

Supporting Information
for
Nucleophilic fluoroalkylation/cyclization route to
fluorinated phthalides

Masanori Inaba¹, Tatsuya Sakai¹, Shun Shinada¹, Tsuyuka Sugiishi¹, Yuta Nishina²,
Norio Shibata³, and Hideki Amii*¹

Address: ¹Division of Molecular Science, Graduate School of Science and
Technology, Gunma University, 1-5-1 Tenjin-cho, Kiryu, Gunma, 376-8515, Japan,
²Research Core for Interdisciplinary Sciences, Okayama University, 3-1-1
Tsushimanaka, Kita-ku, Okayama 700-8530, Japan and ³Department of
Nanopharmaceutical Sciences, Department of Life Science and Applied Chemistry,
Nagoya Institute of Technology Gokiso, Showa-ku, Nagoya 466-8555, Japan

Email: Hideki Amii - amii@gunma-u.ac.jp

* Corresponding author

General methods, synthetic procedures, ¹H and ¹⁹F NMR spectra
for known compound 1a and full characterization
of all new compounds

Contents

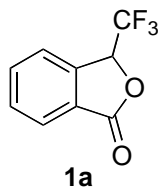
1. General remarks	S2
2. Experimental procedures	S2
3. References	S5
4. Spectral characterization data	S6

1. General remarks

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. Starting materials, reagents, and dry solvent were purchased from commercial suppliers and used without further purification. ^1H NMR spectra were recorded using Me_4Si as an internal standard (δ 0 ppm). ^{19}F NMR spectra were recorded in CDCl_3 on JEOL JNM-ECS300 (300 MHz), JEOL JNM-ECS400 (400 MHz) and JEOL JNM-ECA600 (600 MHz) spectrometers using CFCl_3 as an internal standard (δ 0 ppm). Splitting patterns were reported as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

2. Experimental procedures

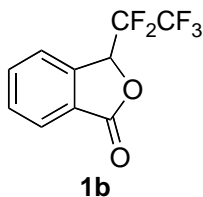
3-(Trifluoromethyl)phthalide (**1a**) [CAS Registry No. 76284-62-3]¹



Conditions A: To a mixture of 2-cyanobenzaldehyde (65.6 mg, 0.50 mmol), KF (20.9 mg, 0.36 mmol), and DMF (2.5 mL) was added trifluoromethyl(trimethyl)silane (85.3 mg, 0.60 mmol) at room temperature. The reaction mixture was stirred at room temperature in an atmosphere of nitrogen for 1 h and quenched with 1 M HCl (2.5 mL). The reaction mixture was stirred at 100 °C for 6 h. The aqueous layer was extracted with ethyl acetate. Then, the combined organic phase was washed with water, dried over anhydrous Na_2SO_4 . Purification

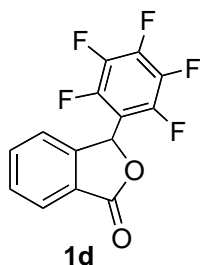
by column chromatography on silica gel (hexane/ethyl acetate = 5/1) gave 95.9 mg (0.474 mmol, 95%) of 3-(trifluoromethyl)phthalide (**1a**) as a colorless oil; Mp 40.2-41.6 °C; IR (neat) 1780 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.68 (1H, q, $J = 5.7$ Hz), 7.66-7.72 (2H, m), 7.78-7.82 (1H, m), 8.00 (1H, d, $J = 7.6$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -77.0 (3F, s); EI-MS m/z (%) 202 (M^+ , 1), 155 (6), 133 (100), 105 (19), 77 (14).

3-(Pentafluoroethyl)phthalide (**1b**)



The title compound was prepared according to the procedure A using 2-cyanobenzaldehyde (65.6 mg, 0.50 mmol), KF (20.9 mg, 0.36 mmol), and DMF (2.5 mL) was added pentafluoroethyl(trimethyl)silane (115.3 mg, 0.60 mmol) and purified by column chromatography (hexane/ethyl acetate = 5/1) to give colorless solid (97.0 mg, 0.385 mmol, 77%); Mp 60.8-62.9 °C; IR (neat) 1775 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.76 (1H, dd, $J = 2.4, 17.6$ Hz), 7.65-7.73 (2H, m), 7.79-7.83 (1H, m), 8.00 (1H, d, $J = 7.6$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 74.9 (dd, $J = 25.8, 33.0$ Hz), 111.5 (ddq, $J = 261, 253, 37.8$ Hz), 118.3 (qt, $J = 286, 34.5$ Hz), 124.0 (d, $J = 2.9$ Hz), 126.0, 126.4, 131.2, 134.9, 140.5, 168.1; ^{19}F NMR (376 MHz, CDCl_3) δ -130.6 (1F, dd, $J = 17.6, 282$ Hz), -122.4 (1F, d, $J = 282$ Hz), -82.8--81.9 (3F, m); EI-MS m/z (%) 252 (M^+ , 1), 205 (8), 133 (100), 105 (91), 77 (96). Anal. Calcd for $\text{C}_{10}\text{H}_5\text{O}_2\text{F}_5$: C, 47.64; H, 2.00. Found: C, 47.50; H, 2.17.

