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Synthesis of aminophenyl and methoxyphenyl perfluoroalkyl ketones

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Abstract

The title compounds are obtained by direct hydrolysis of the corresponding 2/4-perfluoroalkyl-substituted anilines and anisoles by the system AcOH/HBr/H_2O/Al_2O_3. A two-step preparation of 2/4-perfluoroacylanilines involves the treatment of the 2/4-perfluoroalkylaniline with sodium ethoxide followed by hydrolysis of the resultant diethyl acetal with hydriodic acid.

Keywords: Perfluoroalkyl anilines; Perfluoroalkyl anisoles; Perfluoroalkyl acetals; Hydrolysis

1. Introduction

Aryl perfluoroalkyl ketones [1] are important substrates for the synthesis of substituted pyrazoles [2], pyrimidines [2], and quinolines [3] that exhibit a range of biological activity; however, the available synthetic routes to the 2-substituted aryl ketones are limited and inefficient. In particular, there are only two reports on the preparation of 2-perfluoroacylanilines, namely (i) acid catalyzed hydrolysis of acetal **3a** (Scheme 1) to give ketone **4a** in 30–35% yields, as reported by us recently [3], and (ii) a prolonged treatment (several days) of a 2-perfluoroalkylaniline with acid to give the 2-perfluoroacylaniline in a 20% yield [4]. Furthermore, the corresponding 2-perfluoroacylanisoles are an unknown class of compounds. It has been reported that direct perfluoroacylation of *N,N*-dimethylaniline gives an *N,N*-dimethyl-4-perfluoroacylaniline regioselectively but is inefficient [5]. Interestingly, the same product is obtained in high yield by simple treatment of an *N,N*-dimethyl-4-perfluoroalkylaniline with wet silica gel [6]. Unfortunately, *N,N*-dimethyl-2-perfluoroalkylanilines, 2-perfluoroalkylanilines, and 2- and 4-perfluoroalkylanisoles are stable to silica gel even under elevated temperatures. In this paper we report practical synthetic routes to 2-perfluoroacyl-substituted anilines and anisoles. The methods are also suitable for the synthesis of 4-perfluoroacyl isomers. Our studies were encouraged by the ready availability of the starting materials, namely perfluoroalkyl-substituted anilines and anisoles [6–10]. In order to compare directly the several approaches studied, the optimized procedures are illustrated for preparation of heptafluorobutanoyl derivatives **4** and **8**. Also, for the sake of clarity of presentation, the isomeric compounds are distinguished by the suffixes **a** and **b** for the *ortho* and *para* isomers, respectively.

2. Results and discussion

The high hydrolytic stability and inefficient hydrolysis of perfluoroalkyl-substituted acetals are well known [11]. Nevertheless, our initial attempts were focused on finding suitable conditions for hydrolysis of acetals **3a,b** (Schemes 1 and 2) because these compounds are produced in an almost quantitative yield by the reaction of **1a,b** with sodium ethoxide [12]. After numerous experiments with a variety of solvents and acids we found that **3a,b** are hydrolyzed efficiently to **4a,b** in acetic acid in the presence of iodine-free hydriodic acid (Method A). Under optimized conditions the GC yields (obtained with biphenyl as an internal standard, added to hydrolyzed, cold mixtures) were greater than 85%. The remaining balance of material consisted of a number of minor products. After isolation and purification, the yields of ketones **4a,b** were in the range of 74–75%. This method requires high purity hydriodic acid. For example, both the GC and isolated yields of the ketones decreased by 25% for reactions conducted with yellow samples of acid that contained iodine.

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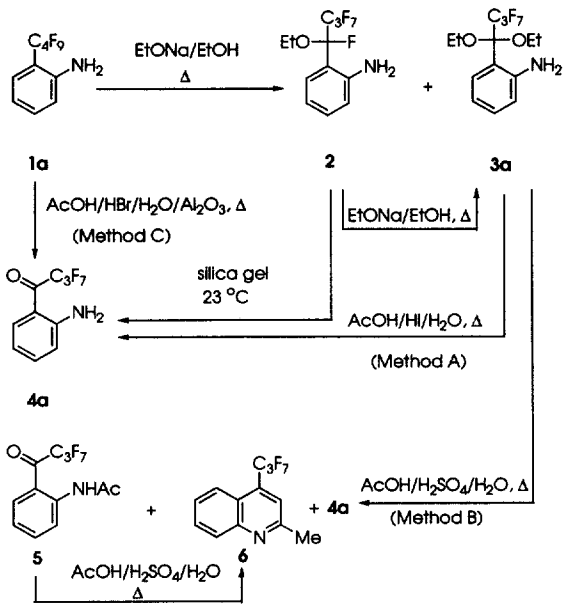
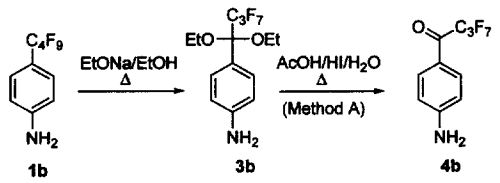


Scheme 1.



