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Base-Mediated Reactions of *ortho*- and *para*-Perfluoroalkylanilines

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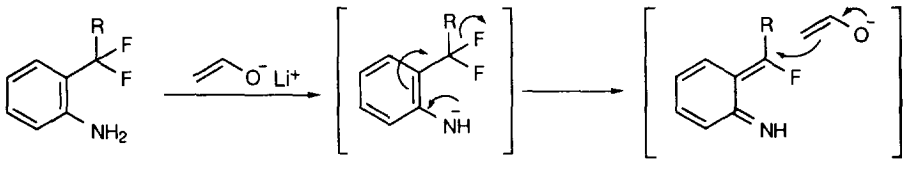
Abstract: The title chemistry involves regioselectively a benzylic position of the perfluoroalkyl group and provides an easy access to substituted quinolines and methanes. Copyright © 1996 Elsevier Science Ltd

An ionically activated trifluoromethyl group, such as in the anion derived from **1a** (Scheme 1), has recently emerged as a valuable synthon for various functionalities and heterocyclic compounds.[1] A facile one-pot synthesis of 4-fluoroquinoline (**4**) by the reaction of **1a** with lithium enolate of acetaldehyde is given in Scheme 1 for illustration.[2] Evidence has been accumulating that the imine-difluoromethide **3** (R = F) derived from **1a** by ionization followed by elimination of fluoride from the resultant ion is an intermediate product in this and similar transformations. The intermediary of analogs of **3** has been postulated in related syntheses.[3] The attractiveness of this novel chemistry as a synthetic tool is stressed by commercial availability of **1a**, its para isomer **1b**, and a large number of their substituted analogs.

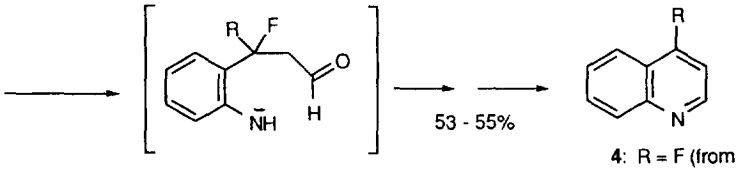
In this paper we report for the first time base-mediated chemistry of higher perfluoroalkyl-substituted anilines which are readily available by the Ullmann condensation of an iodoaniline with a perfluoroalkyl iodide.[4]

Scheme 1



1a: R = F
2a: R = C_3F_7

3



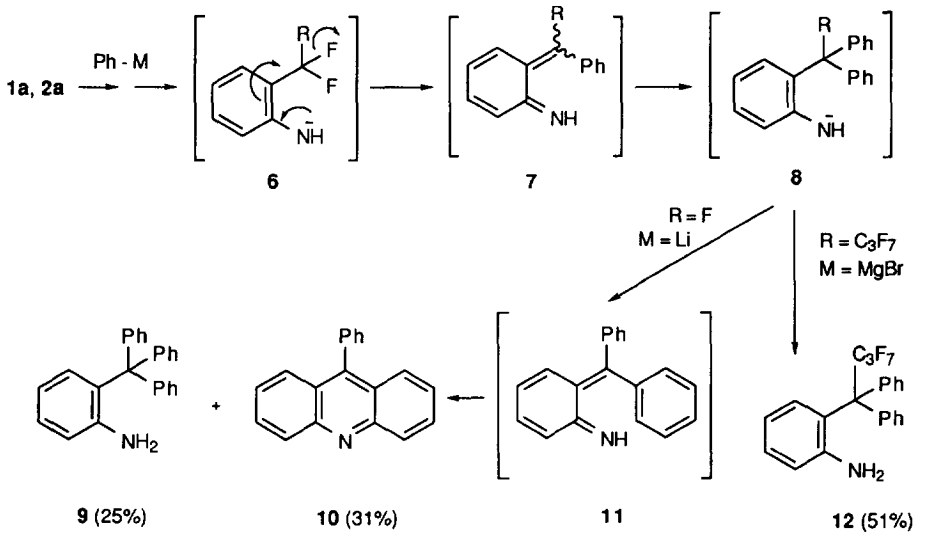
4: R = F (from **1a**)
5: R = C_3F_7 (from **2a**)

The described transformations are regioselective in that they involve the α-CF_2 moiety of the perfluoroalkyl group and provide a facile one-pot entry to several new classes of organofluorine compounds containing a $C_{n-1}F_{2n-1}$ group derived from the C_nF_{2n+1} substituent of the substrate. For the sake of clarity of presentation, studies with perfluorobutyl derivatives **2a** and **2b** are presented, and in several cases the results are compared to those of the base-induced chemistry of the respective trifluoromethyl analogs **1a** and **1b**. The examples selected are representative of a large number of previously unreported and novel transformations that have been accomplished in this laboratory.

