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Synthesis of 9-($C_{n-1}F_{2n-1}$)-substituted acridine by the reaction of 2-(C_nF_{2n+1})-substituted aniline with *ortho*-methyl-substituted aromatic Grignard reagent

Abstract: Treatment of 2-(perfluoroalkyl)aniline with 2-tolylmagnesium bromide or chloride or their substituted analogs yields an acridine containing a shorter perfluoroalkyl group at the 9 position and devoid of the methyl group of the Grignard substrate. Interestingly, no acridine is produced in an attempted reaction with aryl magnesium bromide without the ortho methyl group. With 2-fluoro-6-methylphenylmagnesium bromide the methyl group is eliminated and the fluorine is retained in the acridine product. Results of the mechanistic studies strongly suggest that loss of the methyl group occurs as methanol during air oxidation and hydrolysis of the intermediate products during aqueous workup.

Keywords: acridines; Grignard reagents; 2-(trifluoromethyl)aniline.

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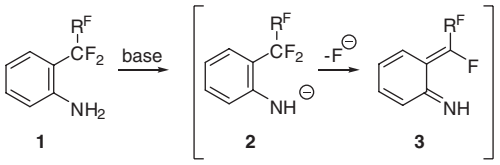
Introduction

The chemistry of aza-*ortho*-xylylene (**3**, R^F = F, Scheme 1) has been of interest both from a theoretical point of view and as an important tool in heterocyclic synthesis. Although the intermediate product **3** can be generated by using many approaches, the anionic activation of the trifluoromethyl group in **1** (R^F = F) to give anion **2** has emerged as the most practical way.

This synthetic chemistry has been reviewed extensively by us [1–4], our former student [5], and others [6, 7]. The chemistry of ionically activated higher homologs **1** ($R^F = C_nF_{2n+1}$, n ≥ 1) has been explored to a much smaller extent [8, 9]. 2-(Perfluoroalkyl)anilines **1** are readily available by a coupling reaction of 2-iodoaniline with a perfluoroalkyl bromide or iodide in the presence of copper bronze [10, 11] or by reductive perfluoroalkylation of aniline with the perfluoroalkyl halide in the presence of Zn and SO_2 [12, 13]. 2-(Trifluoromethyl)aniline is a widely available commercial product. Very recently, we have reported an unusual synthesis of 9-arylacridines by the reaction of **1** (R^F = F) with aromatic Grignard reagents substituted with a methyl or ethyl group at position 2 [14]. This synthesis is unusual in that the alkyl group is eliminated during the reaction. In this report, we describe the reactions of **1** containing a longer perfluoroalkyl chain ($R^F = C_nF_{2n+1}$, n ≥ 1) with aromatic Grignard reagents that contain a methyl group at position 2 or two methyl groups at positions 2 and 6.

Results and discussion

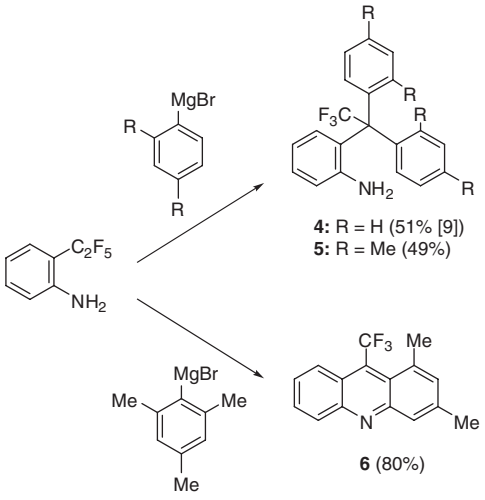
We have previously reported that the treatment of 2-(perfluoroethyl)aniline (Scheme 2) and 2-(perfluorobutyl) aniline (Scheme 3) with phenylmagnesium bromide furnished the respective molecular propellers **4** and **7** [9]. The treatment of the former aniline with 2,4-dimethylphenylmagnesium bromide yielded the analogous compound **5**. Molecular propellers exist in chiral helical conformations in which the helicity and the correlated rotation of the planar substituents (blades) are imposed by severe steric hindrance in the molecule. Depending on the nature of the aryl groups, a single molecule may exist in a large number of conformational isomers [9]. The three fluorine atoms of the CF_3 group in **4** and **5** are anisochronous at -25°C, and they give rise to a clearly defined AA′X absorption pattern in each ^{19}F NMR spectrum. In a similar way, the ^{19}F NMR spectrum of **7** exhibits AB absorption for each CF_2 moiety. The observed single AA′X pattern for CF^3 of **4**, the single AA′X pattern for CF_3 of **5**, and two AB absorptions for the CF_2CF_2 moiety of **7** are consistent with the presence of a single racemic pair in each case. This is an unusual