Scheme 2.

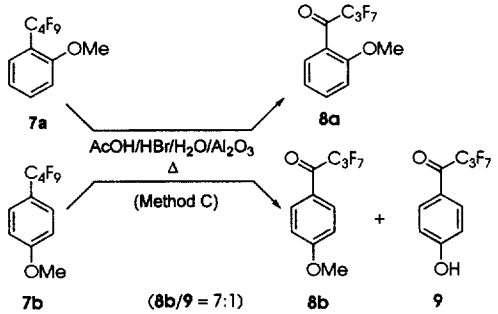
Subsequent study revealed that sulfuric acid may be substituted for hydriodic acid in the catalyzed hydrolysis of **3a** to **4a** although the yield (52%) is modest. Nevertheless, the method (Scheme 1, Method B) may be recommended for its simplicity and high reproducibility. Two additional products were isolated, quinoline **6** and acetamide **5** which is a precursor to **6**. Following isolation, compound **5** was cyclized to quinoline **6** under conditions of the hydrolysis reaction. Also, products **5** [13] and **6** [14] were found to be identical with the respective samples obtained by independent methods.

Since the treatment of **1a,b** with EtONa yields **3a,b**, we have also attempted direct hydrolysis of **1a,b** in the presence of hydroxide ion. All attempts, including phase-transfer conditions, failed to produce **4a,b**.

A third procedure (Method C) constitutes a one-step direct hydrolysis of perfluorobutyl-substituted anilines and anisoles **1** to the corresponding ketones **4** by the system AcOH/HBr/H_2O/Al_2O_3 and is related to the report [6] discussed above. This method was developed following our observation that the intermediate compound **2**, from the reaction of **1a** with sodium ethoxide, is quite unstable in the presence of silica gel. Fluoro ether **2** was separated from a mixture with acetal **3a** by using flash chromatography on silica gel but any separation attempts requiring more than 30 min were not successful. Finally, stirring an analytically pure sample of compound **2** with a slurry of silica gel in pentanes for 12 h resulted in complete hydrolysis to ketone **4a**. Accordingly, it was reasoned that the previously reported acid-mediated hydrolysis of perfluoroalkylanilines to perfluoroacylanilines [4] should be facilitated by silica gel [6]. Indeed, while in our hands it took 14 days for substrate **1a** to be consumed under the reported conditions (AcOH/HBr/H_2O, Δ), only 5 days were required in the presence of silica gel under otherwise similar conditions. The isolated yield of ketone **4a** was increased from 40% in the absence of silica gel to 58% in the presence. Subsequent experiments were conducted in the presence of aluminum derivatives since aluminum exhibits a greater affinity toward fluorine than silicon [15]. Thus, both aluminum sulfate (40 equiv) and aluminum acetate (40 equiv) mediated hydrolysis reactions of **1a** (1 equiv) in the presence of HBr were completed in less than 3 days furnishing ketone **4a** in isolated yields of 56–61%. The yield of **4a** was lower for the hydrolysis of **1a** conducted in the presence of HCl, HI or H_2SO_4 instead of HBr. The best results, however, were obtained with aluminum oxide as the additive to a solution of **1a** in AcOH/HBr. Under optimized conditions (see Section 3) compound **1a** was consumed after 18 h and ketone **4a** was obtained in an isolated yield of 64%. The optimization was conducted by adding increasing amounts of Al_2O_3 to the standard solutions of **1a** in AcOH/HBr. The first incremental amounts of Al_2O_3 reacted completely with the acidic medium providing a homogeneous medium with a continuous decrease in reaction time and increase in the yield of **4a** as the amount of Al_2O_3 increased. Interestingly, these features continued to be observed even after the mixture become heterogeneous, and under the optimized conditions the reaction was completed in the presence of a large amount of Al_2O_3 that remained suspended. This result suggests that, at least in part, the aluminum mediated hydrolysis is heterogeneous in nature.