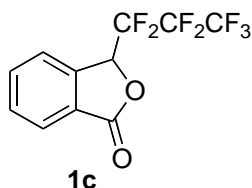
3-(Pentafluorophenyl)phthalide (**1d**)



The title compound was prepared according to the procedure A using 2-cyanobenzaldehyde (65.6 mg, 0.50 mmol), KF (20.9 mg, 0.36 mmol), and DMF (2.5 mL) was added pentafluorophenyl(trimethyl)silane (144.2 mg, 0.60 mmol) and purified by column chromatography (hexane/ethyl acetate = 5/1) to give colorless solid (129.6 mg, 0.432 mmol, 86%); Mp 110.0-112.6 °C; IR (neat) 1760 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.74 (1H, s), 7.34 (1H, d, $J = 8.4$ Hz), 7.61 (1H, t, $J = 7.6$ Hz), 7.70-7.74 (1H, m), 8.00 (1H, d, $J = 7.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 71.9, 110.3 (t, $J = 12.0$ Hz), 122.0, 125.6, 126.1, 130.1, 134.7, 137.8 (d, $J = 245$ Hz), 145.0 (d, $J = 250$ Hz), 145.5 (d, $J = 250$ Hz),

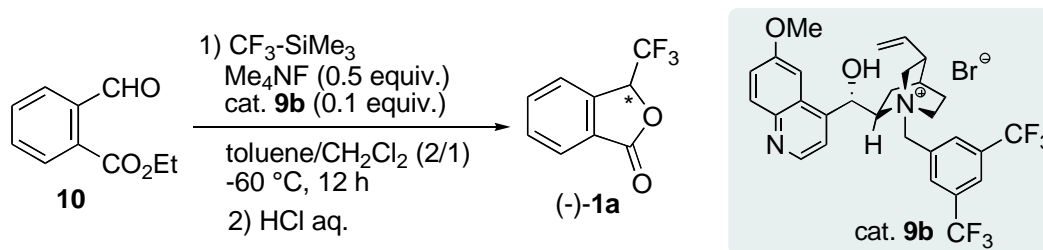
146.7, 169.3; ^{19}F NMR (376 MHz, CDCl_3) δ -160.6--160.5 (2F, m), -151.0 (1F, t, $J = 23.0$ Hz), -142.8 (2F, dd, $J = 6.0, 23.0$ Hz); EI-MS m/z (%) 300 (M^+ , 1), 255 (9), 237 (19), 133 (11), 105 (100), 77 (23). Anal. Calcd for $\text{C}_{14}\text{H}_5\text{O}_2\text{F}_5$: C, 56.02; H, 1.68. Found: C, 55.95; H, 1.77.

3-(Heptafluoropropyl)phthalide (**1c**)



Conditions B: To a mixture of 2-cyanobenzaldehyde (65.6 mg, 0.50 mmol), triethylamine (50.5 mg, 0.50 mmol), and DMF (2.5 mL) was added heptafluoropropyl(trimethyl)silane (145.3 mg, 0.60 mmol) at room temperature. The reaction mixture was stirred at room temperature in an atmosphere of nitrogen for 1 h and quenched with 4 M HCl (2.5 mL). The reaction mixture was stirred at 100 °C for 1 h. The aqueous layer was extracted with ethyl acetate. Then, the combined organic phase was washed with water, dried over anhydrous Na_2SO_4 . Purification by column chromatography on silica gel (hexane/ethyl acetate = 5/1) gave 90.5 mg (0.300 mmol, 60%) of 3-(heptafluoropropyl)phthalide (**1c**) as colorless solid; Mp 45.0-46.2 °C; IR (neat) 1782 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.83 (1H, d, $J = 18.4$ Hz), 7.68-7.73 (2H, m), 7.78-7.82 (1H, m), 8.00 (1H, d, $J = 7.6$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 75.0 (dd, $J = 26.0, 34.0$ Hz), 108.8 (tq, $J = 265, 36.7$ Hz), 113.3 (ddt, $J = 252, 264, 30.7$ Hz), 117.5 (qt, $J = 286, 33.0$ Hz), 124.2, 126.1, 126.3, 131.2, 134.9, 140.5, 168.2; ^{19}F NMR (376 MHz, CDCl_3) δ -127.2 (1F, d, $J = 298$ Hz), -126.6 (1F, d, $J = 291$ Hz), -125.7 (1F, d, $J = 291$ Hz), -120.2 (1F, d, $J = 298$ Hz), -80.9 (3F, t, $J = 15.4$ Hz); EI-MS m/z (%) 302 (M^+ , 1), 169 (7), 133 (100), 105 (63), 77 (78). Anal. Calcd for $\text{C}_{14}\text{H}_5\text{O}_2\text{F}_5$: C, C 43.73; H, 1.67. Found: C, 43.29; H, 1.81.

