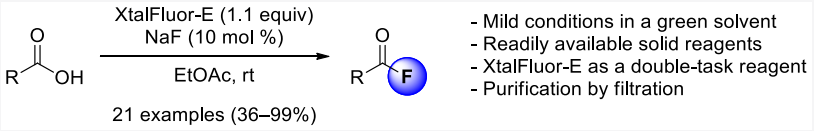
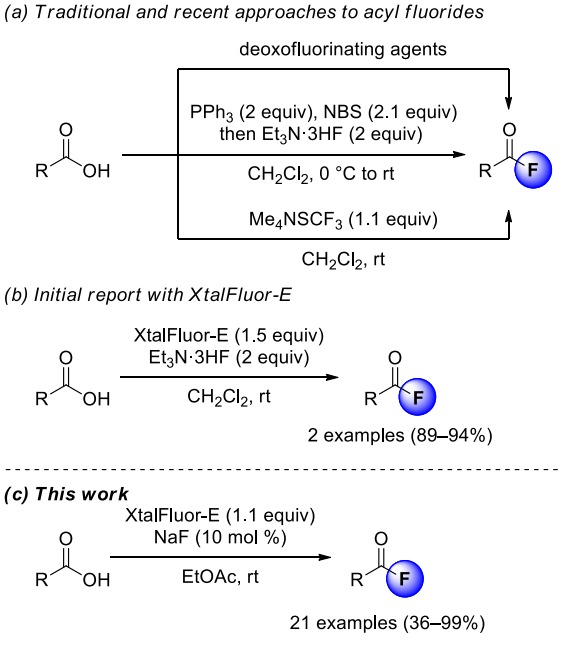


ABSTRACT: The synthesis of acyl fluorides using the deoxofluorination reaction of carboxylic acids using XtalFluor-E is described. This transformation, assisted by a catalytic amount of NaF, occurs at room temperature in EtOAc, where XtalFluor-E behaves as the activating agent and the fluoride source. A wide range of acyl fluorides were obtained in moderate to excellent yields (36−99%) after a simple filtration on a pad of silica gel. We also demonstrated that sequential deoxofluorination/amidation was possible.

Acyl fluorides are key intermediates/reagents in organic synthesis with a wide range of applications.[1] A number of approaches for their preparation[2] have been explored over the years, though the main route remains the direct conversion of a carboxylic acid to the corresponding acyl fluoride.[3] This transformation can be accomplished using deoxofluorinating agents, mainly DAST (diethylaminosulfur trifluoride)[4a] and Deoxo-Fluor (bis(2-methoxyethyl)aminosulfur trifluoride)[4b] as well as other reagents (Scheme 1a).[5] Recently, the use of $(Me_4N)SCF_3$ or a PPh_3/NBS/$Et_3N{\cdot}3HF$ system has been proposed as alternative conditions (Scheme 1a).[6−8] While most of these methods provide the acyl fluoride in good yields, there is still room for improvement in terms of availability/prices/sustainability of the reagents (including the fluoride source and the solvent) and the stoichiometry/sustainability/atom economy of the reaction.[9]

Scheme 1. Deoxofluorination of Carboxylic Acids



Diethylaminodifluorosulfinium tetrafluoroborate ($[Et_2NSF_2]BF_4$), XtalFluor-E, has been developed as a practical alternative to DAST and DeoxoFluor in deoxofluorination reactions due to its crystallinity and enhanced thermal stability.[10] In two single examples, the potential for XtalFluor-E to promote the deoxofluorination of carboxylic acids was demonstrated in the initial report (Scheme 1b),[10a,b,11] though under nonideal conditions (CH_2Cl_2 as the solvent, unfavorable stoichiometry and $Et_3N{\cdot}3HF$ as the HF source).[9]

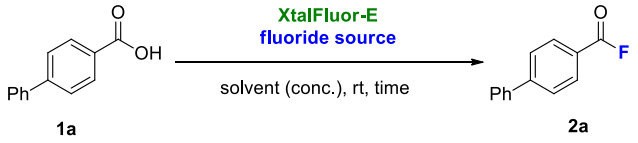
Herein, we report new reaction conditions for the synthesis of acyl fluorides from carboxylic acids using XtalFluor-E (Scheme 1c). Notably, this reaction, assisted by a catalytic amount of NaF, showcases the use of XtalFluor-E as a double-task reagent, i.e., the activating agent and the fluoride source, and occurs at room temperature in EtOAc, a desirable solvent.[9a,b] A variety of acyl fluorides were obtained in moderate to excellent yields after simple filtration on a pad of silica gel.

Selected results for the optimization of 4-phenylbenzoic acid (**1a**) as the model substrate are shown in Table 1. Under the initial conditions reported (Table 1, entry 1),[10a,b] the

Received: June 10, 2020
Published: July 21, 2020

https://dx.doi.org/10.1021/acs.joc.0c01377
J. Org. Chem. 2020, 85, 10253−10260

Table 1. Selected Optimization Results for the Deoxofluorination of 1a Using XtalFluor-E[a]