The synthetic entry to 4-(perfluoroalkyl)quinolines is illustrated in Scheme 1 by a facile preparation of 4-(heptafluoropropyl)quinoline (**5**) upon treatment of *ortho*-(nonafluorobutyl)aniline (**2a**) with lithium enolate of acetaldehyde. Compound **5** was the only major, low molecular weight product in the crude mixture and was obtained in a 55% yield after flash chromatography.[5,6] The mechanistic pathway apparently involves addition of acetaldehyde enolate ion to the intermediate product **3** (R = C_3F_7) derived from **2a** as shown in Scheme 1.

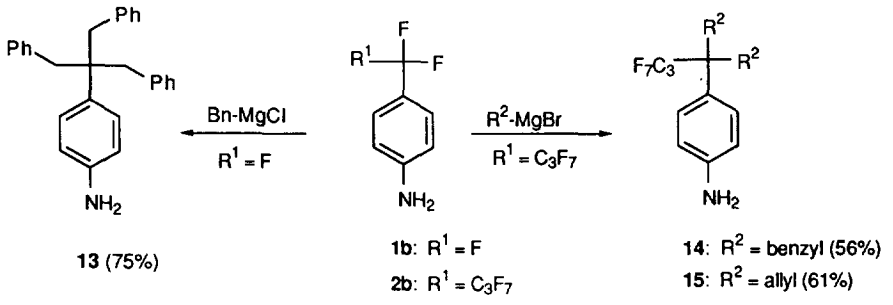
The reaction of **2a** with phenylmagnesium bromide yielded a perfluoropropyl-substituted triarylmethane **12**[5,6] (Scheme 2). The formation of **12** can be explained in terms of internal nucleophilic displacements of the two benzylic fluorines of the C_4F_9 group and a nucleophilic addition of the Grignard reagent to the respective intermediate products **3** and **7** (R = C_3F_7) after each displacement step. A similar treatment of **2a** with phenyllithium resulted in the formation of an intractable tar and many products, none of them major. Interestingly, the reaction of a trifluoromethyl analog **1a** with phenyllithium gave a mixture of a tetraarylmethane **9**[5,6] and 9-phenylacridine (**10**).[5,6] It can be suggested that acridine **10** is formed by electrocyclization of the intermediate imine-diphenylmethide **11** with the involvement of a formal C-C double bond of the phenyl group followed by oxidation of the resultant dihydroacridine during workup. Compound **9** is formed by the addition reaction of phenyllithiun with the same intermediate **11**.[7]

Scheme 2



Scheme 3 provides examples of the synthesis of tetrasubstituted methanes **13-15** by the reactions of para-(perfluoroalkyl)anilines **1b** and **2b** with Grignard reagents.[5,6] In a pattern consistent with the reactivity of **2a**, C_3F_7-substituted products **14, 15** were obtained from the aniline **2b**.

Scheme 3



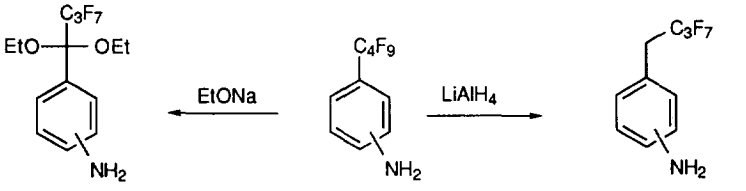
13 (75%)

1b: $R^1 = F$
2b: $R^1 = C_3F_7$

14: R^2 = benzyl (56%)
15: R^2 = allyl (61%)

An efficient preparation of ketals[8] is illustrated in Scheme 4 by the reaction of ethoxide ion with *ortho*- and *para*-(perfluorobutyl)anilines **2a** and **2b** yielding the respective diethoxy derivatives[6] **16a** and **16b**. In a related transformation, the treatment of **2a,b** with $LiAlH_4$ resulted in selective reduction at the benzylic position to give the respective products **17a,b**.[6,9] The suggested anionic nature of the $LiAlH_4$ reduction of **2** is consistent with the previous finding that these substrates are inert under conditions of a catalytic hydrogenation.[10] Also, in agreement with the general mechanism proposed, the *meta* isomer of **2** could not be reduced upon treatment with $LiAlH_4$. This *meta* isomer was also inert under conditions of other transformations described in this paper.