(-)-3-(Trifluoromethyl)phthalide ((-)-**1a**)



To a mixture of ethyl 2-formylbenzoate (**10**; 89.1 mg, 0.50 mmol), **9b** (15.8 mg, 0.025 mmol), ² tetramethylammonium fluoride (9.3 mg, 0.10 mmol), toluene (4.0 mL), and dichloromethane (2.0 mL) was added trifluoromethyl(trimethyl)silane (141.3 mg, 1.0 mmol) at -60 °C. The reaction mixture was stirred at room temperature in an atmosphere of

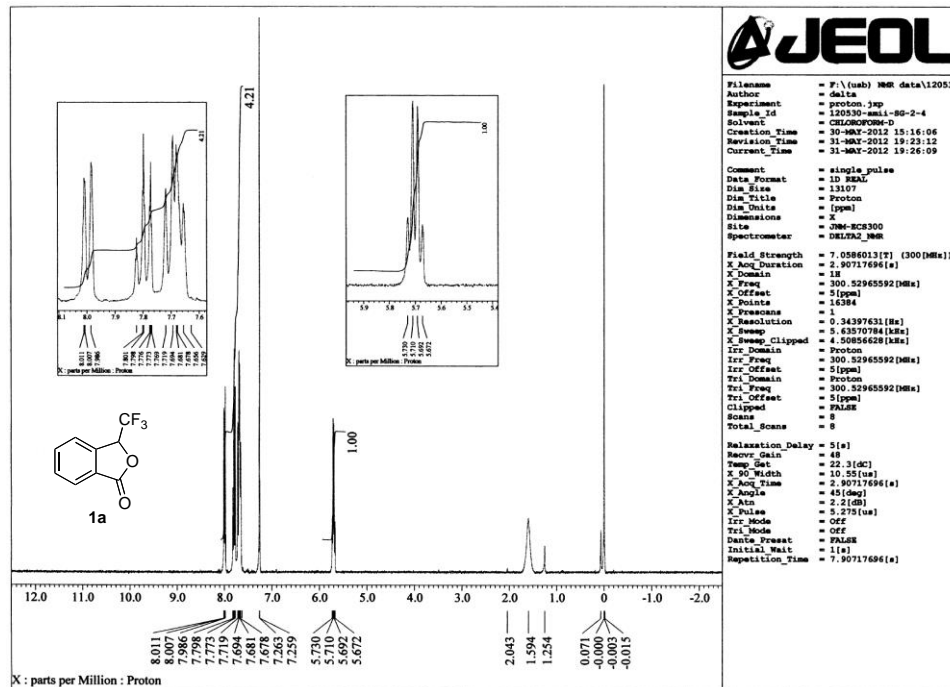
nitrogen at $-60\text{ }^{\circ}\text{C}$ for 24 h and quenched with sat. NH_4Cl aq (5 mL). The aqueous layer was extracted with ethyl acetate. Then, the combined organic phase was washed with water, dried over anhydrous Na_2SO_4 . After removal of the solvent under reduced pressure, to the residue was added DMF (2.5 mL) and 1 M HCl (2.5 mL). The reaction mixture was stirred at $100\text{ }^{\circ}\text{C}$ for 6 h. The aqueous layer was extracted with ethyl acetate. Then, the combined organic phase was washed with water, dried over anhydrous Na_2SO_4 . Purification by column chromatography on silica gel (hexane/ethyl acetate = 5:1) gave 78.8 mg (0.39 mmol, 78% yield, 27% ee) of 3-(trifluoromethyl)phthalide (**1a**) as a colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 5.68 (1H, q, $J = 5.7$ Hz), 7.66-7.72 (2H, m), 7.78-7.82 (1H, m), 8.00 (1H, d, $J = 7.6$ Hz); HPLC condition: Chiralcel OD-H, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 224 nm, temp. = $30\text{ }^{\circ}\text{C}$, $t_{\text{R}} = 8.5$ min for (-)-**1a** and $t_{\text{R}} = 12.0$ min for (+)-**1a**.¹