Scheme 1

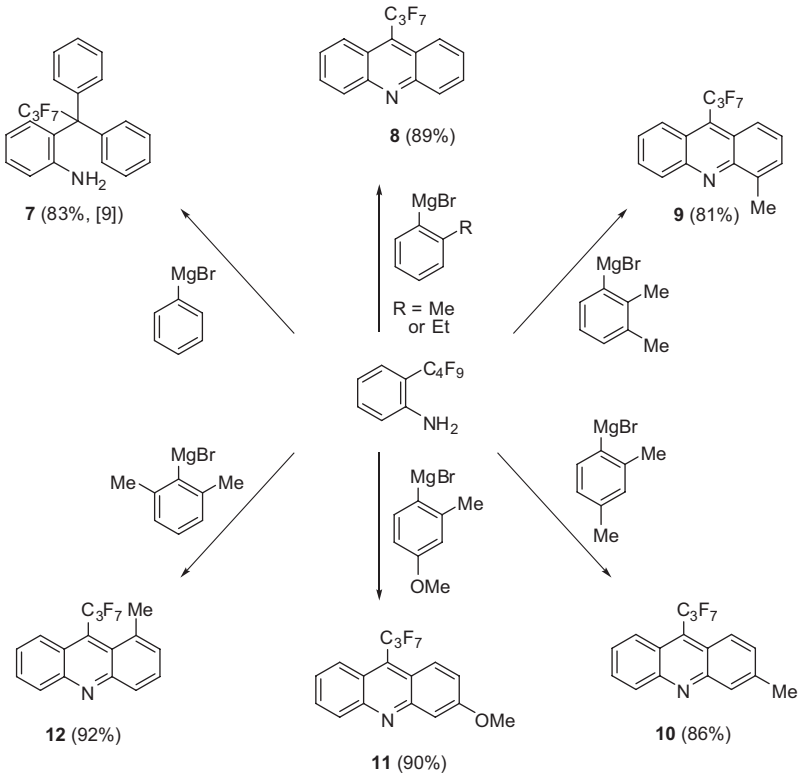
finding because two racemic pairs, due to two different orientations of the aminophenyl moiety in **4**, **5**, and **7**, and an additional set of orientations of the 2,4-dimethylphenyl groups in **5** relative to the perfluoroalkyl group in the molecular propeller (syn and anti) can be predicted [9]. The observed absorption patterns in the ^{19}F NMR spectra taken at low temperature give rise to a broad singlet with increasing temperature. The coalescence temperature is 21°C, 52°C, and 81°C for **4**, **5**, and **7**, respectively. It can be concluded that the order of steric hindrance in these molecules parallels the order of activation energy for racemization, as indicated by the coalescence temperatures.

Mechanistically, the formation of a molecular propeller requires addition of the Grignard reagent with the intermediate product **3** (Scheme 1) followed by elimination of fluoride from the adduct and the consecutive addition of a second molecule of the Grignard reagent with the resultant aryl-substituted analog of **3**. The treatment



Scheme 2

of 2-(perfluoroethyl)aniline with the more sterically hindered mesitylmagnesium bromide produced acridine **6** instead of the expected molecular propeller. It can clearly be seen that the molecule of **6** incorporates elements of the starting aniline and the Grignard reagent without one methyl group. The formation of acridines with the unusual pattern of the loss of the *ortho*-methyl group from the arylmagnesium bromide was also observed for the reactions