Nonafluorobutylanisoles **7a,b** are also hydrolyzed to the respective ketones **8a,b** (Scheme 3). The decreased acidity of the medium, due to the reaction of acid with Al_2O_3, has an added benefit in that the formation of **8a** from **7a** is not accompanied by hydrolysis of the methoxy function, and only a small amount of hydroxyphenyl ketone **9** is formed by the hydrolysis of **7b**. This is in a sharp contrast to the reactions conducted in the absence of Al_2O_3 in which hydroxyphenyl ketones are the only products [4].

Attempts to hydrolyze *meta* isomers of **1** or **7**, *ortho*-nonafluorobutyltoluene and its *para* isomer were all unsuccess-



Scheme 3.

ful. It appears that the mechanistic pathway from **1a,b** and **7a,b** to the respective ketones **4a,b** and **8a,b** involves the intermediacy of a benzylic cation. The generation of this cation is facilitated by interaction of the benzylic fluorine atoms with silicon or alumina [15], with concomitant cation stabilization by an *ortho/para*-amino or -methoxy substituent.

In summary, we have described two synthetic approaches to ketones **4,8** from readily available substrates **1,7**. The two-step method requires the preparation of acetals **3** and, as such, is limited to the synthesis of 2/4-aminophenyl perfluoroalkyl ketones. Direct hydrolysis of **1,7** by the system AcOH/HBr/H_2O/Al_2O_3 provides a facile entry to all respective ketones **4,8**.

3. Experimental details

3.1. General data

Melting points (Pyrex capillary) are not corrected. ^1H NMR (300 MHz) and ^{19}F NMR (282 MHz) were recorded in $CDCl_3$ solutions with TMS and C_6F_6 as the respective internal standards. All resonances for CF_2 and CF_3 groups in the ^{19}F NMR spectra of **1**, **3–5**, **7** and **8** are broad singlets or narrow multiplets due to small values of coupling constants ($J_{F-F}<12$ Hz). Crude mixtures were analyzed, and mass spectra of pure components were obtained on a GC-MS instrument equipped with an on-column injector, a poly(dimethylsiloxane)-coated capillary column, and a mass selective detector operating at 70 eV. The purity of compounds reported below was analyzed by GC and found to be greater than 96% in all cases. Also, all samples were not contaminated by non-volatile impurities because no residue was observed following evaporation under reduced pressure.

3.2. Synthesis of compounds 1 and 7

2-(Nonafluorobutyl)aniline (**1a**) and 4-(nonafluorobutyl)aniline (**1b**) were prepared by the reaction of 2-iodoaniline and 4-iodoaniline, respectively, with nonafluorobutyl iodide in the presence of copper bronze by using a general procedure [7]. New anisole derivatives **7a,b** were synthesized in a similar manner [7] starting with the respective iodoanisoles. All compounds **1,7** were purified by distillation on a Kugelrohr (90–100°C/1.5 mm Hg).

2-(Nonafluorobutyl)anisole (**7a**): yield 75%; an oil; ^1H NMR δ 3.87 (s, 3H), 7.04 (d, $J=8$ Hz, 1H), 7.06 (t, $J=8$ Hz, 1H), 7.52 (t, $J=8$ Hz, 1H), 7.53 (d, $J=8$ Hz, 1H); ^{19}F NMR δ 36.2 (2F), 40.2 (2F), 54.5 (2F), 81.2 (3F); MS *m/z* 157 (80), 326 (100, M^+); HRMS exact mass calc. for $C_{11}H_7F_9O$ 326.0353, found 326.0357.

4-(Nonafluorobutyl)anisole (**7b**): yield 77%; an oil; ^1H NMR δ 3.87 (s, 3H), 7.00 (d, $J=9$ Hz, 2H), 7.53 (d, $J=8$ Hz, 2H); ^{19}F NMR δ 36.5 (2F), 39.2 (2F), 52.2 (2F), 80.9 (3F); MS *m/z* 157 (100), 307 (20), 326 (50, M^+); HRMS exact mass calc. for $C_{11}H_7F_9O$ 326.0353, found 326.0349.

