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Improved synthesis of perfluorooctylpropyl amine

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Abstract

Hydrazinolysis of *N*-perfluorooctylpropyl phthalimide is an easy route to scale up for the title compound. Both the alkylation of potassium phthalimide with perfluorooctylpropyl iodide and the hydrogenolysis of the adduct of perfluoroctyl iodide to *N*-allyl-phthalimide provide this amine precursor in good yields. The latter procedure, however, has a better atom economy, since it requires only three steps from perfluorooctyl iodide.
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1. Introduction

Perfluorooctylpropyl amine is a nucleophilic scavenger and important fluorophilic compound, which can also be used as a precursor for the synthesis of novel fluorous reagents, ligands, catalysts, tags, scavengers and protecting groups [1,2]. It is accessible by multistep syntheses (Scheme 1) starting from perfluorooctylpropyl alcohol [3]. According to a general protocol, developed by Gladysz and co-workers [4], alcohol **1** first was oxidized to aldehyde **2**, which then reacted with benzylamine in the presence of sodium triacetoxy-hydridoborate to yield intermediate **3**, and its hydrogenolysis afforded amine **4** in excellent yield. While in the method of Rábai and co-workers [5] perfluorooctylpropyl iodide **5** [6] on treatment with a pressurized solution of ammonia in THF afforded a separable mixture of the primary and the corresponding secondary amines. Although this amine has recently become commercially available [7], we aimed to develop more efficient methods for the production of primary *F*-alkylpropyl amines, and as a consequence, to facilitate the access to novel amine based fluorous reagents.

2. Results and discussion

An alternative route to amine **4**, involves the radical chain addition of perfluorooctyl iodide **6** to protected allyl amine **7** and subsequent dehalogenation followed by deprotection (Scheme 2). The strategy of using *N*-allyl-phthalimide **7** in combination with perfluoroalkyl iodides was first introduced by Commeyras and co-workers [8] and recently further elaborated for the synthesis of amino terminated semifluorinated long-chain alkanethiols by Amato and Calas [9].

We have found that heating *N*-allyl-phthalimide **7** and perfluorooctyl iodide **6** in *iso*-octane for 2 days with periodic addition of azobisisobutyronitrile (AIBN) results in the formation of the iodo-adduct **8** in excellent yield. Then, compound **8** was hydrogenated in THF over an Pd/C catalyst in the presence of a slight excess of triethyl amine to afford *N*-perfluorooctylpropyl phthalimide **9**. Finally, the protecting group was removed by heating with hydrazine hydrate in methanol and then with 6 N hydrochloric acid. Amine **4** was obtained from the solid precipitate with ether/NaOH–H_2O partition and consecutive fractionation of the organic phase. This three-step procedure resulted in a 60% overall yield of **4** from *F*-alkyliodide **6**.

Phthalimide **9** can also be prepared in excellent yield by heating a DMF solution of potassium phthalimide and iodide **5** as partly disclosed by us [10] (Scheme 2).The efficacy of different routes for the preparation of amine **4** depends on