1a 2a

entry	F^- source (equiv)	XtalFluor-E (equiv)	solvent	conc (M)	time (h)	yield (%)[b]
1	$Et_3N{\cdot}3HF$ (2)	1.5	CH_2Cl_2	0.33	3	100
2	$Et_3N{\cdot}3HF$ (1)	1.5	CH_2Cl_2	0.33	3	100
3	$Et_3N{\cdot}3HF$ (1)	1.5	cyclohexane	0.33	3	100
4	$Et_3N{\cdot}3HF$ (1)	1.5	toluene	0.33	3	100
5	$Et_3N{\cdot}3HF$ (1)	1.5	CH_3CN	0.33	3	90
6	$Et_3N{\cdot}3HF$ (1)	1.5	MTBE	0.33	3	80
7	$Et_3N{\cdot}3HF$ (1)	1.5	2-MeTHF	0.33	3	37
8	$Et_3N{\cdot}3HF$ (1)	1.5	acetone	0.33	3	67
9	$Et_3N{\cdot}3HF$ (1)	1.5	EtOAc	0.33	3	91
10	TBAT (1)[c]	1.5	EtOAc	0.33	3	95
11	TBAF (1)[d,e]	1.5	EtOAc	0.33	3	37
12	Me_4NF (1)	1.5	EtOAc	0.33	3	87
13	KF (1)	1.5	EtOAc	0.33	3	65
14	NaF (1)	1.5	EtOAc	0.33	3	92
15	NaF (1)	1.1	EtOAc	0.33	3	89
16	NaF (1)	1.1	EtOAc	0.5	3	90
17	NaF (1)	1.1	EtOAc	1	3	81
18	NaF (0.25)	1.1	EtOAc	0.5	3	47
19	NaF (0.25)	1.1	EtOAc	0.5	24	98
20	NaF (0.1)	1.1	EtOAc	0.5	24	99 (94)[f]
21		1.1	EtOAc	0.5	24	27
22	NaF (0.1)		EtOAc	0.5	24	0

[a]See the Experimental Section for the detailed experimental procedures. [b]Yield estimated by ^{19}F NMR using 2-fluoro-4-nitrotoluene as the internal standard. [c]TBAT = tetrabutylammonium difluorotriphenylsilicate. [d]TBAF = tetrabutylammonium fluoride. [e]A 1 M solution of TBAF in THF was used. [f]Yield of **2a** after filtration on a silica gel pad.

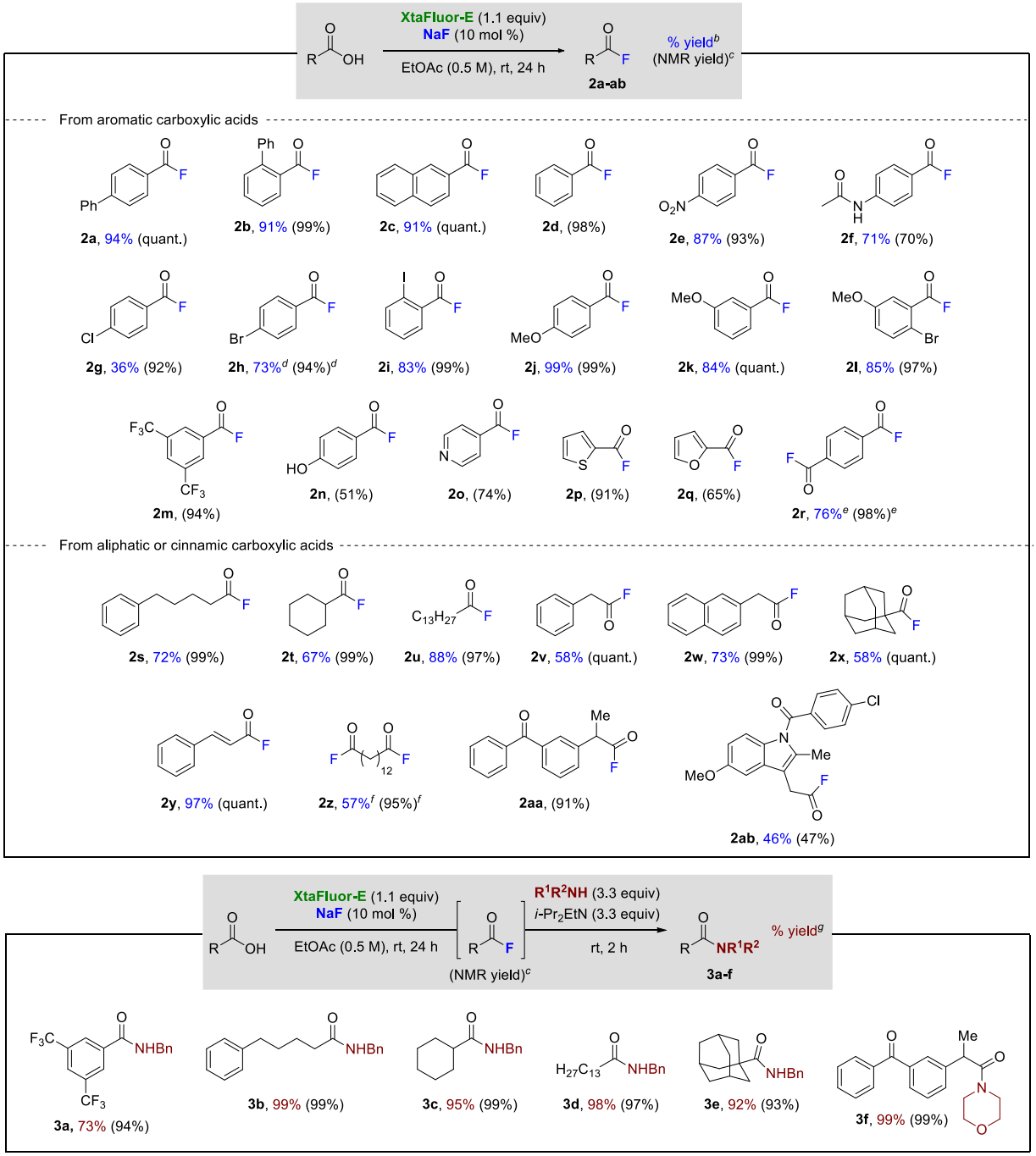
corresponding acyl fluoride **2a** was observed in a quantitative yield. Excess of $Et_3N{\cdot}3HF$ is not necessary as the use of 1.0 equiv also provided a quantitative yield (Table 1, entry 2). We next investigated the choice of the solvent as CH_2Cl_2 is considered a highly hazardous solvent in various solvent guides.[9a,b] Other usable, but not ideal, solvents[9a,b] such as cyclohexane, toluene, CH_3CN, MTBE, or 2-MeTHF were evaluated (Table 1, entries 3−7), and aside from 2-MeTHF (37%), all provided **2a** in >80% yield. The use of acetone, a much-preferred solvent, provided only a moderate yield of **2a** (Table 1, entry 8). Nonetheless, this result is still interesting considering that XtalFluor-E is known to mediate the deoxofluorination of ketones.[10] Finally, the reaction in EtOAc, a recommended solvent,[11a,b] provided the acyl fluoride in 91% yield (Table 1, entry 9), a yield high enough to pursue the optimization using this solvent. We next turned our attention to the fluoride source as the GSK reagents guide for fluorination,[9c] indicating that $Et_3N{\cdot}3HF$ presents major drawbacks. A survey of various fluoride sources (Table 1, entries 10−14) revealed that NaF could provide a similar result to $Et_3N{\cdot}3HF$. Some fine-tuning showed that the equivalent of XtaFluor-E could be reduced to 1.1 and that the concentration could be increased to 0.5 M with almost no impact on the yield (Table 1, entries 15−17). Finally, further optimization (Table 1, entries 18−20) showed that a catalytic amount of NaF (10 mol %) could be used with a longer reaction time to provide a virtually full conversion and a yield of the acyl fluoride of 94% after a simple filtration on a pad of silica gel. Importantly, this result indicates that XtalFluor-E behaves as the fluoride source under those conditions. In that regard, without NaF, a low conversion of 27% is observed (Table 1, entry 21). Finally, a reaction without XtalFluor-E, for which no conversion was observed, confirmed the need for the reagent. (Table 1, entry 22). Overall, the conditions reported in entry 20 were determined to be optimal and thus used for the rest of the study.

