CHEMISTRY OF THE ANIONICALLY ACTIVATED PERFLUOROALKYL GROUP IN HETEROCYCLIC SYNTHESIS

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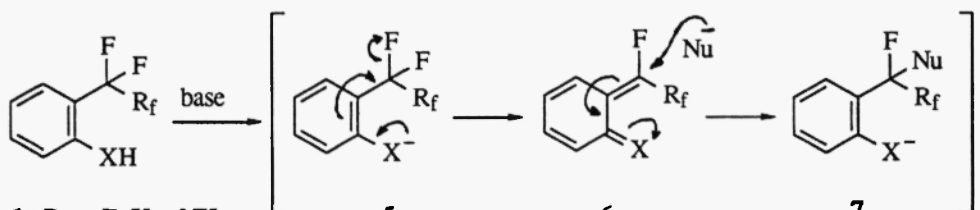
Abstract: One-pot reactions of 2-(perfluoroalkyl)anilines **1** and **2** with the corresponding heteroaryllithium reagents provide facile synthetic entries into heteroaryl-substituted methanes **9**, **11**, **13**, fused quinolines **10**, and quinolines **14-17**. In a similar fashion, 2-(trifluoromethyl)benzyl chloride (**3**) is a building block for the construction of fused tetracyclic systems of thiophene, furan, and *N*-methylpyrrole **18-20**. Potassium *tert*-butoxide-mediated self-condensation of [2-(trifluoromethyl)phenyl]acetonitrile (**4**) yields a substituted naphthalene **21**, the 2-amino-1-cyano functionality of which may serve as a building block for fused pyrimidines.

The high reactivity of *ortho*- and *para*-(perfluoroalkyl)anilines, such as **1**,**2**, and a high stability of their *meta* isomers under basic conditions are well understood (1). Briefly, as illustrated in Scheme 1, the anion **5** derived from **1** or **2** undergoes elimination of fluoride ion from a benzylic position, and then the resultant non-aromatic intermediate product **6** is aromatized by the addition reaction with a nucleophile to generate **7**. The subsequent steps depend on the nature of the nucleophilic species and may include an analogous elimination/addition pathway and/or cyclization with the involvement of the *ortho* amino group. Facile synthetic entries to diverse classes of heterocyclic, carbocyclic, and acyclic classes of compounds by using this mechanism-based approach have been developed (1-4). Yet, in this paper we report new applications of **1** and **2** in heterocyclic synthesis. We also describe a novel chemistry of 2-(trifluoromethy)benzyl chloride (**3**) and [2-(trifluoromethyl)phenyl]acetonitrile (**4**) under basic conditions (5).

