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An Unconventional Synthetic Approach to Fluoro Heteroaromatic Compounds by a Novel Transformation of an Anionically Activated Trifluoromethyl Group

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Summary: *Lithium reagents derived from acetophenone, phenylacetylene, and substituted acetonitritriles undergo a reaction with 2-(trifluoromethyl)aniline (1) to give the corresponding 4-fluoroquinolines 8, 10a-d. A related reaction of 2-benzo[b]thienyllithium with 2-(trifluoromethyl)benzyl chloride (12) yields 6-fluorobenzo[b]naphtho[2,3-d]thiophene (17).*

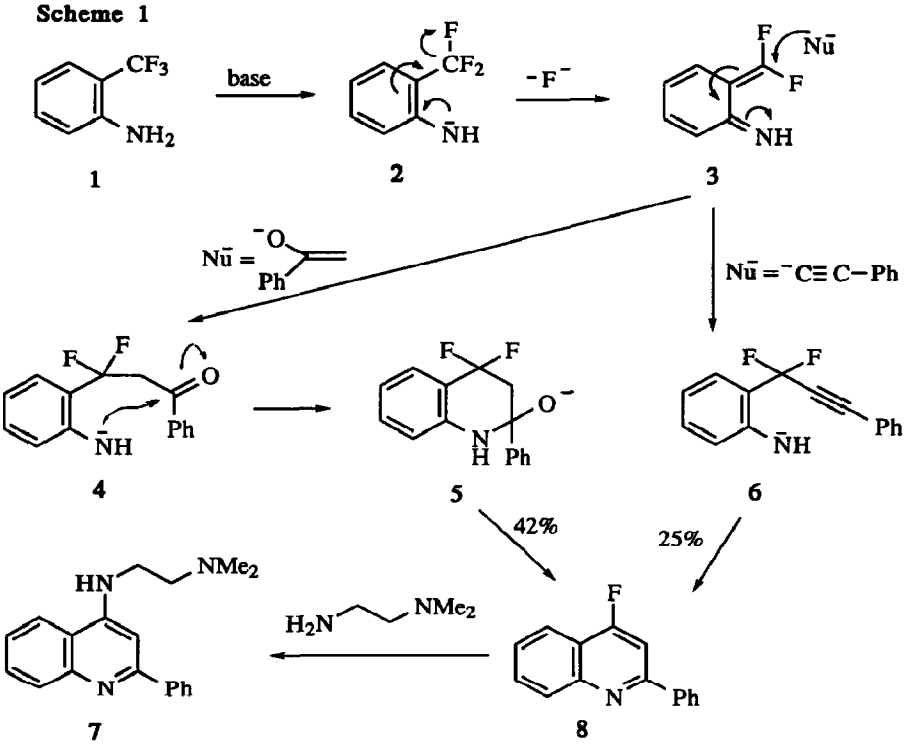
The major approaches to the synthesis of fluoroaromatic compounds[1] are (i) direct fluorination with elemental fluorine or electrophilic fluorinating reagents, (ii) cleavage of an aryl-metal bond by elemental fluorine or the electrophilic reagents, (iii) halogen exchange by fluoride (the Finger reaction), (iv) thermal decomposition of a diazonium tetrafluoroborate and related salts (the Balz-Schiemann reaction), and (v) electrochemical fluorination. Elemental fluorine is highly toxic, corrosive, and difficult to handle. Electrophilic fluorinating reagents, such as xenon difluoride,[1] hypofluorites,[1] *N*-fluorosulfonamides,[2] and *N*-fluoropyridinium salts[3] require elemental fluorine for their preparation or generation *in situ*. As a general rule the Finger reaction is conducted with substrates activated by electron-withdrawing groups, in the presence of the "naked" fluoride ion, and often under harsh temperature conditions.[4] The classical Balz-Schiemann reaction and modifications[5] appear to be the most general, but the yields are often low. The electrochemical processes are mostly used to prepare perfluoro compounds.[1a]

In this paper we report that ortho trifluoromethyl-amino and trifluoromethyl-chloromethyl functionalities, such as in **1**[6] (Schemes 1 and 2) and **12** (Scheme 3), are building blocks for the construction of fluorine-substituted heteroaromatic compounds by the reaction with certain carbanions. Overall, two fluoride ions are eliminated from the trifluoromethyl group in processes that involve anionic activation. The remaining fluorine is a substituent at the heteroaromatic system formed by cyclization.