The scope of the transformation was next examined, and the results are shown in Scheme 2 (top). A wide range of aromatic, heteroaromatic, and aliphatic acids could be used and provided the corresponding acyl fluorides in moderate to excellent yields (36−99%) after filtration on a pad of silica gel. For some acyl fluorides, only NMR yields are provided because of their high volatility (**2d**,**p**,**q**), their instability upon filtration on silica gel (**2m**,**o**), and for the isolated compound presented significant impurities (**2n**) or hydrolyzed readily upon isolation (**2aa**). We next showed that a sequential deoxofluorination/amidation reaction was possible, thus avoiding the need to isolate the intermediate acyl fluoride (Scheme 2, bottom).[12] In those cases, the amine (benzylamine or morpholine) and *i*-Pr_2EtN (the base) were added to the crude acyl fluorides. With this procedure, the corresponding amides were isolated in good to excellent yields (73−99%) even for problematic acyl fluorides (i.e., **2m** and **2aa**).

With respect to the mechanism, we suggest that the reaction of the carboxylic acid with XtalFluor-E would first generate the activated carboxylic acid, (diethylamino)difluoro-λ^4-sulfanyl carboxylate (**4**), an intermediate suggested for other reactions involving carboxylic acid and XtalFluor-E.[13] An S_NAcyl

https://dx.doi.org/10.1021/acs.joc.0c01377
J. Org. Chem. 2020, 85, 10253−10260

Scheme 2. NaF-Assisted Deoxofluorination of Carboxylic Acids Using XtalFluor-E[a]



[a]All reactions were performed on a 1 mmol scale except for **2aa** (0.09 mmol), **2ab** (0.5 mol), and **3f** (0.25 mmol). [b]Yield after filtration on a pad of silica gel. [c]Yield of the acyl fluoride estimated by ^{19}F NMR using 2-fluoro-4-nitrotoluene or 4-trifluoromethylbenzaldehyde as the internal standard. [d]One equiv of NaF was used. [e]2.2 equiv of XtalFluor-E was used along with a reaction temperature of 80 °C. [f]2.2 equiv of XtalFluor-E was used. [g]Yield after purification by flash chromatography on silica gel.

reaction of a fluoride ion with intermediate **4** would produce the desired acyl fluoride along with a fluoride ion, which could re-enter the cycle. The introduction of a substoichiometric amount of NaF likely serves to facilitate the first turnover of the cycle. Indeed, without the added NaF, the activated carboxylic acid (**4**) likely only slowly releases fluoride,[10] explaining the low conversion observed without NaF (cf. entry 21 in Table 1).

In conclusion, we have described the NaF-assisted deoxofluorination reaction of carboxylic acids using XtalFluor-E as a practical approach to acyl fluorides. Notably, the reaction takes place in a green solvent, EtOAc, at room temperature using readily available solid reagents, where XtalFluor-E acts as a double-task reagent. A wide range of acyl fluorides were obtained after simple filtration on a pad of silica gel.

EXPERIMENTAL SECTION

General Information. The following includes general experimental procedures, specific details for representative reactions,

https://dx.doi.org/10.1021/acs.joc.0c01377
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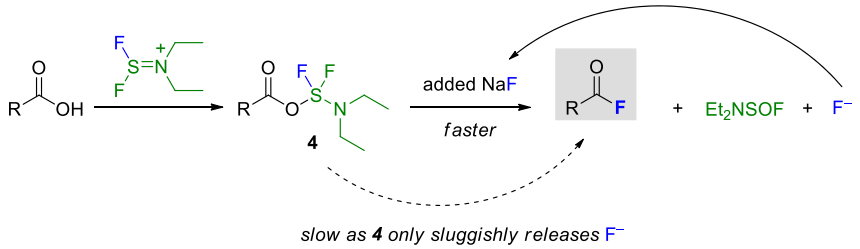
Scheme 3. Mechanistic Hypothesis[a]