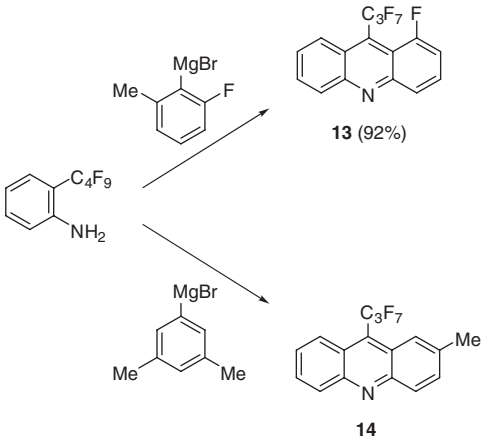


Scheme 3

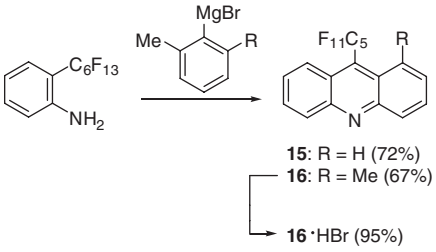
of 2-(perfluorobutyl)aniline (Scheme 3). Interestingly, the reactions with the arylmagnesium reagents substituted with the methyl group at the *ortho* position and containing no substituent at the second *ortho* position also resulted in elimination of the methyl group. This is clearly seen from Scheme 3 by the synthesis of acridines **8**–**11**. The reaction of 2-ethylphenylmagnesium bromide also yielded acridine **8** devoid of the ethyl group. As with the synthesis of acridine **6** discussed above, the treatment of 2-(perfluorobutyl) aniline with a 2,6-disubstituted phenylmagnesium bromide furnished acridine **12** devoid of the methyl group. To better understand this unusual reaction, 2-(perfluorobutyl) aniline was allowed to react with 2-fluoro-6-methylphenylmagnesium bromide (Scheme 4). Again, the methyl group was eliminated during this high-yield reaction to give fluorine substituted acridine **13**. The treatment of this aniline with 3,5-dimethylphenylmagnesium bromide (no substituents at the ortho positions) gave a complicated mixture of products, none of them major. GC-MS analysis of the crude mixture indicated the presence of <1% of a product with the molecular ion peak for the apparent acridine **14**.

As can be seen from Scheme 5, this novel acridine synthesis proceeds well with 2-(perfluorohexyl)aniline. As expected, the 9-(perfluoropentyl)acridines **15** and **16** are oils. Product **16** was transformed into a solid salt by treatment with hydrobromic acid and the salt was crystallized for purification.

Several syntheses reported above were also conducted with chloride analogs of the bromide Grignard reagents. In all cases, the reaction times and the yields were comparable. Isolation of the perfluoro-substituted products is considered as important information. These molecules are highly volatile and it would not be unusual to obtain low yields by concentrating solutions in relatively high-boiling solvents under reduced pressure. The use of pentanes and ether is strongly recommended. Another treatment against loss of product is to precipitate a hydrobromide salt from solution.



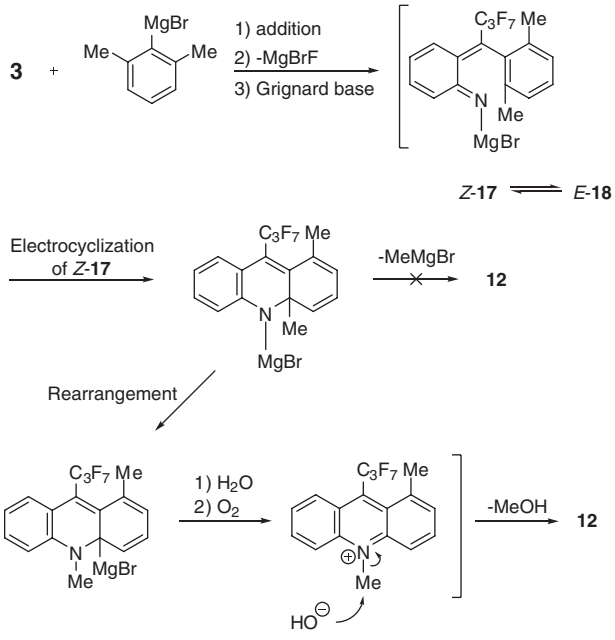
Scheme 4



Scheme 5

Conclusion and final remarks

This report describes the scope and limitations of a novel synthesis of 9-(perfluoroalkyl)acridines. We have conducted detailed mechanistic studies that are summarized in Scheme 6 and will be described in our forthcoming paper. An important observation is that the final acridine product is formed during workup following quenching of the mixture with water and exposure to air. The mechanistic report will address the generation of two isomers of the intermediate product **17**, their equilibration, and electrocyclization of the isomer *Z*-**17**.