3. References

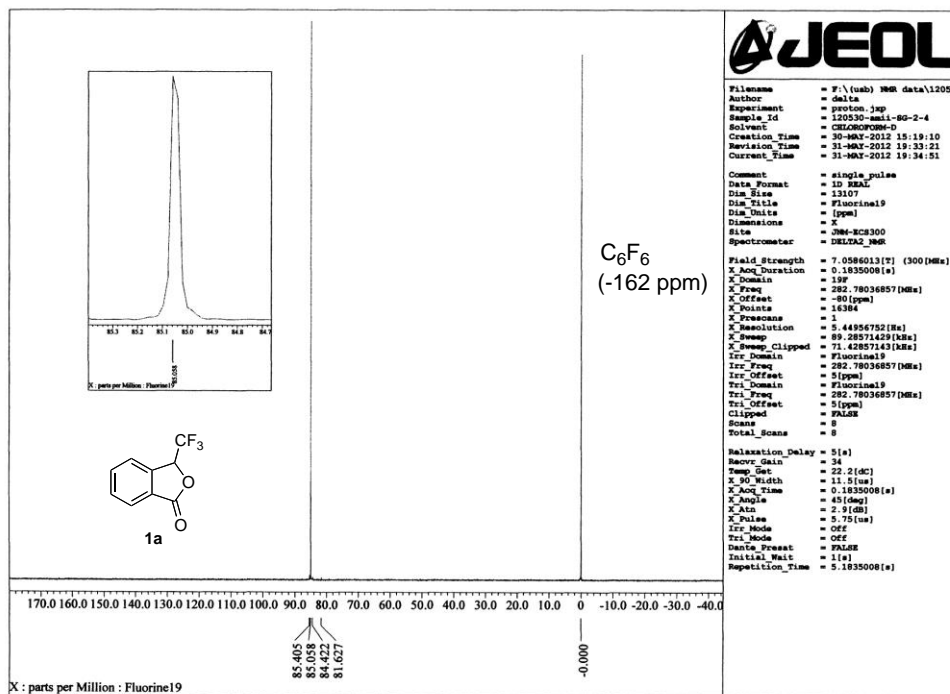
- 1) R. Pedrosa, S. Sayalero, M. Vicente, *Tetrahedron* **2006**, *62*, 10400.
- 2) S. Mizuta, N. Shibata, S. Akiti, H. Fujimoto, S. Nakamura, T. Toru, *Org. Lett.* **2007**, *9*, 3707.

4. Spectral Characterization Data

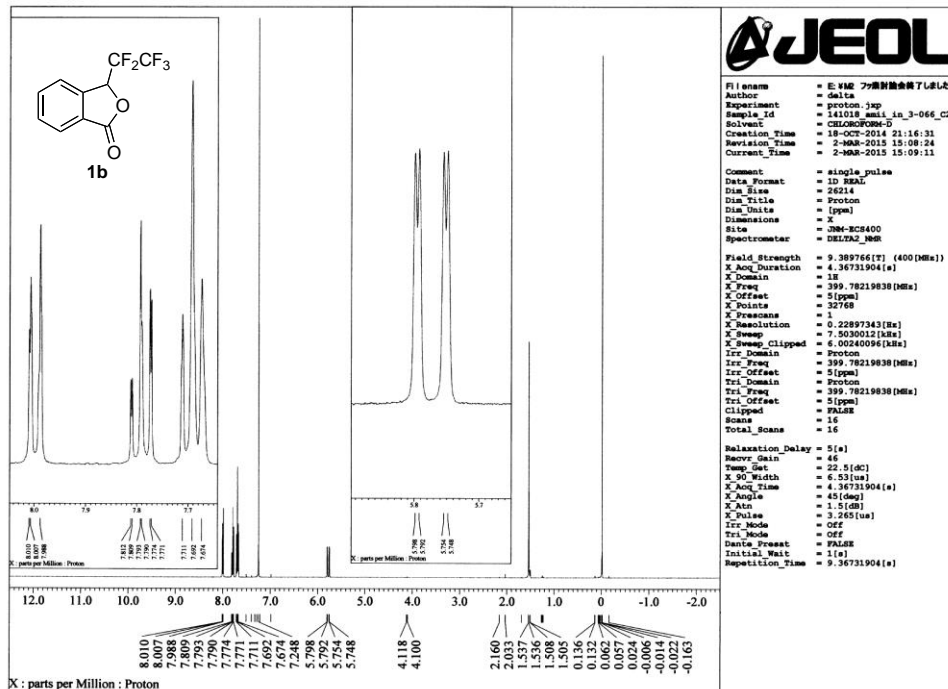
¹H NMR Spectrum of 3-(trifluoromethyl)phthalide (1a)