Scheme 4



16a (98%)
16b (95%)

2a, b

a: *ortho*
b: *para*

17a (69%)
17b (54%)

Acknowledgment. We thank NIH-NIAID (grant AI-27196) and the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

References and Notes

1. For reviews, see: a) Strekowski, L.; Kiselyov, A.S. *Trends Heterocycl. Chem.* **1993**, *3*, 73. b) Kiselyov, A.S.; Strekowski, L. *Org. Prep. Proc. Int.* **1996** (in press.)
2. Strekowski, L.; Kiselyov, A.S.; Hojjat, M. *J. Org. Chem.* 1994, *59*, 5886.
3. a) Kiselyov, A.S. *Tetrahedron Lett.* **1995**, *36*, 1383. b) Strekowski, L.; Patterson, S.E.; Janda, L.; Wydra, R.L.; Harden, D.B.; Lipowska, M.; Cegla, M.T. *J. Org. Chem.* **1992**, *57*, 196.
4. a) Yoshino, N.; Kitamura, M.; Seto, T.; Shibata, Y.; Abe, M.; Ogino, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2141. b) Chen, Q.-Y.; Chen, Y.-X.; Huang, W.-Y. *Acta Chim. Sinica* **1984**, *42*, 906.
5. **General Procedure for 5, 9, 10, 12-15.** A solution of 1 or **2** (1 mmol) in THF (20 mL) was treated dropwise with a solution of the corresponding organometallic reagent (10 mmol) at -78 °C and under a nitrogen atmosphere. The mixture was stirred at -78 °C for 30 min and then at 0 °C until TLC analysis showed the absence of 1 or **2** (10 min - 1 h). Addition of aqueous NaOH (10%, 2 mL) and then ether (20 mL) was followed by drying of the organic layer ($MgSO_4$), concentration, and silica gel chromatography with pentanes/ether (5:1) as an eluent.
6. All new compounds **5, 9, 12-17** gave molecular ion peaks in mass spectra and were fully characterized by elemental analysis or HRMS, ^{1}H-NMR, and ^{13}C-NMR. ^{19}F-NMR spectra were obtained for fluorine-containing products **5, 12, 14-17**. Compound **9** had mp 205-207 °C, compound **13** had mp 151-152 °C, and the remaining new compounds **5, 12, 14-17** were oils. The ^{1}H-NMR spectrum of compound **10** (mp 181-182 °C) was virtually identical with the spectrum of 9-phenylacridine obtained by an independent method: Lehmstedt, K.; Dostal, F. *Chem. Ber.* 1939, *72*, 804 (reported mp 183 °C).
7. An alternative S_N2' mechanism of cyclization of **8**, in which the amide anion would undergo intramolecular addition to position *ortho* of the phenyl group and fluoride ion would be eliminated, is less likely because amide bases exhibit relatively low nucleophilicity.
8. A solution of EtONa (prepared from 0.23 g of sodium, 10 mmol) and **2a** or **2b** (0.62 g, 2 mmol) in EtOH (10 mL) was heated under reflux and under a nitrogen atmosphere for 4 h. Standard workup was followed by Kugelrohr distillation (170 °C/10 mm Hg).
9. A suspension of $LiAlH_4$ (1.0 g, 26 mmol) in ether (25 mL) was treated dropwise with a solution of **2a** or **2b** (0.4 g, 1.3 mmol) in ether (2 mL) under a nitrogen atmosphere and the resultant mixture was heated under reflux for 18 h. Standard workup was followed by chromatography on silica gel with pentanes/ether (5:1) as an eluent.
10. Bernardin, J.; Pechmeze, J. *Ger. Offen.* DE 2606982, Aug. 26, 1976 (*Chem. Abstr. 85*:192333).

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