Scheme 6

Experimental

General

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use, and all reactions were conducted under an atmosphere of nitrogen. Flasks were fitted with rubber septa and Teflon-coated magnetic stirring bars were used. 2-(Perfluoroalkyl) anilines were prepared by coupling 2-iodoaniline with perfluoroalkyl iodides in the presence of copper bronze as previously described [10, 11]. Grignard reagents were generated in THF by treatment of magnesium turnings with aryl bromide or chloride at 70°C and used immediately for the reactions with 2-(perfluoroalkyl)anilines. Crude reaction mixtures were analyzed and mass spectra of pure components were obtained on a Shimadzu GC instrument coupled with an electron impact mass spectrometer operating at 70 eV. The ^{1}H NMR spectra (300 MHz), ^{13}C NMR spectra (75 MHz), and ^{19}F NMR spectra (298 MHz, C_6F_6 as an internal standard) of free bases were taken at 23°C in $CDCl_3$ solution. The NMR spectra of hydrobromide salts were taken in DMSO-d_6. High resolution mass spectra (HRMS) were taken on a VG Analytical 70-SE spectrometer. The ^{13}C NMR spectra reported below do not contain signals for carbon atoms that are extensively coupled with the adjacent fluorine atoms.

Synthesis of molecular propellers 4, 5, 7 and acridines 6, 8–13, 15

A solution of Grignard reagent (5 mmol) in THF (5 mL) was stirred at -70°C under a nitrogen atmosphere and treated dropwise with a solution of 2-(perfluoroalkyl)aniline (1.5 mmol) in THF (5 mL). The resultant brown mixture was allowed to reach 23°C within 1 h and then stirred at 23°C until GC-MS analyses showed the absence of the starting aniline (2–24 h). The mixture was quenched with water (5 mL) and nitrogen in the flask was purged with air. After concentration on a rotary evaporator to half a volume, the residue was extracted with ether (3 × 20 mL) and the extract was dried over Na_2SO_4 and concentrated. The product was purified by radial chromatography on silica gel eluting with pentanes (**5**, **8**, **9**, **12**, **13**, **15**), pentanes/ether (10:1, **6**, **10**) and pentanes/ether (4:1, **11**).

2-(2,2,2-Trifluoro-1,1-diphenylethyl)aniline (4) This compound was obtained from 2-(perfluoroethyl)aniline and phenylmagnesium bromide; reaction time 1 h at 23°C; yield 51%; mp 92–93°C (from pentanes); ^{19}F NMR: δ 102.5 (AA′X pattern at -60°C, bs at the coalescence temperature of 21°C) [9].

2-[1,1-Bis-(2,4-dimethylphenyl)-2,2,2-trifluoroethyl]aniline (5) This compound was obtained from 2-(perfluoroethyl)aniline and 2,4-dimethylphenylmagnesium bromide; reaction time 2 h at 23°C; yield 49%; a brown oil; ^{1}H NMR: δ 2.12 (s, 6H), 2,34 (s, 6H), 3.51 (bs, exchangeable with D_2O, 2H), 6.54–7.26 (m, 10H); ^{19}F NMR: δ 112 (A,A′X pattern at -60°C, bs at the coalescence temperature of 52°C); MS: m/z 384 (100, M^+ +1); HRMS: Calcd for $C_{24}H_{24}NF_3$: m/z 383.1861. Found: m/z 383.1857.