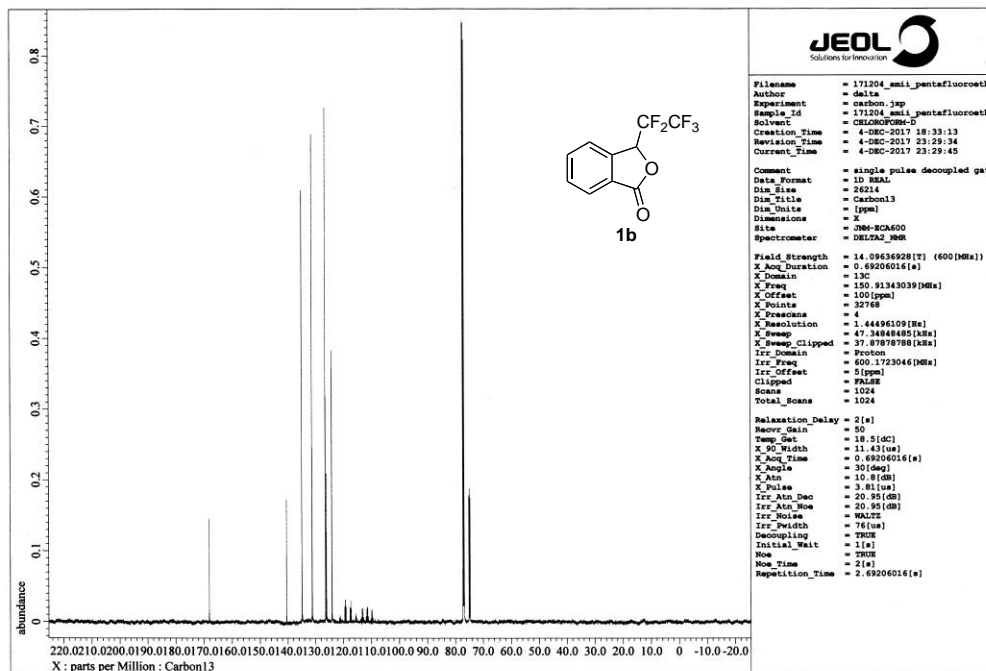
¹⁹F NMR Spectrum of 3-(trifluoromethyl)phthalide (1a)



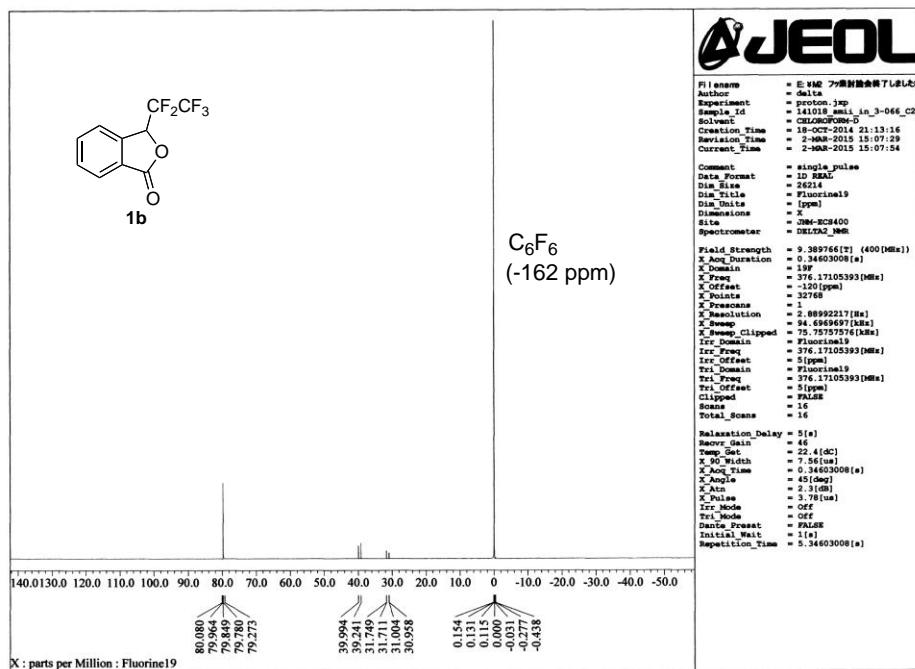
¹H NMR Spectrum of 3-(pentafluoroethyl)phthalide (**1b**)



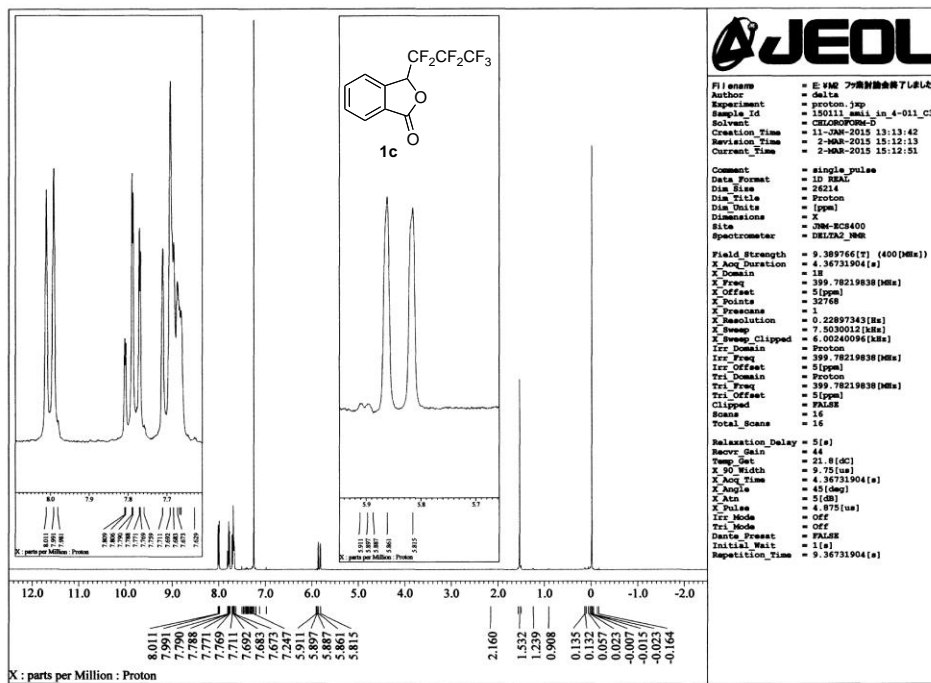
¹³C NMR Spectrum of 3-(pentafluoroethyl)phthalide (**1b**)