The treatment of lithium enolate of acetophenone or lithium phenylacetylide with **1** (Scheme 1) yielded[7] 4-fluoro-2-phenylquinoline[8] (**8**). A nucleophilic displacement of the fluorine in **8** by *N,N*-dimethylethylenediamine furnished the amino derivative **7** obtained also by an independent method,[9] thus establishing the structure of **8**. The suggested mechanism involves ionization of **1** followed by elimination of fluoride from the resultant anion **2** to give a key intermediate product[6] **3**. These processes are followed by a nucleophilic addition of carbanion with **3**. With acetophenone enolate the adduct **4** undergoes intramolecular cyclization, as shown, to give **5**, a precursor to **8**. The addition of phenylacetylide anion with **3** generates **6** which may undergo intramolecular cyclization by the addition of the amide anion to the carbon-carbon triple bond.

An extension of this heterocyclization method to the synthesis of 3-substituted 2-amino-4-fluoroquinolines[10] **10a-d** by the reaction of **1** with anions derived from substituted acetonitriles is presented in

Scheme 1



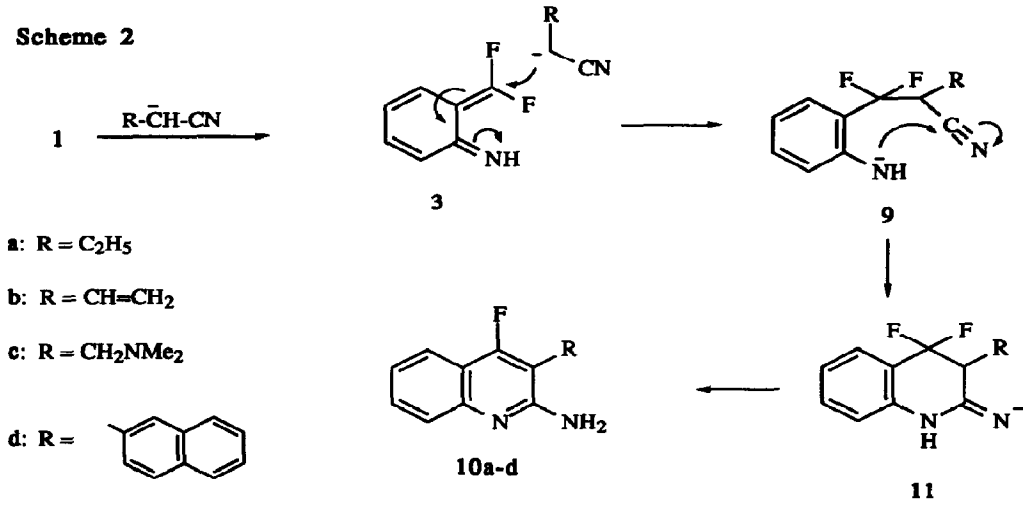
Scheme 2. The formation of **10** is rationalized in terms of a nucleophilic addition of the carbonitrile anion with **3**, then intramolecular cyclization of the resultant adduct **9** with the involvement of the carbonitrile function to give **11**, and followed by aromatization of **11**.

A related synthesis of 6-fluorobenzo[b]naphtho[2,3-d]thiophene[7,10] (**17**) by the reaction of 2-(trifluoromethyl)benzyl chloride (**12**) with 2-benzo[b]thienyllithium is given in Scheme 3. The structure of **17** was assigned by proton NOE experiments. Thus, irradiation of H11 at δ 8.40, the only singlet in the ^{1}H NMR spectrum, produced two doublets at δ 8.23 and δ 8.03 corresponding to H1 and H10, respectively. The irradiation of H1 gave an NOE enhancement for H11 and an additional multiplet at δ 7.50 assigned to H2. In a similar way, the NOE signals for H11 and H9 (δ 7.56) were observed upon irradiation of H10. These results rule out an isomer of **17** in which the fluoronaphthalene and benzothiophene portions are fused in a different orientation (**i** in footnote 11).