[a]The BF_4^- counterion of XtalFluor-E and the Na^+ counterion of sodium fluoride have been omitted for clarity.

isolation, and spectroscopic information for the compounds prepared. Solvents were used as purchased unless stated as dry. CH_3CN, CH_2Cl_2, and toluene were purified using a Vacuum Atmospheres Inc. solvent purification system. All air- and water-sensitive reactions were carried out under an argon atmosphere. Reactions were monitored by TLC on precoated plates (SiliCycle, silica gel 60 Å F254 230−240 mesh), and products were visualized under 254 nm UV light followed by staining with $KMnO_4$, 2,4-dinitrophénylhydrazine (DNPH), cerium ammonium molybdate (CAM), phosphomolybdic acid (PMA), or bromocresol green when appropriate. Purifications were carried out using a Biotage Isolera one flash chromatography system using Biotage KPSIL SNAP or SiliCycle SiliaSep silica gel cartridges or under flash column chromatography (SiliCycle, silica gel 60 Å F254). NMR spectra were recorded on an Agilent DD2 500 or a Varian Inova 400 spectrometer in the indicated deuterated solvent at 298 K. Chemical shifts are reported on the δ scale in ppm. For ^1H and ^{13}C spectra, chemical shifts are referenced to residual solvent references or the internal TMS reference. For ^{19}F spectra, calibration was performed using a unified scale.[14] Resonances are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = pentaplet, m = multiplet, or a combination of the above), coupling constant (Hz), integration. High-resolution mass (HRMS) spectra were recorded on an LC/MS-TOF Agilent 6210 using atmospheric pressure photoionization (APPI) or electrospray ionization (ESI) in positive mode. Infrared spectra (IR) were recorded on an ABB MB 3000 FT-IR spectrometer and on a Thermo Scientific Nicolet 380 FT-IR spectrometer. Absorptions are reported in cm^{-1}. Melting points were measured on a Stanford Research System OptiMelt MPA100 automated melting point apparatus.

General Procedure for the Synthesis of Acyl Fluorides. To a solution of carboxylic acid (1.0 equiv, 1.0 mmol) in dry EtOAc (0.5 M) was added NaF (10 mol %, 0.10 mmol, 4.2 mg), followed by XtalFluor-E (1.1 equiv, 1.1 mmol, 252 mg). After 24 h of stirring at room temperature under argon, the reaction mixture was purified by filtration over a pad of silica gel.

*[1,1′-Biphenyl]-4-carbonyl Fluoride (**2a**).* According to a general procedure starting with [1,1′-biphenyl]-4-carboxylic acid (1.0 mmol, 198 mg), acyl fluoride **2a** was observed in a quantitative ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard and isolated as a white solid (189 mg, 94%) after filtration over silica using hexanes as the eluent. ^1H NMR (500 MHz, $CDCl_3$): δ 8.13−8.09 (m, 2H), 7.76−7.71 (m, 2H), 7.66−7.61 (m, 2H), 7.52−7.47 (m, 2H), 7.46−7.41 (m, 1H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 18.1 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[11a]

*[1,1′-Biphenyl]-2-carbonyl Fluoride (**2b**).* According to a general procedure starting with [1,1′-biphenyl]-2-carboxylic acid (1.0 mmol, 198 mg), acyl fluoride **2b** was observed in 99% ^{19}F NMR yield using 4-(trifluoromethyl)benzaldehyde as an internal standard and isolated as a yellowish oil (183 mg, 91%) after filtration over silica using hexanes as the eluent. ^1H NMR (500 MHz, $CDCl_3$): δ 8.03 (dd, J = 7.9, 1.4 Hz, 1H), 7.66 (td, J = 7.6, 1.4 Hz, 1H), 7.49 (tt, J = 7.7, 1.2 Hz, 1H), 7.45−7.40 (m, 4H), 7.34−7.31 (m, 2H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 35.0 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[6]

*2-Naphthoyl Fluoride (**2c**).* According to a general procedure starting with 2-naphthoic acid (1.0 mmol, 172 mg), acyl fluoride **2c** was observed in a quantitative ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard and isolated as a white solid (159 mg, 91%) after filtration over silica using pentane as the eluent. ^1H NMR (500 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.02−7.91 (m, 4H), 7.69 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.62 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 18.1 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[7]

*Benzoyl Fluoride (**2d**).* According to a general procedure starting with benzoic acid (1.0 mmol, 122 mg), acyl fluoride **2d** was observed in 98% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene (49.2 mg) as an internal standard. ^{19}F NMR (470 MHz, $CDCl_3$): δ 18.0 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[7]

*4-Nitrobenzoyl Fluoride (**2e**).* According to a general procedure starting with 4-nitrobenzoic acid (1.0 mmol, 167 mg), acyl fluoride **2e** was observed in 93% ^{19}F NMR yield using 4-(trifluoromethyl)-benzaldehyde as an internal standard and isolated as a yellowish solid (147 mg, 87%) after filtration over silica using an 80:20 hexanes/EtOAc mixture as the eluent. ^1H NMR (500 MHz, $CDCl_3$): δ 8.42−8.38 (m, 2H), 8.29−8.25 (m, 2H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 21.3 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[6]

*4-Acetamidobenzoyl Fluoride (**2f**).* According to a general procedure starting with 4-acetamidobenzoic acid (1.0 mmol, 179 mg), acyl fluoride **2f** was observed in 70% ^{19}F NMR yield using 4-(trifluoromethyl)benzaldehyde as an internal standard and isolated as a yellowish solid (129 mg, 71%) after filtration over silica using a 50:50 hexanes/EtOAc mixture as the eluent. ^1H NMR (500 MHz, $(CD_3)_2CO$): δ 9.67 (br s, 1H), 8.02−7.99 (m, 2H), 7.90−7.87 (m, 2H), 2.16 (s, 3H). ^{19}F NMR (470 MHz, $(CD_3)_2CO$): δ 14.5 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[6]