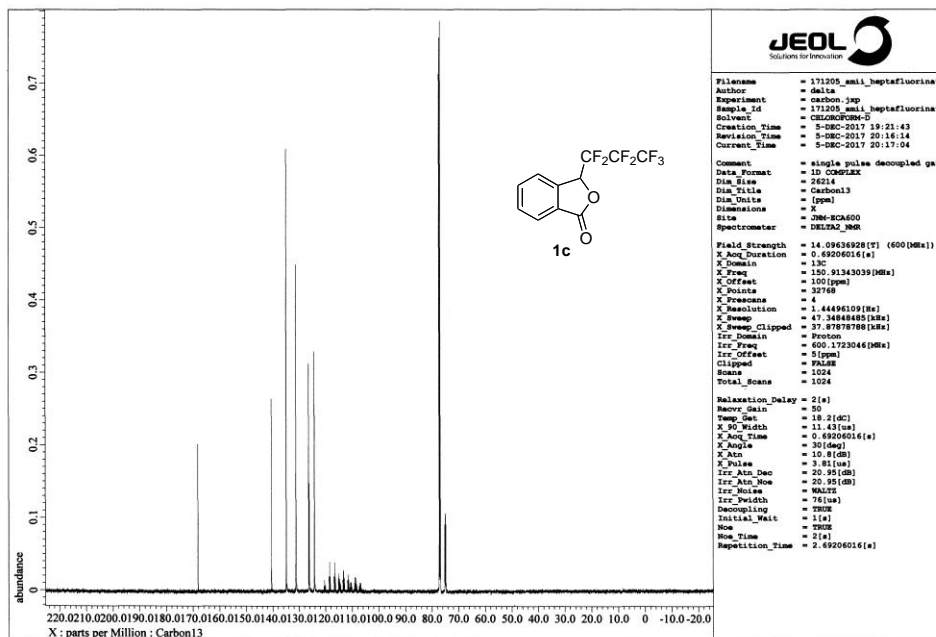
¹⁹F NMR Spectrum of 3-(pentafluoroethyl)phthalide (**1b**)



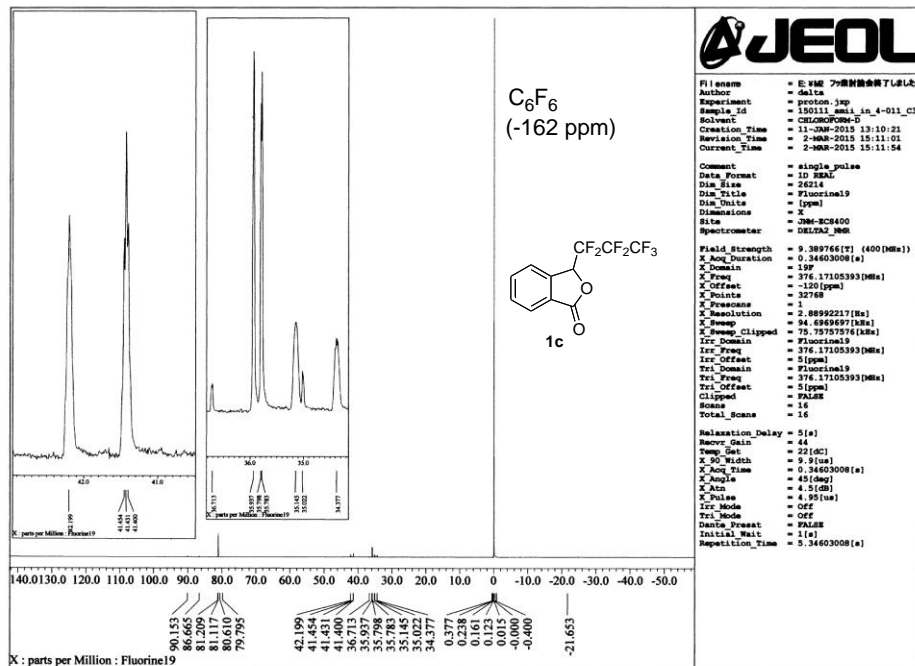
¹H NMR Spectrum of 3-(heptafluoropropyl)phthalide (**1c**)