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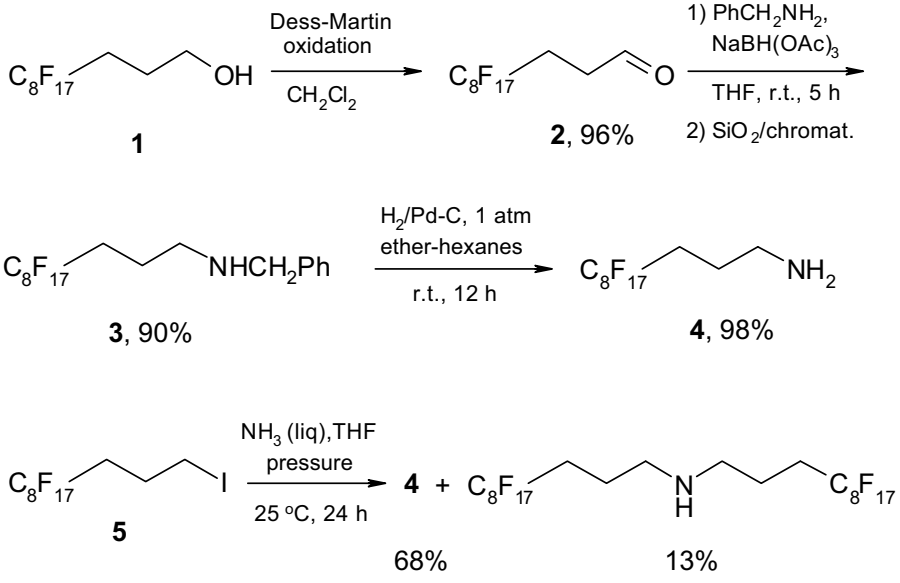
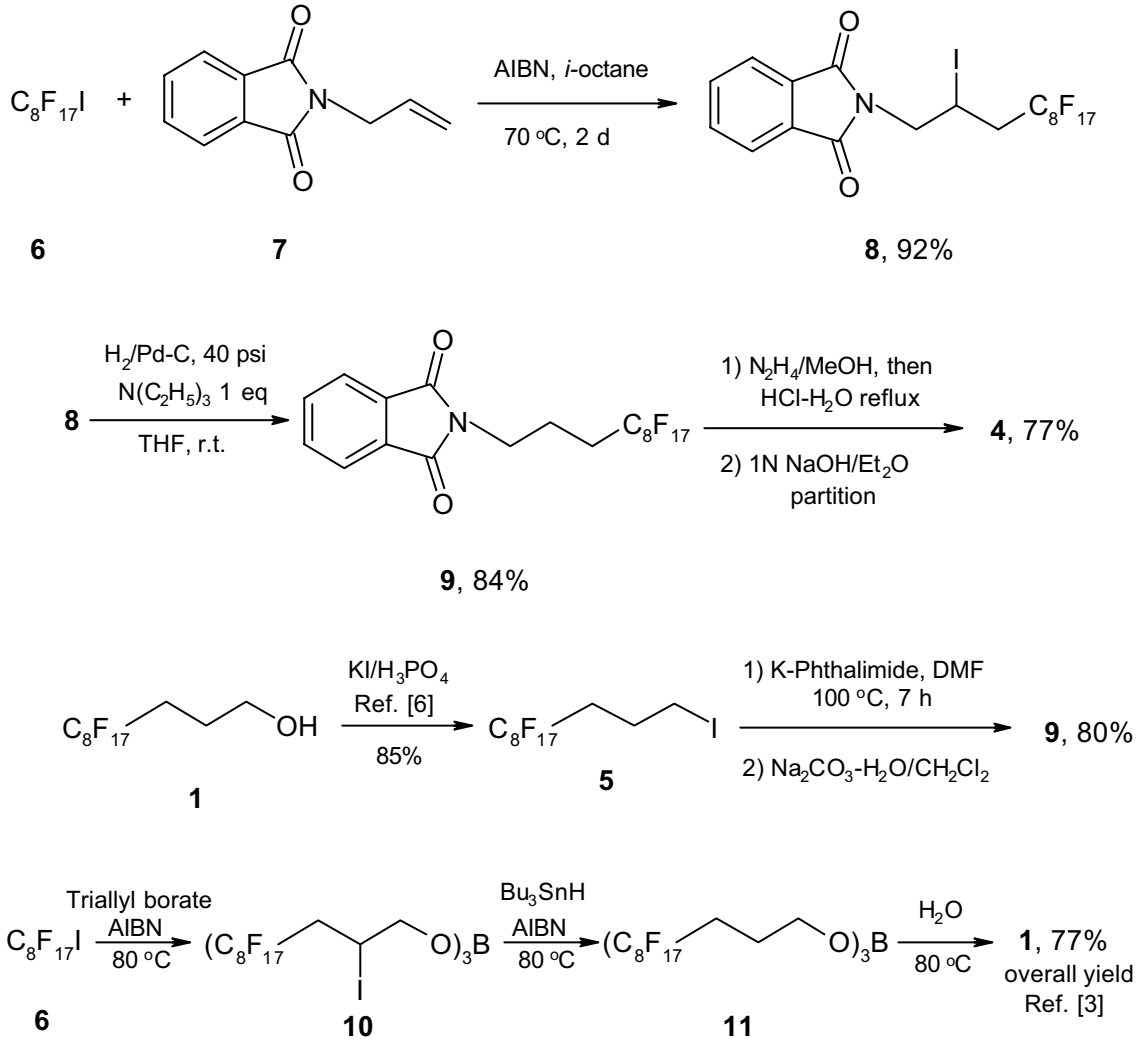


Scheme 1. Synthesis of amine **4** from the precursor alcohol **1** or iodide **5**.