*4-Chlorobenzoyl Fluoride (**2g**).* According to a general procedure starting with 4-chlorobenzoic acid (1.0 mmol, 156 mg), acyl fluoride **2g** was observed in 92% ^{19}F NMR yield using 4-(trifluoromethyl)-benzaldehyde as an internal standard and isolated as a white solid (57 mg, 36%) after filtration over silica using hexanes as the eluent. ^1H NMR (500 MHz, $CDCl_3$): δ 8.01−7.97 (m, 2H), 7.54−7.49 (m, 2H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 18.4 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[6]

*4-Bromobenzoyl Fluoride (**2h**).* According to a general procedure starting with 4-bromobenzoic acid (1.0 mmol, 200 mg), acyl fluoride **2h** was observed in 94% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard and isolated as a white solid (147 mg, 73%) after filtration over silica using hexanes as the eluent. ^1H NMR (500 MHz, $CDCl_3$): δ 7.92−7.89 (m, 2H), 7.71−7.67 (m, 2H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 18.4 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[7]

*2-Iodobenzoyl Fluoride (**2i**).* According to a general procedure starting with 2-iodobenzoic acid (1.0 mmol, 248 mg), acyl fluoride **2i** was observed in 99% ^{19}F NMR yield using 4-(trifluoromethyl)-benzaldehyde as an internal standard and isolated as a yellowish solid (207 mg, 83%) after filtration over silica using hexanes as the eluent. ^1H NMR (500 MHz, $CDCl_3$): δ 8.13 (dt, J = 8.0, 1.4 Hz, 1H), 8.03

https://dx.doi.org/10.1021/acs.joc.0c01377
J. Org. Chem. 2020, 85, 10253−10260

(dd, J = 7.9, 1.7 Hz, 1H), 7.51 (td, J = 7.7, 1.2 Hz, 1H), 7.31 (ddd, J = 8.0, 7.4, 1.7 Hz, 1H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 28.6 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[15]

*4-Methoxybenzoyl Fluoride (**2j**).* According to a general procedure starting with 4-methoxybenzoic acid (1.0 mmol, 309 mg), acyl fluoride **2j** was observed in 99% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard and isolated as a colorless oil (152 mg, 99%) after filtration over silica using hexanes as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09−8.05 (m, 2H), 6.97−6.94 (m, 2H), 3.88 (s, 3H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 15.9 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[7]

*3-Methoxybenzoyl Fluoride (**2k**).* According to a general procedure starting with 3-methoxybenzoic acid (1.0 mmol, 152 mg), acyl fluoride **2k** was observed in quantitative ^{19}F NMR yield using 4-(trifluoromethyl)benzaldehyde as an internal standard and isolated as a colorless oil (129 mg, 84%) after filtration over silica using hexanes as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (ddd, J = 7.7, 1.6, 1.1 Hz, 1H), 7.54−7.52 (m, 1H), 7.45−7.40 (m, 1H), 7.24 (ddd, J = 8.3, 2.7, 1.0 Hz, 1H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.1 (d, J_{C-F} = 1.9 Hz), 157.5 (d, J_{C-F} = 344.7 Hz), 130.3 (d, J_{C-F} = 1.2 Hz), 126.2 (d, J_{C-F} = 60.7 Hz), 124.0 (d, J_{C-F} = 3.4 Hz), 122.2, 115.6 (d, J_{C-F} = 4.3 Hz), 55.7. ^{19}F NMR (470 MHz, $CDCl_3$): δ 18.6 (s, 1F). FT-IR (ν/cm^{-1}): 3011, 2962, 2945, 2916, 2849, 1805, 1601, 1489, 1431, 1292, 1271, 1205, 1176, 1020, 870. HRMS: Under all of the conditions tested for MS analysis (ESI-TOF or APPI-TOF with or without additives), no significant ions could be detected.

*2-Bromo-5-methoxybenzoyl Fluoride (**2l**).* According to a general procedure, starting with 2-bromo-5-methoxybenzoic acid (1.0 mmol, 231 mg), acyl fluoride **2l** was observed in 97% ^{19}F NMR yield using 4-(trifluoromethyl)benzaldehyde as an internal standard and isolated as a white solid (198 mg, 85%) after filtration over silica using hexanes as the eluent. Mp = 37.1−39.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (dd, J = 8.8, 1.4 Hz, 1H), 7.51 (d, J = 3.1 Hz, 1H), 7.05 (dd, J = 8.8, 3.1 Hz, 1H), 3.85 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 158.8, 154.8 (d, J_{C-F} = 345.3 Hz), 136.1 (d, J_{C-F} = 4.0 Hz), 125.9 (d, J_{C-F} = 61.3 Hz), 121.9 (d, J_{C-F} = 1.4 Hz), 118.3 (d, J_{C-F} = 2.0 Hz), 115.0 (d, J_{C-F} = 4.1 Hz), 55.8. ^{19}F NMR (470 MHz, $CDCl_3$): δ 31.3 (s, 1F). FT-IR (ν/cm^{-1}): 2964, 2939, 2916, 2849, 1819, 1568, 1597, 1477, 1398, 1321, 1283, 1242, 1200, 1176, 1132, 1095, 1030. HRMS (APPI-TOF), m/z: $[M + NH_4]^+$ calcd for $C_8H_{10}BrFNO_2$, 249.9873; found, 249.9879.