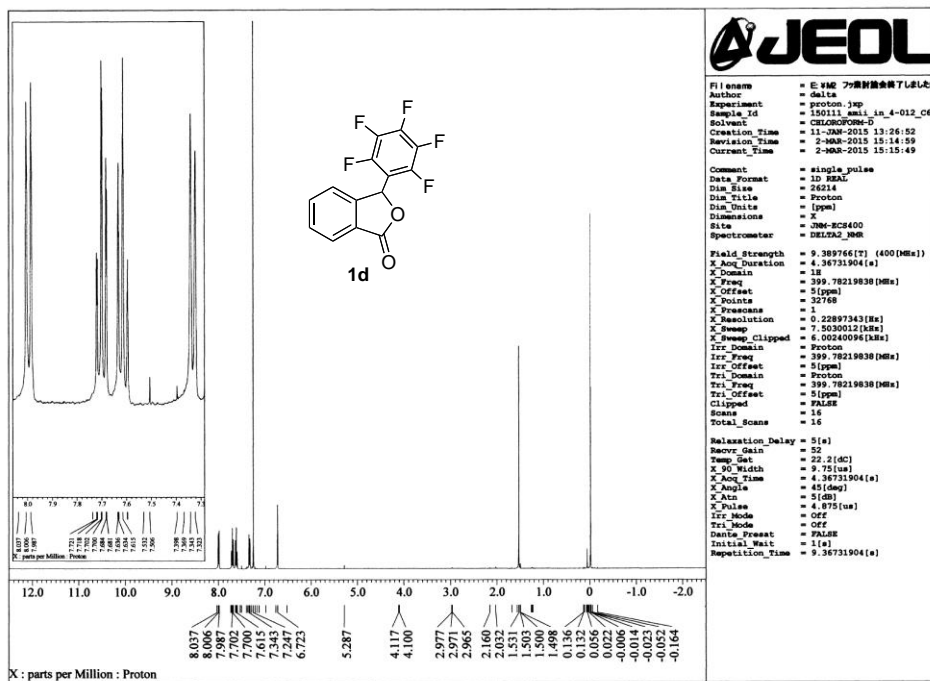
¹³C NMR Spectrum of 3-(heptafluoropropyl)phthalide (1c)



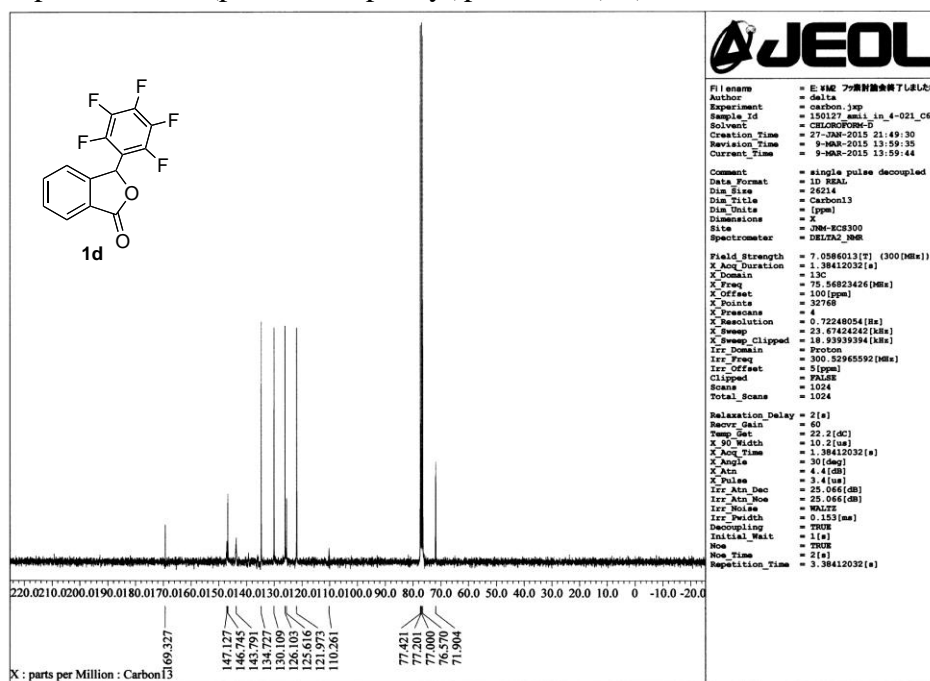
¹⁹F NMR Spectrum of 3-(heptafluoropropyl)phthalide (1c)