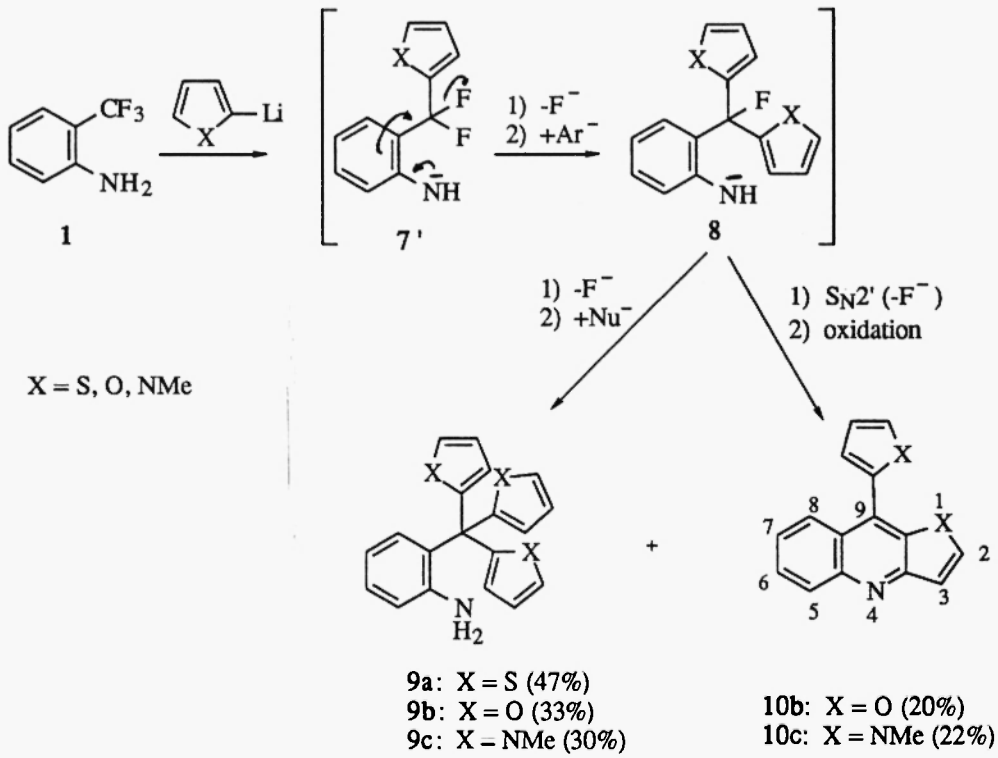
Scheme 1



1: $R_f = F$, X = NH
2: $R_f = C_3F_7$, X = NH
3: $R_f = F$, X = CHCl
4: $R_f = F$, X = CHCN

It should be noted that the preparations discussed below are all simple one-pot procedures. In a typical experiment, a solution of an organometallic reagent (5-10 mmol) in anhydrous THF (20 mL) is stirred under a nitrogen atmosphere at -60 °C and treated dropwise with a solution of **1-4** (1 mmol) in THF (1 mL). The resultant mixture is then stirred under the temperature and time conditions specified in the following text for each particular class of reaction and then quenched with water. Standard workup is followed by chromatography on silica gel eluting with hexanes/ether (from 9:1 to 4:1).

Scheme 2



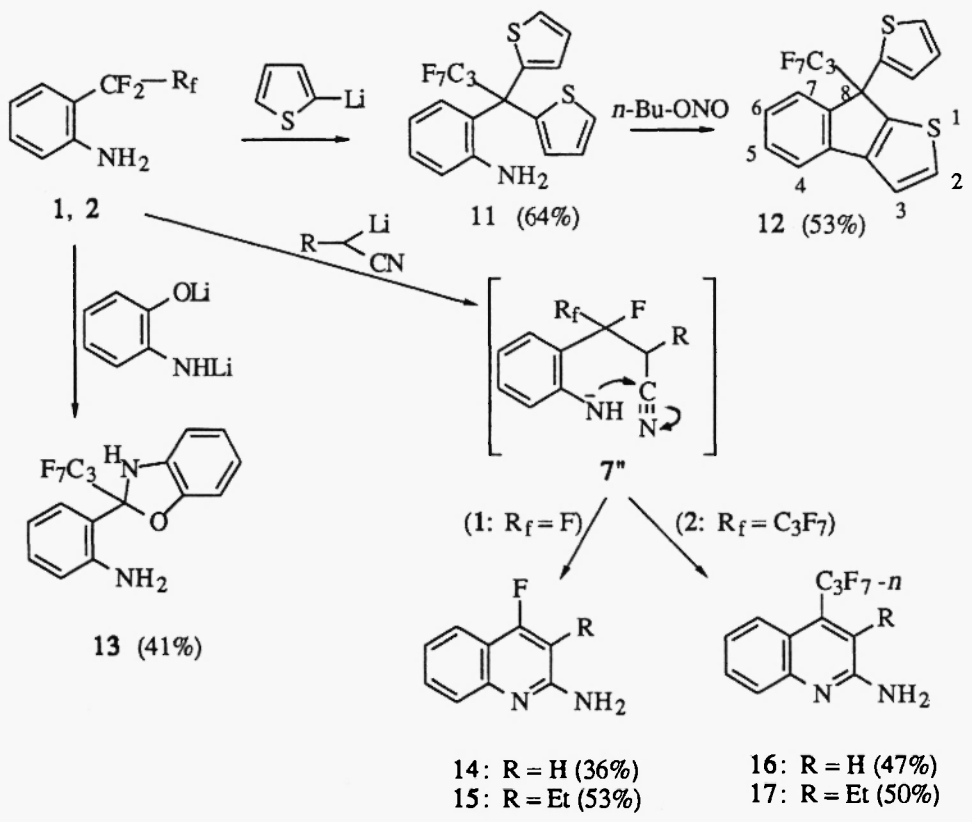
The reaction of **1** with 2-thienyllithium (6) (23 °C, 2 h) yielded a tetraarylmethane **9a** (Scheme 2). A similar treatment of **1** with 2-furyllithium or 1-methyl-2-pyrrolyllithium gave the respective mixture of **9** and a fused quinoline **10**. The formation of **9** can be explained in terms of three consecutive steps of fluoride ion elimination followed by heteroaryl anion addition to the resultant intermediate product after each elimination step. These reactions involve the benzene system, as already discussed. By contrast, the elimination of fluoride ion from **8** by an intramolecular S_N2' reaction with the involvement of a heteroaromatic ring leads to a fused quinoline **10**. The absence of the corresponding thieno[3,2-*b*]quinoline **10a** is consistent with a facile lithiation reaction of a thiophene system (6). Such lithiation would effectively hinder the intramolecular S_N2' reaction of **8**, and the elimination/addition pathway with the involvement of the benzene system would result in the formation of **9a**, as observed.