3.3. Reactions of compounds 1 with sodium ethoxide

A solution of sodium ethoxide prepared from sodium (0.23 g, 10 mmol) and absolute ethanol (15 ml) was treated with **1a** (0.62 g, 2 mmol) and the mixture was heated to 60°C under a nitrogen atmosphere. A GC analysis showed the absence of **1a** and the presence of **2** and **3a** (1:1) after 12 h of heating. The optimized preparation of **3a** or **3b** required heating of the respective mixture (containing **1a** or **1b**, 2 mmol) under reflux for 24 h. The mixture was cooled to 23°C, treated with water (30 ml) and then extracted with ether (4×25 ml). The extract was dried over $MgSO_4$ and concentrated. Fluoro ether **2** was separated from acetal **3a** by silica gel chromatography on a chromatotron eluting with pentanes (separation time < 30 min). Acetals **3a** and **3b** were distilled on a Kugelrohr (160–180°C/15 mm Hg).

1-(2-Aminophenyl)-1-ethoxyoctafluorobutane (**2**): yield 45%; an oil; ^1H NMR δ 1.24 (t, $J=7$ Hz, 3H), 3.66 (m, 1H), 3.75 (m, 1H), 4.25 (br s, 2H, exchangeable with D_2O), 6.58 (d, $J=8$ Hz, 1H), 6.68 (t, $J=8$ Hz, 1H), 7.15 (t, $J=8$ Hz, 1H), 7.26 (d, $J=8$ Hz, 1H); ^{19}F NMR δ 36.4 (dd, $J_{gem}=290$ Hz, $J_{vic}=17$ Hz, 1F), 38.0 (dd, $J_{gem}=290$ Hz, $J_{vic}=10$ Hz, 1F), 40.0 (br s, 2F), 41.4 (br s, 1F), 81.0 (m, 3F); MS *m/z* 120 (100), 337 (20, M^+); HRMS exact mass calc. for $C_{12}H_{11}F_8NO$ 337.0713, found 337.0725.

1-(2-Aminophenyl)-1,1-diethoxyheptafluorobutane (**3a**): yield 98%; an oil; ^1H NMR δ 1.33 (t, $J=7$ Hz, 6H), 3.74 (m, 4H), 4.56 (br s, 2H, exchangeable with D_2O), 6.65 (d, $J=8$ Hz, 1H), 6.72 (t, $J=8$ Hz, 1H), 7.16 (t, $J=8$ Hz, 1H), 7.44 (d, $J=8$ Hz, 1H); ^{19}F NMR δ 37.1 (2F), 45.8 (2F), 81.2 (3F); MS *m/z* 120 (100), 363 (10, M^+); HRMS exact mass calc. for $C_{14}H_{16}F_7NO_2$ 363.1069, found 363.1056.

1-(4-Aminophenyl)-1,1-diethoxyheptafluorobutane (**3b**): yield 95%; mp 45–46°C (from *n*-pentane); ^1H NMR δ 1.25 (t, $J=7$ Hz, 6H), 3.60 (m, 4H), 3.73 (br s, 2H, exchangeable with D_2O), 6.64 (d, $J=9$ Hz, 2H), 7.37 (d, $J=9$ Hz, 2H); ^{19}F NMR δ 37.6 (2F), 44.3 (2F), 81.0 (3F); MS *m/z* 194 (100), 363 (10, M^+); HRMS exact mass calcd for $C_{14}H_{16}F_7NO_2$ 363.1069, found 363.1073. Analysis: Calc. for $C_{14}H_{16}F_7NO_2$: C, 46.29; H, 4.44; N, 3.86. Found: C, 46.45; H, 4.29; N, 3.72.

3.4. Synthesis of ketones 4 and 8

3.4.1. Method A

A solution composed of acetal **3a** or **3b** (0.36 g, 1 mmol), glacial acetic acid (20 ml), and hydriodic acid (57%, 1 ml, a colorless solution) was heated under reflux under a nitrogen atmosphere for 4 h. The mixture was cooled, poured onto ice water (100 ml), stirred, treated slowly with solid Na_2CO_3 (20 g), and the alkaline mixture was extracted with ether (5×30 ml). The extract was washed successfully with saturated solutions of $Na_2S_2O_3$ and NaCl, dried over $MgSO_4$,

and then concentrated. The crude ketone **4a** or **4b** was purified by chromatography on silica gel eluting with pentanes/CH_2Cl_2 (4:1).

3.4.2. Method B

A solution composed of acetal **3a** (0.36 g, 1 mmol), glacial acetic acid (20 ml), and aqueous sulfuric acid (15%, 6 ml) was heated under reflux for 8 h and then worked-up as described above. Chromatography gave, in order of elution, **6**, **4a**, and **5**.