*3,5-Bis(trifluoromethyl)benzoyl Fluoride (**2m**).* According to a general procedure starting with 3,5-bis(trifluoromethyl)benzoic acid (1.0 mmol, 258 mg), acyl fluoride **2m** was observed in 94% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene (68.6 mg) as an internal standard. ^{19}F NMR (470 MHz, $CDCl_3$): δ 19.9 (s, 1F), − 63.2 (s, 6F).

*4-Hydroxybenzoyl Fluoride (**2n**).* According to a general procedure starting with 4-hydroxybenzoic acid (1.0 mmol, 138 mg), acyl fluoride **2n** was observed in 51% ^{19}F NMR yield using 4-(trifluoromethyl)benzaldehyde (36.9 mg) as an internal standard. ^{19}F NMR (470 MHz, $CDCl_3$): δ 15.3 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[7]

*Isonicotinoyl Fluoride (**2o**).* According to a general procedure starting with isonicotinic acid (1.0 mmol, 123 mg), acyl fluoride **2o** was observed in 74% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene (33.4 mg) as an internal standard. ^{19}F NMR (470 MHz, $CDCl_3$): δ 20.9 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[3a]

*Thiophene-2-carbonyl Fluoride (**2p**).* According to a general procedure starting with 2-thiophenecarboxylic acid (1.0 mmol, 128 mg), acyl fluoride **2p** was observed in 91% ^{19}F NMR yield using 4-(trifluoromethyl)benzaldehyde (45.0 mg) as an internal standard. ^{19}F NMR (470 MHz, $CDCl_3$): δ 24.3 (s, 1F).

*Furan-2-carbonyl Fluoride (**2q**).* According to a general procedure starting with 2-furanoic acid (1.0 mmol, 112 mg), acyl fluoride **2q** was observed in 65% ^{19}F NMR yield using 4-(trifluoromethyl)-benzaldehyde (54.7 mg) as an internal standard. ^{19}F NMR (470 MHz, $CDCl_3$): δ 15.3 (s, 1F).

*Terephtaloyl Difluoride (**2r**).* According to a general procedure starting with terephthalic acid (1.0 mmol, 166 mg) and using 2.2 equiv of XtalFluor-E instead of 1.1 equiv, acyl fluoride **2r** was observed in 98% ^{19}F NMR yield using 4-(trifluoromethyl)-benzaldehyde as an internal standard and isolated as a white solid (91 mg, 76%) after filtration over silica using hexanes as the eluent. Mp = 118.6−121.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.9 (d, J_{C-F} = 346.7 Hz), 131.8 (dd, J_{C-F} = 3.7, 1.1 Hz), 130.7 (d, J_{C-F} = 62.6 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 20.9 (s, 2F). FT-IR (ν/cm^{-1}): 3109, 3063, 2955, 2918, 2849, 1809, 1416, 1404, 1232, 1034, 1007, 906. HRMS: Under all the conditions tested for MS analysis (ESI-TOF or APPI-TOF with or without additives), no significant ions could be detected.

*5-Phenylpentanoyl Fluoride (**2s**).* According to a general procedure starting with 5-phenylpentanoic acid (1.0 mmol, 178 mg), acyl fluoride **2s** was observed in 99% ^{19}F NMR yield using 4-(trifluoromethyl)benzaldehyde as an internal standard and isolated as a transparent oil (130 mg, 72%) after filtration over silica using pentane as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32−7.28 (m, 2H), 7.23−7.17 (m, 3H), 2.69−2.64 (m, 2H), 2.55−2.50 (m, 2H), 1.75−1.70 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 163.6 (d, J_{C-F} = 360.3 Hz), 141.7, 128.6, 128.5, 126.1, 35.5, 32.1 (d, J_{C-F} = 50.4 Hz), 30.5, 23.6 (d, J_{C-F} = 1.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 45.5 (s, 1F). FT-IR (ν/cm^{-1}): 3063, 3024, 2932, 2862, 1836, 1751, 1713, 1065, 1497, 1458, 1412, 1366, 1080, 864, 702. HRMS: Under all the conditions tested for MS analysis (ESI-TOF or APPI-TOF with or without additives), no significant ions could be detected.

*Cyclohexanecarbonyl Fluoride (**2t**).* According to a general procedure starting with cyclohexanecarboxylic acid (1.0 mmol, 128 mg), acyl fluoride **2t** was observed in 99% ^{19}F NMR yield using 4-(trifluoromethyl)benzaldehyde as an internal standard and isolated as a transparent oil (87 mg, 67%) after filtration over silica using pentane as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.51 (tt, J = 10.8, 3.8 Hz, 1H), 2.02−1.95 (m, 2H), 1.82−1.74 (m, 2H), 1.65 (m, 1H), 1.59−1.49 (m, 2H), 1.38−1.23 (m, 3H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 36.7 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[16]

*Tetradecanoyl Fluoride (**2u**).* According to a general procedure starting with tetradecanoic acid (1.0 mmol, 228 mg), acyl fluoride **2u** was observed in 97% ^{19}F NMR yield using 4-(trifluoromethyl)-benzaldehyde as an internal standard and isolated as a transparent oil (202 mg, 88%) after filtration over silica using pentane as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.50 (td, J = 7.4, 1.2 Hz, 2H), 1.67 (q, J = 7.4 Hz, 2H), 1.40−1.23 (m, 20H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 163.8 (d, J_{C-F} = 360.7 Hz), 32.3 (d, J_{C-F} = 49.4 Hz), 32.1, 29.8, 29.8, 29.8, 29.7, 29.5, 29.5, 29.2, 28.9, 24.1 (d, J_{C-F} = 2.1 Hz), 22.8, 14.3. ^{19}F NMR (470 MHz, $CDCl_3$): δ 45.4 (s, 1F). FT-IR (ν/cm^{-1}): 2924, 2854, 1842, 1711, 1468, 1414, 1377, 1132, 1078, 862, 719. HRMS: Under all the conditions tested for MS analysis (ESI-TOF or APPI-TOF with or without additives), no significant ions could be detected.