A related reaction of 2-thienyllithium with 2-(perfluorobutyi)aniline (2) is given in Scheme 3. The presence of a perfluoropropyl group in the product **11** is evident from its ^{19}F NMR spectrum ($CDCl_3/C_6F_6$) which gave a set of three narrow multiplets due to coupling of vicinal fluorine atoms (J_{vic} ~10 Hz): δ 44.6 (CF_2), 60.1 (CF_2), and 80.8 (CF_3). In order to obtain additional support for the proposed structure **11**, this compound (0.1 mmol) was cyclized by treatment with *n*-butyl nitrite (1.0 mmol) in DMF (0.3 mL, 65 °C, 2 h) and the resultant product **12** was fully characterized. In particular, the presence of an asymmetric center (C8) adjacent to the perfluoropropyl group in **12** resulted in a dramatically different pattern of coupling in the ^{19}F NMR spectrum in comparison to that of **11** [δ 39.8, AB, J = 285 Hz, CF_2; 54.3, AB, J = 282 Hz, CF_2; 80.7, CF_3]. The AB patterns for geminal fluorine atoms are fully consistent with the asymmetric environment in the molecule of **12**.

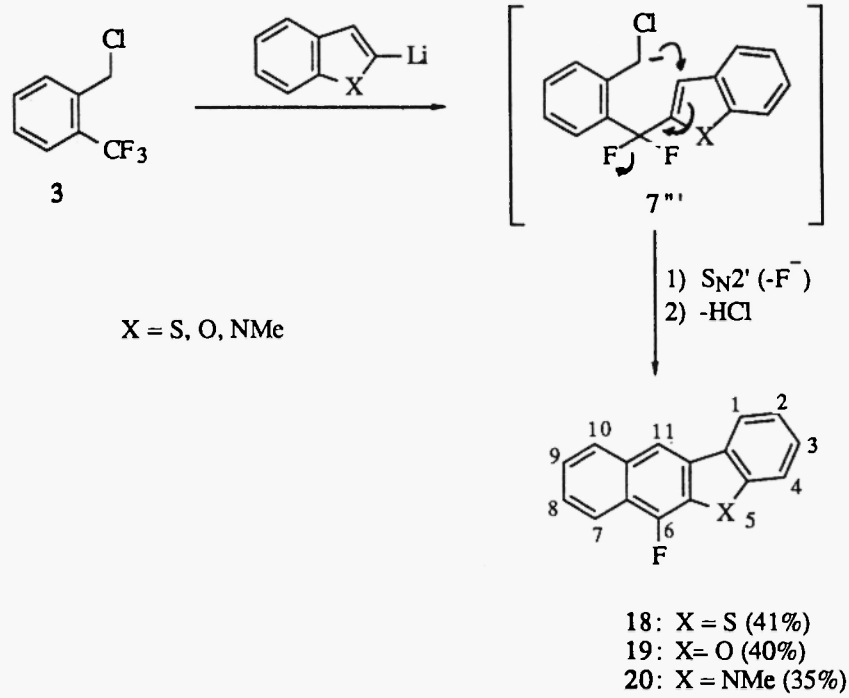
As expected, similar AB patterns were observed for geminal fluorines of a perfluoropropyl derivative **13**. Compound **13** was obtained by the reaction of **2** with a bifunctional lithium reagent derived from 2-aminophenol (-40 °C, 1 h; 23 °C, 1 h) (Scheme 3).

A novel synthesis of substituted 2-aminoquinolines is by cyclization of 2-(perfluoroalkyl)anilines with 2-lithioacetonitriles generated from R-CH_2CN and *n*-BuLi (1 equiv each, THF, -70 °C, 1 h). As can be seen from Scheme 3, the reaction of a CF_3-substituted substrate **1** (-40 °C, 1 h; 23 °C, 1 h) yields a 2-amino-4-fluoroquinoline exemplified by **14** and **15**. The use of higher C_nF_{2n+1}-substituted anilines provides easy access to the corresponding quinolines substituted with a $C_{n-1}F_{2n-1}$ group at the 4-position. This is illustrated by the synthesis of **16** and **17** starting with **2**.

Scheme 3



Scheme 4



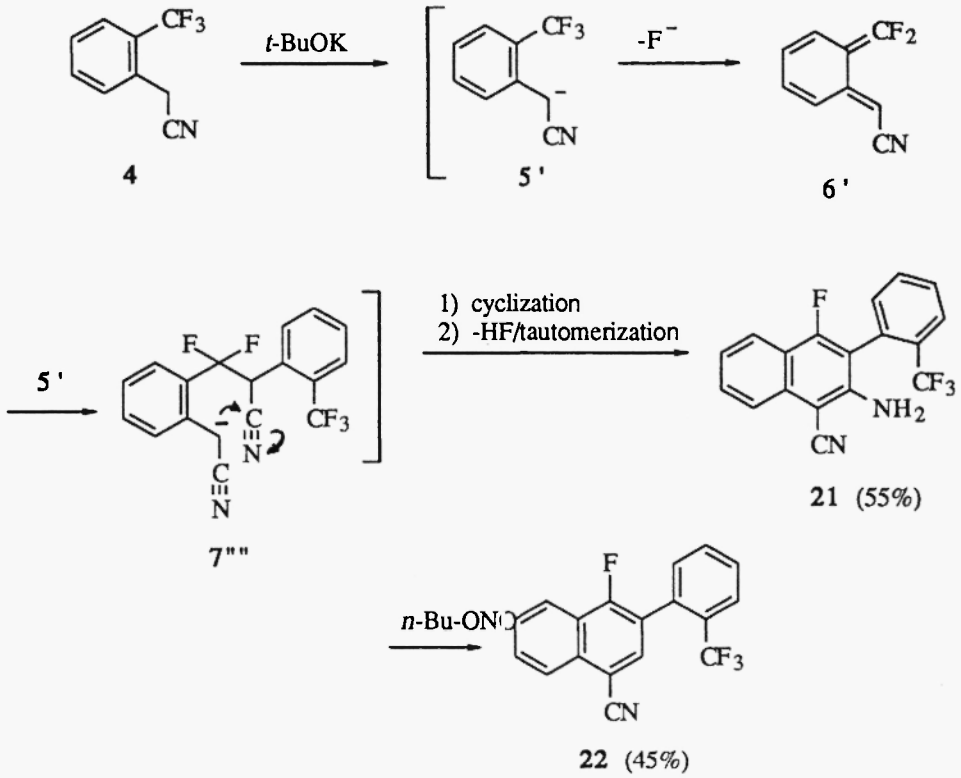
18: X = S (41%)
19: X= O (40%)
20: X = NMe (35%)