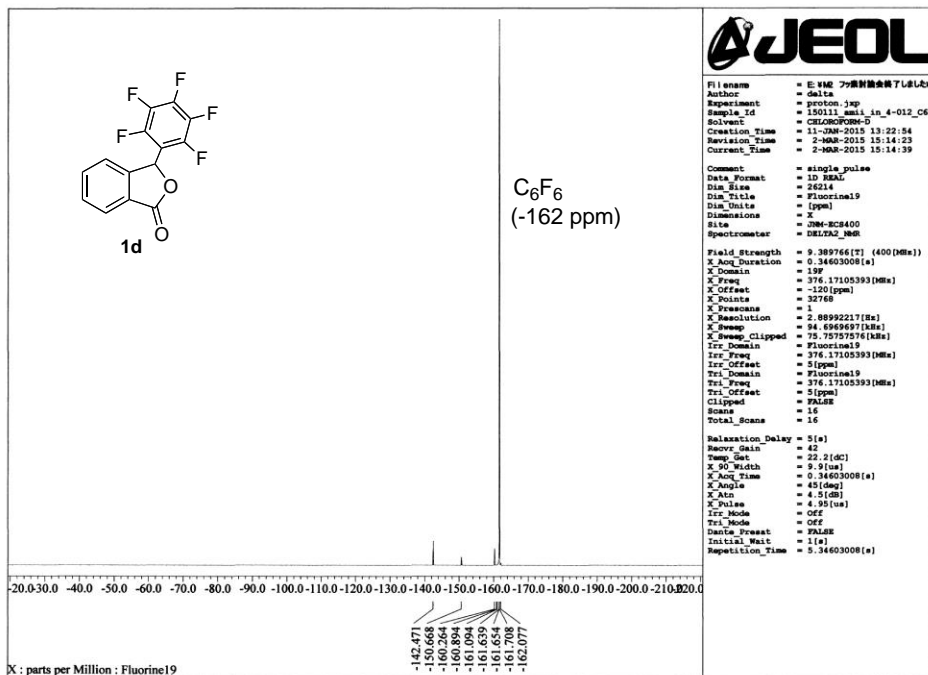
¹H NMR Spectrum of 3-(pentafluorophenyl)phthalide (**1d**)



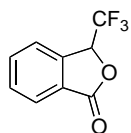
¹³C NMR Spectrum of 3-(pentafluorophenyl)phthalide (**1d**)



¹⁹F NMR Spectrum of 3-(pentafluorophenyl)phthalide (1d)

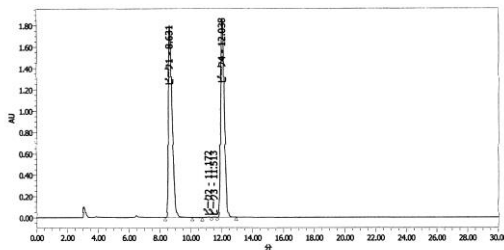


HPLC Analytical Data of 3-(trifluoromethyl)phthalide (1a)

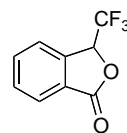


個別レポートDefault

サンプル情報			
サンプル名:	150124_M1_223	分析担当書:	System
サンプルの種類:	未知試料	サンプル名:	150124_M1_221
バリエーション:	7	取り込みメソッドセット:	150124_M1_221
注入量:	10.00 μL	解析メソッド:	150124_M1_223
分析時間:	30.00 分	チャンネル名:	2998
		解析チャンネルの説明:	PDA 219.7 nm (210-250)nm
分析日:	2015/01/24 2:01:02 JST		
解析日:	2015/01/24 2:50:06 JST		

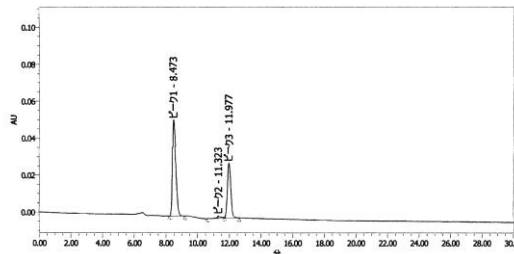


成分名	保持時間 (分)	面積 (μV秒)	%面積	高さ (μV)
1 ピーク1	8.631	31013021	49.98	1798444
2 ピーク2	11.172	51819	0.08	3535
3 ピーク3	11.513	42631	0.07	2594
4 ピーク4	12.038	30942364	49.87	1863154



(27% ee) 個別レポートDefault

サンプル情報			
サンプル名:	150209_M1_230	分析担当書:	System
サンプルの種類:	未知試料	サンプル名:	150209_M1_230
バリエーション:	8	取り込みメソッドセット:	150209_M1_230
注入量:	10.00 μL	解析メソッド:	150209_M1_230
分析時間:	30.00 分	チャンネル名:	2998
		解析チャンネルの説明:	PDA 250.1 nm (210-250)nm
分析日:	2015/02/09 12:16:32 JST		
解析日:	2015/02/09 12:51:31 JST		



成分名	保持時間 (分)	面積 (μV秒)	%面積	高さ (μV)
1 ピーク1	8.473	785284	62.18	52147
2 ピーク2	11.323	25760	2.04	1554
3 ピーク3	11.977	451785	35.78	29986