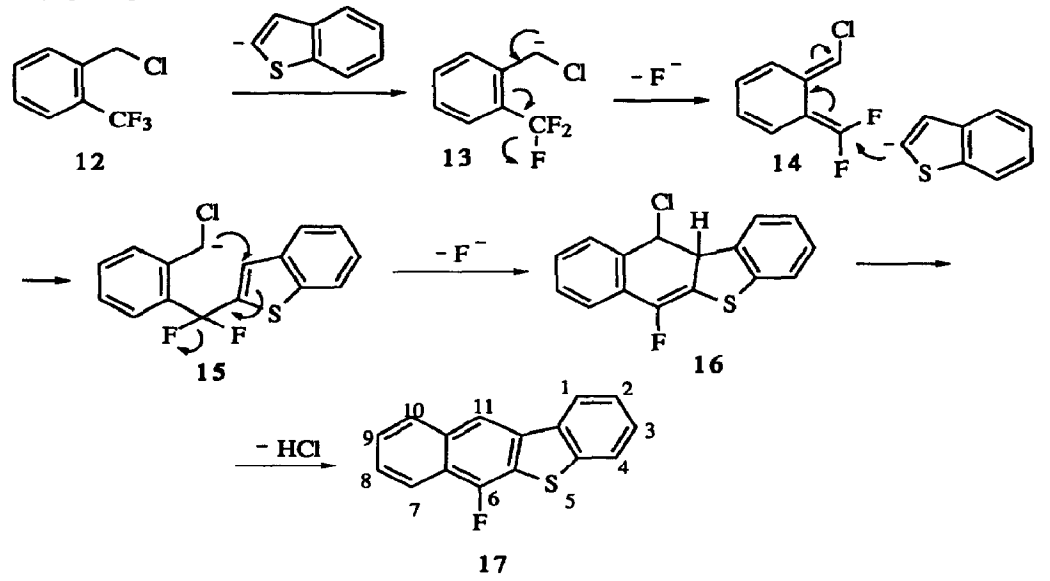
The mechanism for **17** apparently involves the intermediacy of **14** generated in a fashion similar to that of **3**. We strongly suggest that 2-benzo[b]thienyl anion undergoes addition with **14** to give an intermediate anion **15**. The major reaction pathway[11] from this stage apparently involves an intramolecular addition-elimination in **15** to give an intermediate **16**, a direct precursor to the observed product **17**.

We are currently studying the scope and limitations of this novel chemistry for the preparation of other substituted quinolines and heterocyclic analogs of **17**. A detailed report will be published in due course.

Scheme 2



Scheme 3



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References and Notes

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6. For other transformations of **1**, see: Kiselyov, A.S.; Hojjat, M.; Van Aken, K.; Strekowski, L. *Heterocycles* **1994**, *37*, 775; and references cited therein.
7. Lithium derivatives of acetophenone, phenylacetylene and substituted acetonitriles were generated by a slow addition of a solution of a parent compound (10 mmol) in THF (5 mL) to LDA (10.5 mmol) in THF (25 mL) at -50°C under a nitrogen atmosphere. A solution of the lithium reagent was stirred and treated dropwise at -60°C with **1** (400 mg, 2.5 mmol) dissolved in THF (2 mL). The mixture was allowed to reach 23°C within 1h and then stirred at 23°C (1-2h) until TLC analysis (silica gel, hexanes/ether, 1:1) showed the absence of **1**. Quenching with water (1 mL) was followed by standard workup and silica gel chromatography eluting with hexanes (**8**) or hexanes/ether (1:2, **10a-d**). Compounds **10a-d** were crystallized from ethanol. *Note: with a ratio of lithium reagent/1 smaller than 4:1 an annoying side reaction is self-condensation of a ketone or a carbonitrile.* Compound **17** was synthesized in a similar manner.
8. Compound **8** is an oil; MS m/z 222 (85), 223 (100, M^+); HRMS exact mass calcd for $C_{15}H_{10}FN$ 223.0797, found 223.0799; ^{19}F NMR (376.3 MHz, $CDCl_3/CFCl_3$) δ -104 (d, J_{F-H3} = 11 Hz).
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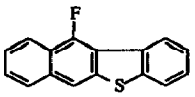
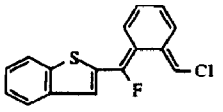
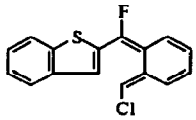
10. Satisfactory elemental analyses (C, ± 0.2; H, ± 0.1; N, ± 0.1), ^1H NMR and mass spectra were obtained for **10a-d** and **17**. Compound, yield, mp, ^{19}F NMR (376.3 MHz, $CDCl_3/CFCl_3$): **10a**, 53%, 105-106°C, δ -121; **10b**, 47%, 111-112°C, δ -117; **10c**, 45%, 171-172°C, δ -121; **10d**, 49%, 225-226°C, δ -117; **17**, 41%, 142-143°C (from cyclohexane), δ -124.
11. The absence of the isomer **i** strongly argues against an alternative reaction pathway that would involve α-elimination of chloride from **13** followed by coupling of the resultant carbene with 2-benzo[b]thienyl anion. The anion **13** is stabilized by the strongly electron-withdrawing trifluoromethyl group, which makes the elimination of fluoride, rather than chloride, a more likely process. Another unlikely mechanism for **17** would involve elimination of fluoride from the adduct **15** to give **ii** and **iii** followed by electrocyclization of **iii** and then elimination of HCl. This pathway would generate **ii** as the major intermediate, and it is not consistent with the relatively high efficiency of the formation of **17**. See also reference 6.



i



ii



iii

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