*2-Phenylacetyl Fluoride (**2v**).* According to a general procedure starting with 2-phenyl acetic acid (1.0 mmol, 136 mg), acyl fluoride **2v** was observed in the quantitative ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard and isolated as a light-yellow oil (80 mg, 58%) after filtration over silica using pentane as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40−7.32 (m, 3H), 7.31−7.28 (m, 2H), 3.82 (d, J = 2.4 Hz, 2H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 44.9 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[7]

*2-(Naphthalen-2-yl)acetyl Fluoride (**2w**).* According to a general procedure starting with 2-(naphthalen-2-yl)acetic acid (1.0 mmol, 186 mg), acyl fluoride **2w** was observed in 99% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard and isolated as a white solid (138 mg, 73%) after filtration over silica using pentane as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88−7.81 (m, 3H), 7.76 (s, 1H), 7.54−7.48 (m, 2H), 7.40 (dd, J = 8.4, 1.8 Hz, 1H), 3.99 (d, J =

https://dx.doi.org/10.1021/acs.joc.0c01377
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2.3 Hz, 2H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 45.2 (t, J = 2.8 Hz, 1F). The analytical data are in agreement with those previously reported in the literature.[6]

*Adamantane-1-carbonyl Fluoride (**2x**).* According to a general procedure starting with 1-adamantanecarboxylic acid (1.0 mmol, 182 mg), acyl fluoride **2x** was observed in a quantitative ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard and isolated as a white solid (106 mg, 58%) after filtration over silica using 1% Et_3N in pentane as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.11−2.02 (m, 3H), 2.00−1.94 (m, 6H), 1.82−1.67 (m, 6H). ^{19}F NMR (376 MHz, $CDCl_3$): δ 23.6 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[7]

*Cinnamoyl Fluoride (**2y**).* According to a general procedure starting with cinnamic acid (1.0 mmol, 148 mg), acyl fluoride **2y** was observed in a quantitative ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard and isolated as a light-yellow oil (145 mg, 97%) after filtration over silica using pentane as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, J = 16 Hz, 1H), 7.58−7.56 (m, 2H), 7.50−7.43 (m, 3H), 6.38 (dd, J = 16.0, 7.3 Hz, 1H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 25.6 (d, J = 7.2 Hz, 1F). The analytical data are in agreement with those previously reported in the literature.[6]

*Tetradecanedioyl Difluoride (**2z**).* According to a general procedure starting with tetradecandioic acid (1.0 mmol, 258 mg) and using 2.2 equiv of XtalFluor-E instead of 1.1 equiv, acyl fluoride **2z** was observed in 95% ^{19}F NMR yield using 4-(trifluoromethyl)-benzaldehyde as an internal standard and isolated as a white solid (150 mg, 57%) after filtration over silica using pentane as the eluent. Mp = 38.7−40.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.50 (td, J = 7.4, 1.1 Hz, 4H), 1.67 (p, J = 7.4 Hz, 4H), 1.40−1.24 (m, 16H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 163.8 (d, J_{C-F} = 360.6 Hz), 32.3 (d, J_{C-F} = 50.0 Hz), 29.6, 29.4, 29.2, 28.8, 24.1 (d, J_{C-F} = 1.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 45.5 (s, 2F). FT-IR (ν/cm^{-1}): 2920, 2853, 1834, 1474, 1408, 1385, 1356, 1310, 1256, 1196, 1088, 1049, 1016, 978, 862, 829, 764, 719. HRMS (ESI-TOF), m/z: [M + NH_4]$^+$ calcd for $C_{14}H_{28}F_2NO_2$, 280.2083; found, 280.2077.

*2-(3-Benzoylphenyl)propanoyl Fluoride (Ketoprofen Fluoride) (**2aa**).* According to a general procedure starting with ketoprofen (0.09 mmol, 22 mg), acyl fluoride **2aa** was observed in 91% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene (38.5 mg) as an internal standard. ^{19}F NMR (470 MHz, $CDCl_3$): δ 39.7 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[7]

*Indomethacin Fluoride (**2ab**).* According to a general procedure starting with indomethacin (0.5 mmol, 179 mg), acyl fluoride **2ab** was observed in 47% ^{19}F NMR yield using 4-(trifluoromethyl)-benzaldehyde as an internal standard and isolated as a yellowish solid (82 mg, 46%) after filtration over silica using an 85:15 hexanes/EtOAc mixture as the eluent. The product was contaminated by ca. 10% of the starting material as estimated by ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70−7.66 (m, 2H), 7.51−7.47 (m, 2H), 6.89 (d, J = 2.5 Hz, 1H), 6.85 (dd, J = 9.0, 0.5 Hz, 1H), 6.70 (dd, J = 9.0, 2.5 Hz, 1H), 3.87 (d, J = 2.5 Hz, 2H), 3.84 (s, 3H), 2.41 (s, 3H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 44.4 (s, 1F). The analytical data are in agreement with those previously reported in the literature.[7]

General Procedure for the Sequential Deoxofluorination/Amidation Reaction. To a solution of carboxylic acid (1 equiv, 1.0 mmol) in dry EtOAc (0.5 M) was added NaF (10 mol %, 0.1 mmol, 4.2 mg), followed by XtalFluor-E (1.1 equiv, 1.1 mmol, 252 mg). After 24 h of stirring at room temperature under argon, benzylamine (3.3 equiv, 3.3 mmol, 360 μL) was added, followed by DIPEA (3.3 equiv, 3.3 mmol, 580 μL). The reaction mixture was quenched after 2 h of stirring at room temperature using a saturated aqueous solution of sodium bicarbonate. The resulting mixture was extracted three times with EtOAc. The organic phases were combined and washed three times with a saturated aqueous solution of ammonium chloride. The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was finally purified on silica gel using an automated flash purification system (AFP).