3.4.3. Method C

A mixture of **1a,b** or **7a,b** (1 mmol), glacial acetic acid (15 ml), hydrobromic acid (48%, 5 ml), and aluminum oxide (5 g, chromatography grade) was heated under reflux under a nitrogen atmosphere until a GC analysis showed the absence of **1** or **7**: **4a** from **1a**, 18 h; **4b** from **1b**, 22 h; **8a** from **7a**, 16 days; **8b** + **9** from **7b**, 20 h. Workup and chromatography were conducted as described above.

1-(2-Aminophenyl)heptafluorobutan-1-one (**4a**): yield 75% by method A, 52% by method B, and 64% by method C; an oil; ^{1}H NMR δ 6.46 (br s, 2H, exchangeable with D_2O), 6.68 (t, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 1H), 7.37 (t, J = 8 Hz, 1H), 7.82 (d, J = 8 Hz, 1H); ^{19}F NMR δ 36.7 (2F), 50.9 (2F), 81.8 (3F); MS *m/z* 120 (100), 289 (30, M^+); HRMS exact mass calc. for $C_{10}H_6F_7NO$ 289.0338, found 289.0328.

1-(4-Aminophenyl)heptafluorobutan-1-one (**4b**): yield 74% by method A and 60% by method C; mp 78–79°C (from pentanes); ^{1}H NMR δ 4.41 (br s, 2H, exchangeable with D_2O), 6.67 (d, J = 8 Hz, 2H), 7.94 (d, J = 8 Hz, 2H); ^{19}F NMR δ 36.3 (2F), 48.8 (2F), 81.7 (3F); MS *m/z* 120 (100), 289 (20, M^+). Analysis: Calc. for $C_{10}H_6F_7NO$: C, 41.54; H, 2.09; N, 4.84. Found: C, 41.66; H, 2.03; N, 4.74.

Heptafluoro-1-(2-methoxyphenyl)butan-1-one (**8a**): yield 43% by method C; an oil; ^{1}H NMR δ 3.88 (s, 3H), 7.01 (d, J = 8 Hz, 1H), 7.04 (t, J = 8 Hz, 1H), 7.48 (d, J = 8 Hz, 1H), 7.55 (t, J = 8 Hz, 1H); ^{19}F NMR δ 36.9 (2F), 45.8 (2F), 81.3 (3F); MS *m/z* 92 (100), 304 (80, M^+); HRMS exact mass calc. for $C_{11}H_7F_7O_2$ 304.0334, found 304.0334.

Heptafluoro-1-(4-methoxyphenyl)butan-1-one (**8b**): yield 65% by method C; an oil; ^{1}H NMR δ 3.91 (s, 3H), 6.99 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H); ^{19}F NMR δ 36.5 (2F), 48.8 (2F), 81.8 (3F); MS *m/z* 135 (100), 304 (10, M^+); HRMS exact mass calc. for $C_{11}H_7F_7O_2$ 304.0334, found 304.0322.

Heptafluoro-1-(4-hydroxyphenyl)butan-1-one (**9**): yield 9%, a by-product from method C; mp 62–64°C (from pentanes); ^{1}H NMR δ 5.87 (br s, 1H, exchangeable with D_2O), 6.95 (d, J = 9 Hz, 2H), 8.05 (d, J = 9 Hz, 2H); ^{19}F NMR δ 36.3 (2F), 48.5 (2F), 81.6 (3F); MS *m/z* 121 (100), 290 (10, M^+). Analysis: Calc. for $C_{10}H_5F_7O_2$: C, 41.40; H, 1.74. Found: C, 41.80; H, 1.76.

1-(2-Acetamidophenyl)heptafluorobutan-1-one (**5**): yield 20%, a by-product from method B; an oil; ^{1}H NMR δ 2.27 (s, 3H), 7.18 (t, J = 8 Hz, 1H), 7.70 (t, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 8.80 (d, J = 8 Hz, 1H), 10.80 (br s, 1H, exchangeable with D_2O); ^{19}F NMR δ 37.0 (2F), 51.7 (2F), 81.8 (3F); MS *m/z* 120 (100), 289 (40), 331 (20, M^+); HRMS exact mass calc. for $C_{12}H_8F_7NO_2$ 331.0443, found 331.0451. This compound was spectroscopically identical with the authentic sample of **5** obtained by acetylation of **4a** by using a general procedure [13].

4-Heptafluoropropyl-2-methylquinoline (**6**): yield 18%, a by-product from method B; an oil. This compound was spectroscopically identical with the authentic sample of **6** obtained by an independent method [14].

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