Scheme 2. An F-efficient sequence (**6**–**8**–**9**–**4**) for the synthesis of amine **4**.

Table 1
Effectiveness of different synthetic sequences for the use of **6** or **1**

Entry	Sequence of steps	No. of steps	Yield (%) from **6** (or **1**)[a]
1	**6** → **10** → **11** → **1** → **2** → **3** → **4**	6 (3)	65 (85)
2	**6** → **10** → **11** → **1** → **5** → **4**	5 (2)	45 (58)
3	**6** → **10** → **11** → **1** → **5** → **9** → **4**	6 (3)	40 (52)
4	**6** → **8** → **9** → **4**	3	60

[a] Calculated by using yield data of Schemes 1 and 2.

both the yields and the number of synthetic steps involved (Table 1). Thus, methods displayed in Entries 1–3 are viable for smaller scale syntheses, especially if they are started at a later step using commercially available precursors, such as alcohol **1** or iodide **5**. On the other hand, Entry 4 provides an easy to scale up and a more cost efficient procedure.

3. Conclusions

The three-step sequence (Entry 4, Table 1), involving the radical chain addition of a perfluoroalkyl iodide to a protected allyl amine, followed by reductive dehalogenation and deprotection, could be the method of choice for amine synthesis, when the price of the F-precursors is a limiting factor.

4. Experimental

Melting points were determined on a Boetius micro melting point apparatus and are uncorrected. Reagents **1**, **4**–**6** were commercially available [7], while **7** was prepared as reported [11]. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer at 500 (^{1}H) and 125 (^{13}C) MHz with Me_4Si as internal standard. ^{19}F NMR spectra were obtained on a Bruker (250 MHz) spectrometer in $CDCl_3$ with $CFCl_3$ as external standard, downfield shifts being designated as negative. All chemical shifts (δ) are expressed in ppm, coupling constants (J) are given in Hz. The letters s, d, t, qa, qi and m designate singlet, doublet, triplet, quartet, quintet and multiplet, respectively. Mass spectra were determined on a VG ZAB-2SEQ tandem mass spectrometer using electron impact (70 eV) for ionization and direct probe for sample introduction at a source temperature of 180 °C. Mass range (m/z) from 25 to 1500 was considered. The accuracy of the HRMS measurements is described by the formula: $(M(\text{found}) - M(\text{calculated}))/M(\text{calculated}) < \pm 5 \times 10^{-6}$. All reaction steps were monitored by gas chromatography (Hewlett-Packard 5890 Series II, PONA 50 m to 0.2 mm, 0.5 μm column, H_2 carrier gas, FID).

4.1. 2-Allyl-isoindole-1,3-dione (7)

To a solution of allyl amine (5.70 g, 100 mmol) in acetic acid (30 ml) phthalic anhydride (14.8 g, 100 mmol) was added with stirring, then the mixture was refluxed for 2 h. It was poured to water (300 ml) and the precipitate formed was filtered and dried in vacuo over KOH pellets. Recrystallization from *iso*-octane afforded 14.0 g (75%) white needles of mp = 68–69 °C, literature mp = 70 °C [11]. ^{1}H NMR δ: 7.79 (m, A part of an AA′XX′ spin system, 2H) and 7.67 (m, X part of an AA′XX′ spin system, 2H, $J_{AX} = 8.1$, $J_{AX'} = 2.6$ Hz); 5.84 (ddt, 1H, $J = 18.4$, 10.2, 1.5 Hz); 5.14 (dqa, 1H, $J = 10.2$, 1.5 Hz); 5.2 (dqa, H_X, 1H, $J = 18.4$, 1.5 Hz); 4.24 (dt, N–C**H$_2$**, 2H, $J = 5.7$, 1.5 Hz). ^{13}C NMR δ: 117.9 (C3′) 131.8 (C2′); 40.3 (C1′); 168.0 (C1, C3); 132.3 (C3a, C7a); 123.5 (C4, C7); 134.2 (C5, C6).