1,3-Dimethyl-9-(trifluoromethyl)acridine (6) This compound was obtained from 2-(perfluoroethyl)aniline and mesitylmagnesium bromide; reaction time 12 h at 23°C; light yellow crystals; mp 101–102°C (from hexanes); ^{1}H NMR: δ 2.54 (d, J = 10 Hz, 3H), 2.70 (t, J = 3 Hz, 3H), 7.31 (d, J = 9 Hz, 1H), 7.57 (t, J = 7 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), 7.79 (m, 2H), 8.21 (t, J = 9 Hz, 1H), 8.31 (s, 1H); ^{19}F NMR: δ 113; ^{13}C NMR: δ 21.2, 24.6, 124.0, 124.4, 125.2, 125.3, 127.0, 127.4, 129.4, 130.0, 133.0, 135.3, 139.3, 148.0, 150.4; MS: m/z 260 (15, M+ -Me), 275 (100, M+); HRMS: Calcd for $C_{16}H_{12}F_3N$: m/z 275.0922. Found: m/z 275.0925. Anal. Calcd for $C_{16}H_{12}F_3N$: C, 69.81; H, 4.39; N, 5.09. Found: C, 69.88; H, 4.56; N, 5.03.

2-(2,2,3,3,4,4,4-Heptafluoro-1,1-diphenylbutyl)aniline (7) This compound was obtained from 2-(perfluorobutyl)aniline and phenylmagnesium bromide, reaction time 1 h at 23°C; yield 83%, mp 108–110°C (from hexanes) [9].

9-(Perfluoropropyl)acridine (8) This compound was obtained from 2-(perfluorobutyl)aniline and 2-tolylmagnesium bromide; reaction time 2 h at 23°C; light yellow needles; mp 90–91°C (from hexanes).

4-Methyl-9-(perfluoropropyl)acridine (9) This compound was obtained from 2-(perfluorobutyl)aniline and 2,3-dimethylphenylmagnesium bromide; reaction time 12 h at 23°C; an oil; yield 81%; ^{1}H NMR: δ 2.94 (s, 3H), 7.51 (dd, J = 10 Hz, J = 7 Hz, 1H), 7.61 (m, 2H), 7.77 (t, J = 7 Hz, 1H), 8.19 (d, J = 10 Hz, 1H), 8.33 (m, 2H); ^{19}F NMR: δ 38.3 (2F), 66.0 (2F), 82.0 (3F); MS: m/z 242 (100, M^+ -C_2F_5), 361 (60, M^+); HRMS: Calcd for $C_{17}H_{10}F_7N$: m/z 361.0702. Found: m/z 361.0728.

3-Methyl-9-(perfluoropropyl)acridine (10) This compound was obtained from 2-(perfluorobutyl)aniline and 2,4-dimethylphenylmagnesium bromide; reaction time 8 h at 23°C; a yellow oil; yield 81%; MS: m/z 242 (100, M^+ -C_2F_5), 361 (30, M^+); HRMS: Calcd for $C_{17}H_{10}F_7N$: m/z 361.0702. Found: m/z 361.0717.

3-Methoxy-9-(perfluoropropyl)acridine (11) This compound was obtained from 2-(perfluorobutyl)aniline and 4-methoxy-3-methylphenylmagnesium bromide; reaction time 12 h at 23°C; a light yellow oil; yield 90%; ^{1}H NMR: δ 4.03 (s, 3H), 7.33 (dd, J = 9 Hz, J = 3 Hz, 1H), 7.51 (d, J = 3 Hz, 1H), 7.58 (t, J = 7 Hz, 1H), 7.79 (t, J = 7 Hz, 1H), 8.23 (m, 2H), 8.32 (d, J = 9 Hz, 1H); ^{19}F NMR: δ 38.1 (2F), 65.6 (2F), 81.3 (3F); ^{13}C NMR: δ 55.7, 106.0, 123.6, 126.2, 126.9, 129.8, 130.0, 149.1, 150.9, 160.4; MS: m/z 258 (100, M^+ -C_2F_7), 377 (80, M^+); HRMS: Calcd for $C_{17}H_{10}F_7NO$: m/z 377.0651. Found: m/z 377.0635.