Recently, we have communicated a one-step synthesis of 6-fluorobenzo[*b*]naphtho[2,3-*d*]thiophene (**18**) by the reaction of 2-(trifluoromethyl)benzyl chloride (3) with 2-benzo[*b*]thienyllithium (23 °C, 2 h) (7). In this paper we report that the treatment of **3** with 2-benzo[*b*]furyllithium and 1-methyl-2-indolyllithium under similar conditions yields 6-fluorobenzo[*b*]naphtho[2,3-*d*]furan (**19**) and 6-fluoro-5-methylnaphtho[2,3-b]indole (**20**), respectively (Scheme 4). On the other hand, attempted reactions of **3** with lithium reagents derived from thiophene, furan, and 1-methylpyrrole failed to produce any analogous products. The structure of **19** and **20** was determined by extensive proton NOE experiments, as discussed previously for **18** (7).

Finally, we wish to report *tert*-butoxide ion-mediated self-condensation of [2-(trifluoromethyl)phenyl]acetonitrile (**4**) (23 °C, 2 h) (Scheme 5). The 2-amino-1-cyano functionality at the resultant polysubstituted naphthalene **21** may serve as an interesting building block for fused pyrimidines, e.g., by the reaction with an isothiocyanate. The treatment of **21** with *n*-butyl nitrite in DMF gave a de-aminated naphthalene **22**. This is in sharp contrast to the cyclization reaction of **11** discussed above. Cyclization of **21** would require an electrophilic substitution reaction at the electron-deficient 2-(trifluoromethyl)phenyl moiety.

In summary, we have described several new reactions which are of synthetic value. All products discussed in this paper are the major products and, as such, are easily identifiable by TLC or GC. In particular, a GC-MS analysis is of special value because all these compounds give an intense molecular ion peak in their mass spectra. The brevity of this report does not permit a full listing of spectral data which, together with optimization of the reaction conditions will be reported in due course (8).

Scheme 5



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References and Notes

(1) For recent reviews, see: (a) A.S. Kiselyov and L. Strekowski, *Org. Prep. Proc. Int. 28*, 289 (1996); (b) L. Strekowski and A.S. Kiselyov, *Trends Heterocycl. Chem. 3*, 73 (1993).

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(5) Compounds **1**, **3** and **4** are commercially available (Aldrich). For synthesis of **2** and other perfluoroalkyl-substituted anilines, see: N. Yoshino, M. Kitamura, T. Seto, Y. Shibata, M. Abe and K. Ogino, *Bull. Chem. Soc. Jpn. 65*, 2141 (1992).

(6) For the generation of heteroaryllithium reagents, see: L. Strekowski, D.B. Harden, W. Grubbs, S.E. Patterson, A. Czarny, M.J. Mokrosz, M.T. Cegla and R.L. Wydra, *J. Heterocycl. Chem. 27*, 1393 (1990).

(7) A.S. Kiselyov and L. Strekowski, *Tetrahedron Lett. 35*, 7597 (1994).

(8) The reported yields correspond to isolated products with purity better than 96% as determined by GC analysis. All these compounds gave satisfactory microanalysis or HRMS results and were characterized by ^{1}H NMR and, if applicable, by ^{19}F NMR.

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