*N-Benzyl-3,5-bis(trifluoromethyl)benzamide (**3a**).* According to a general procedure starting with 3,5-bis(trifluoromethyl)benzoic acid (1.0 mmol, 258 mg), the corresponding acyl fluoride was observed in 94% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard, and amide **3a** was isolated as a yellow solid (255 mg, 73%) after purification by AFP (0−50% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26−8.20 (m, 2H), 8.01 (s, 1H), 7.41−7.30 (m, 5H), 6.57 (br s, 1H), 4.67 (d, J = 5.6 Hz, 2H). ^{19}F NMR (470 MHz, $CDCl_3$): δ − 62.9 (s, 6F). The analytical data are in agreement with those previously reported in the literature.[17]

*N-Benzyl-5-phenylpentanamide (**3b**).* According to a general procedure starting with 5-phenylpentanoic acid (1.0 mmol, 178 mg), the corresponding acyl fluoride was observed in 99% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard, and amide **3b** was isolated as a yellowish solid (265 mg, 99%) after purification by AFP (0−100% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.31 (m, 2H), 7.30−7.25 (m, 5H), 7.20−7.14 (m, 3H), 5.70 (br s, 1H), 4.43 (d, J = 5.6 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 2.23 (t, J = 7.5 Hz, 2H), 1.75−1.62 (m, 4H). The analytical data are in agreement with those previously reported in the literature.[18]

*N-Benzylcyclohexanecarboxamide (**3c**).* According to a general procedure starting with cyclohexanecarboxylic acid (1.0 mmol, 128 mg), the corresponding acyl fluoride was observed in 99% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard, and amide **3c** was isolated as a yellowish solid (206 mg, 95%) after purification by AFP (0−100% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.31 (m, 2H), 7.30−7.25 (m, 3H), 5.70 (br s, 1H), 4.44 (d, J = 5.7 Hz, 2H), 2.11 (tt, J = 11.8, 3.5 Hz, 1H), 1.93−1.86 (m, 2H), 1.83−1.76 (m, 2H), 1.67 (m, 1H), 1.47 (qd, J = 12.2, 3.3 Hz, 2H), 1.32−1.19 (m, 3H). The analytical data are in agreement with those previously reported in the literature.[19]

*N-Benzyltetradecanamide (**3d**).* According to a general procedure starting with tetradecanoic acid (1.0 mmol, 228 mg), the corresponding acyl fluoride was observed in 97% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard, and amide **3d** was isolated as a white solid (265 mg, 98%) after purification by AFP (0−100% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.31 (m, 2H), 7.30−7.26 (m, 3H), 5.75 (br s, 1H), 4.44 (d, J = 5.8 Hz, 2H), 2.21 (t, J = 7.6 Hz, 2H), 1.65 (p, J = 7.5 Hz, 2H), 1.37−1.20 (m, 20H), 0.88 (t, J = 7.0 Hz, 3H). The analytical data are in agreement with those previously reported in the literature.[20]

*N-Benzyladamantane-1-carboxamide (**3e**).* According to general procedure B starting with 1-adamantanecarboxylic acid (1.0 mmol, 180 mg), the corresponding acyl fluoride was observed in 93% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard, and amide **3e** was isolated as a white solid (247 mg, 92%) after purification by AFP (0−100% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.24 (m, 5H), 5.85 (br s, 1H), 4.44 (d, J = 5.6 Hz, 2H), 2.10−1.99 (m, 3H), 1.89 (d, J = 2.9 Hz, 6H), 1.78−1.66 (m, 6H). The analytical data are in rough agreement with those previously reported in the literature.[21]

*2-(3-Benzoylphenyl)-1-morpholinopropan-1-one (Ketoprofen Derivative) (**3f**).* According to a general procedure starting with ketoprofen (0.25 mmol, 64 mg) and using morpholine instead of benzylamine, the corresponding acyl fluoride was observed in 99% ^{19}F NMR yield using 2-fluoro-4-nitrotoluene as an internal standard, and amide **3f** was isolated as a colorless oil (80 mg, 99%) after purification by AFP (50−70% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82−7.77 (m, 2H), 7.70 (t, J = 1.8 Hz, 1H), 7.67−7.58 (m, 2H), 7.54−7.43 (m, 4H), 3.96 (q, J = 6.9 Hz, 1H), 3.79−3.64 (m, 2H), 3.61−3.52 (m, 3H), 3.50−3.42 (m, 1H), 3.33 (ddd, J = 13.2, 5.9, 2.9 Hz, 1H), 3.24 (ddd, J = 10.6, 7.1, 3.0 Hz, 1H), 1.50 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 196.5, 171.7, 142.2, 138.2, 137.4, 132.7, 131.1, 130.0, 128.9, 128.9, 128.8, 128.4, 66.8, 66.4, 46.1, 42.8, 42.4, 20.5. FT-IR (ν/cm^{-1}): 2970, 2928, 2854, 1641, 1580, 1429, 1360, 1317, 1281, 1269, 1113, 1028. HRMS (APPI-TOF), m/z: [M + H]$^+$ calcd for $C_{20}H_{21}NO_3$, 323.1521; found, 323.1545.

https://dx.doi.org/10.1021/acs.joc.0c01377
J. Org. Chem. 2020, 85, 10253−10260

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01377.

NMR spectra for the known (^{1}H, ^{19}F) and new (^{1}H, ^{13}C, ^{19}F) compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Fonds de recherche du Québec, Nature et technologies (FRQNT), OmegaChem, and the Université Laval.

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https://dx.doi.org/10.1021/acs.joc.0c01377
J. Org. Chem. 2020, 85, 10253−10260