1-Methyl-9-(perfluoropropyl)acridine (12) This compound was obtained from 2-(perfluorobutyl)aniline and 2,6-dimethylphenylmagnesium bromide; reaction time 8 h at 23°C; a yellow oil; yield 92%; ^{1}H NMR: δ 2.70 (t, J = 5 Hz, 3H), 7.52 (d, J = 7 Hz, 1H), 7.64 (m, 2H), 7.78 (t, J = 7 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 8.25 (d, J = 9 Hz, 1H), 8.37 (d, J = 9 Hz, 1H); ^{19}F NMR: δ 46.7 (2F), 80.8 (2F), 82.0 (3F); ^{13}C NMR: δ 24.8, 125.2, 127.5, 128.6, 129.1, 129.5, 130.1, 132.1, 133.6, 147.9, 149.9; MS: m/z 242 (100, M^+ -C_2F_5), 361 (45, M^+); HRMS: Calcd m/z for $C_{17}H_{10}F_7N$: m/z 361.0702. Found: m/z 361.0730.

1-Fluoro-9-(perfluoropropyl)acridine (13) This compound was obtained from 2-(perfluorobutyl)aniline and 2-fluoro-6-methylphenylmagnesium bromide; reaction time 24 h at 23°C; a yellow oil; yield 92%; ^{1}H NMR: δ 7.64 (m, 2H), 7.80 (t, J = 8 Hz, 1H), 7.97 (d, J = 12 Hz, 1H), 8.30 (m, 3H); ^{19}F NMR: δ 38.0 (1F), 54.1 (2F), 64.4 (2F), 81.3 (3F); MS: m/z 246 (100, M^+ -C_2F_5), 365 (25, M^+); HRMS: Calcd for $C_{16}H_7F_8N$: m/z 365.0451. Found: m/z 365.0470.

9-(perfluoropentyl)acridine (15) This compound was obtained from 2-(perfluorobutyl)aniline and 2-tolylmagnesium bromide; reaction time 6 h at 23°C; light yellow oil; yield 72%; ^{1}H NMR: δ 7.66 (t, *J* = 8 Hz, 2H), 7.83 (t, *J* = 8 Hz, 2H), 8.23 (d, *J* = 9 Hz, 2H), 8.32 (d, *J* = 9 Hz, 2H); ^{19}F NMR: δ 35.8 (2F), 39.5 (2F), 42.5 (2F), 66.3 (2F), 81.0 (3F); MS: m/z 228 (100, M^+-C_4H_9), 447 (25, M^+); HRMS: Calcd for $C_{18}H_8F_{11}N$: m/z 448.0560. Found: m/z 448.0534.

1-Methyl-9-(perfluoropentyl)acridine (16) This compound was obtained from 2-(perfluorobutyl)aniline and 2,6-dimethylphenylmagnesium bromide; reaction time 12 h at 23°C; a yellow oil; yield 67%; ^{1}H NMR: δ 2.75 (t, *J* = 5 Hz, 3H), 7.52 (d, *J* = 8 Hz, 1H), 7.64 (m, 2H), 7.78 (t, *J* = 8 Hz, 1H), 8.09 (d, *J* = 8 Hz, 1H), 8.25 (d, *J* = 9 Hz, 1H), 8.39 (d, *J* = 9 Hz, 1H); ^{19}F NMR: δ 36.0 (2F), 39.8 (2F), 50.0 (2F), 66.0 (2F), 81.3 (3F); ^{13}C NMR: δ 25.0, 125.3, 127.6, 129.2, 129.5, 130.2, 132.2, 132.3, 133.7, 148.0, 149.9; MS: m/z 242 (100, M^+-C_4F_9), 461 (45, M^+); HRMS: Calcd for $C_{19}H_{10}F_{11}N$: m/z 462.0716. Found: m/z 462.0709.

16·HBr This salt was obtained by treatment of a solution of **16** in ether with a mixture of hydrobromic acid (48%) and ether (1:10). The resultant precipitate was crystallized from ether: yellow crystals; mp 277–278°C. Anal. Calcd for $C_{19}H_{11}BrF_{11}N$: C, 49.47; H, 2.19; N, 3.04. Found: C, 49.61; H, 2.22; N, 2.82.

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