4.2. 2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10, 11,11,11-Heptadecafluoro-2-iodo-undecyl)-isoindole-1,3-dione (8)

A solution of **6** (68.2 g, 125 mmol) and **7** (23.4 g, 125 mmol) in *iso*-octane (30 ml) was stirred and heated to 70 °C under an argon atmosphere, then the reaction was initiated with AIBN (0.15 g). The mixture was stirred and heated at this temperature and in every 3rd h further portion of AIBN (0.15 g) was added. After 46 h reaction, GC analysis showed >95% conversion of **7**. The resulted precipitate was filtered at ice-bath temperature and washed with cold *iso*-octane (30 ml) to afford the crude product as white crystals (84.3 g, 92%; GC purity: 92%). Recrystallization (3×) from methanol (4 ml/g) yielded an analytically pure sample (GC: 98%), mp = 90–92 °C. (Literature mp = 90 °C/MeOH [8].) ^{1}H NMR δ: 7.89 (m, A part of an AA′XX′ spin system, 2H); 7.76 (m, X part of an AA′XX′ spin system, 2H, $J_{AX} = 8.1$, $J_{AX'} = 2.6$ Hz); 4.72 (∼qi, C**H**I, 1H, $J = 7.2$ Hz); 2.92 (2 × m, C**H$_2$**CF$_2$, 2H);. 4.17, 3.98 (NC**H$_2$**, 2 × dd, 2 × 1H, $J = 14.3$, 8.6 Hz, $J = 14.3$, 6.8 Hz). ^{13}C NMR δ: 46.1 (C1′); 13.4 (C2′); 39.8 (t, $J = 21.1$ Hz); 167.9 (C1, C3); 131.9 (C3a, C7a); 123.9 (C4, C7); 134.6 (C5, C6). ^{19}F NMR δ: −112.5, −114.2 (CH$_2$C**F$_2$**, m, A and B parts of an ABX$_2$ spin system, $^{2}J_{FF} = 271$ Hz, $^{4}J_{FF} = 13.8$ Hz); −126.66 (br, 2F); −123.93 (br, 2F); −123.24 (br, 2F); −122.41 (br, 4F); −122.06 (br, 2F); −81.38 (C**F$_3$**, t, 3F, $J = 9.9$ Hz). ^{15}N NMR δ: 162.6. MS (m/z, I%, M − X): 734, 6, $M + 1$; 733, 6, M; 714, 6, M − F; 606, 100, M − I; 586, 15; 160, 45, M − CH(I)CH$_2$(CF$_2$)$_7$CF$_3$. HRMS (m/z) calculated for $C_{19}H_9F_{17}INO_2$, $M^+ = 732.9407$, found $M^+ = 732.9390$.

4.3. 2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl)-isoindole-1,3-dione (9)

4.3.1. Method A

In a 500 ml volume Pyrex bottle of a Parr hydrogenation apparatus were placed the iodo-adduct **8** (33.0 g; 45.0 mmol) dissolved in THF (230 ml), triethyl amine (7.0 ml; 50 mmol) and 10% Pd-C (0.90 g). After removal of air with N_2, this mixture was hydrogenated at room temperature and at a pressure of 40–50 psi until higher than 98% conversion detected (GC). The mixture was then

filtered through a Celite plug (30 g) which finally washed with some THF. The combined filtrates were concentrated in vacuum, and then diluted with water (250 ml). The solid precipitate obtained was filtered, washed thoroughly with water and dried. Recrystallization of the off-white crude product from methanol (300 ml) in the presence of charcoal yielded 22.9 g (84%) white product, mp = 92–93.5 °C, GC: 98%.

4.3.2. Method B

To a stirred suspension of potassium phthalimide (18.5 g, 100 mmol) in DMF (150 ml), iodide **5** (29.4 g, 50.0 mmol) was added and the mixture heated at 100 °C for 7 h. It was poured into 0.5 N Na_2CO_3 (600 ml), extracted with CH_2Cl_2 (3 × 100 ml) and the combined organic phases were filtered through Celite, washed with water (3 × 300 ml) and dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallized from methanol (220 ml) to yield 24.3 g (80%) of pure **3** as pale yellow needles, mp 93.0–93.8 °C (GC: 99.4%).

^{1}H NMR δ: 7.84 (m, A part of an AA′XX′ spin system, 2H); 7.72 (m, X part of an AA′XX′ spin system, 2H, $J_{AX} = 8.1$, $J_{AX'} = 2.6$ Hz); 3.77 (t, 2H, $J = 7.0$ Hz, N–C**H$_2$**); 2.16 (m, 2H, C**H$_2$**C_8F_{17}). 2.02 (qi, 2H, $J = 7.0$ Hz, NCH_2CH_2). ^{19}F NMR δ: −114.72 (∼t, CH_2C**F$_2$**, 2F); −126.68 (br, 2F); −123.87 (br, 2F); −123.27 (br, 2F); −122.01 to −122.69 (br, 6F); −81.43 (C**F$_3$**, t, 3F, $J = 9.9$ Hz). ^{13}C NMR δ: 37.2 (C1′); 20.2 (C2′); 28.9 (t, $J = 22.9$ Hz); 168.4 (C1, C3); 132.2 (C3a, C7a); 123.6 (C4, C7); 134.3 (C5, C6). MS (*m/z*, I%, *M* − X): 607, 25, *M*; 588, 10, *M* − F; 188, 8, *M* − $(CF_2)_7CF_3$; 160, 100, *M* − $(CH_2)_2(CF_2)_7CF_3$. HRMS (*m/z*) calculated for $C_{19}H_{10}F_{17}NO_2$, $M^+ = 607.0440$, found: $M^+ = 607.0449$.

4.4. 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl amine (*4*)

Hydrazine hydrate (98%, 2.00 ml, 41.2 mmol) was added to a stirred solution of **9** (22.8 g, 37.6 mmol) in methanol (85 ml) and the mixture was refluxed for 1 h. This resulted in the formation of a voluminous crystalline precipitate. After addition of 6 N hydrochloric acid (85 ml), the mixture was refluxed for 1 h and filtered at room temperature. Then the filter cake was stirred with a mixture of 1 N NaOH (200 ml) and ether (200 ml) for 3 h to afford a clear solution of phthalylhydrazide in the water phase, and that of **4** in the ether layer. After the separation of the phases the aqueous solution was washed with more ether (2 × 100 ml), then the combined organic phase was dried (Na_2SO_4) and evaporated to yield 13.8 g (77%) colorless liquid (GC: +98%), with bp 140–41 °C/100 mmHg and spectral data agreeable to that reported earlier [4,5]. ^{1}H NMR δ: 2.80 (t, 2H, $J = 6.9$ Hz, CH_2C**H$_2$**NH_2); 2.15 (tt, 2H, $J = 18.9$, 6.9 Hz, $C_8F_{17}C$**H$_2$**); 1.74 (qi, 2H, $J = 6.9$ Hz, C**H$_2$**CH_2NH_2); 1.22 (s, br, 2H, N**H$_2$**). ^{13}C NMR δ: 41.6 (C1); 24.5 (t, $J = 3.2$ Hz, C2); 28.7 (t, $J = 22.5$ Hz, C3). ^{19}F NMR δ: −81.64 (br t, 3F, $J = 9.9$ Hz, C**F$_3$**); −114.87 (∼t, 2F, $J = 13.8$ Hz, CH_2C**F$_2$**); −126.87 (br, 2F); −124.15 (br, 2F); −123.41 (br, 2F); −122.56 (br, 4F); −122.40 (br, 2F). HRMS (*m/z*) calculated for $C_{11}H_7F_{17}N$, $[M-H]^+ = 476.0307$, found: $[M-H]^+ = 476.0302$.

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