An Activated Trifluoromethyl Group as a New Synthon for 4,5-Dihydro-1*H*-imidazole and 1,4,5,6-Tetrahydropyrimidine Systems

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Treatment of 4-(trifluoromethyl)benzenamine **1a** and 2-(trifluoromethyl)benzamine **1b** with lithium 2-aminoethylamide gives 2-(4-aminophenyl)-4,5-dihydro-1*H*-imidazole **3a** and 2-(2-aminophenyl)-4,5-dihydro-1*H*-imidazole **3b**, respectively. Similar reactions of **1a** and **1b** with lithium 3-aminopropylamide produce the respective 2-(aminophenyl)-1,4,5,6-tetrahydropyrimidines **4a** and **4b**. 3-(Trifluoromethyl)benzenamine **1c** is recovered unchanged from analogous mixtures. The mechanism is discussed.

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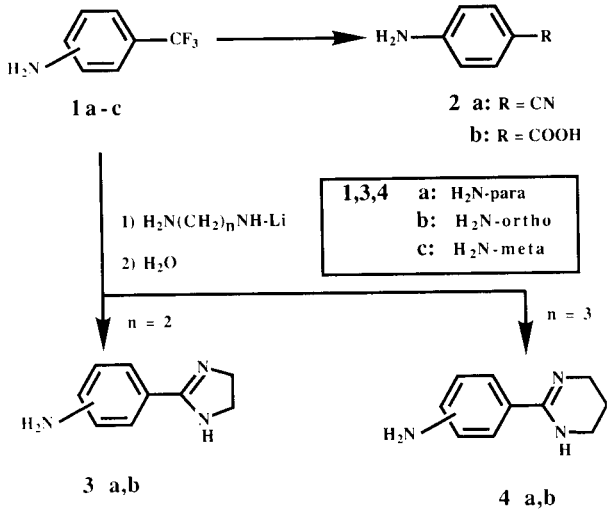
Fluoroalkyl substituents are generally very stable groups [1]. Evidence has been obtained, however, that certain molecular features increase reactivity of the fluorine atoms in these groups toward formal nucleophilic substitutions. [2-6]. In particular, it has been reported that treatment of 4-(trifluoromethyl)benzenamine **1a** with sodium amide in liquid ammonia produces 4-aminobenzonitrile **2a** (Scheme I) as the only low molecular product albeit in a low yield [5]. Alkaline hydrolysis of **1a** gives 4-aminobenzoic acid **2b** [6].

Scheme I

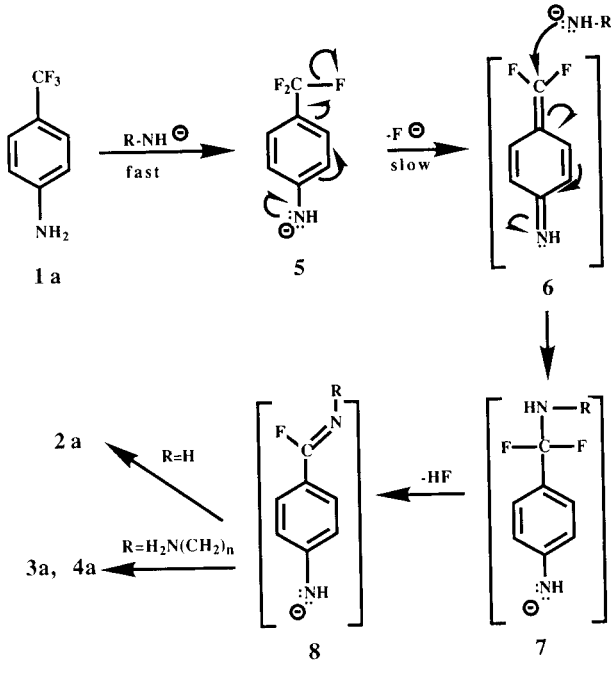


In this paper we report for the first time that the trifluoromethyl group in appropriately substituted aromatic compounds is a useful synthon for 2-aryl-4,5-dihydro-1*H*-imidazoles **3** and 2-aryl-1,4,5,6-tetrahydropyrimidines **4** (Scheme I). To our knowledge this work constitutes the first application of trifluoromethyl derivatives in the synthesis of heterocyclic compounds.

We have found that **1a** reacts with a lithium reagent obtained from two molar equivalents of 1,2-ethanediamine and one molar equivalent of *n*-butyllithium in ether to give 2-(4-aminophenyl)-4,5-dihydro-1*H*-imidazole **3a**. A similar reaction of this lithium reagent with 2-(trifluoromethyl)-benzenamine **1b** furnished 2-(2-aminophenyl)-4,5-dihydro-1*H*-imidazole **3b**. Moreover, substitution of 1,3-propanediamine for 1,2-ethanediamine gave 2-(4-aminophenyl)-1,4,-5,6-tetrahydropyrimidine **4a** and 2-(2-aminophenyl)-1,4,5,-6-tetrahydropyrimidine **4b** from **1a** and **1b**, respectively. Products **3** and **4** were isolated in 68-85% yields as analytically pure hydrochloride salts, and their structures were fully consistent with ^{1}H nmr spectra, ms spectra and elemental analysis. The *meta* isomer **1c** was recovered unchanged from analogous mixtures.

The proposed mechanism, consistent with the obtained experimental data, is given in Scheme II for the reactions of **1a**. Since acidities of benzenamines are about nine orders of magnitude larger than the acidities of aliphatic amines [7,8], compound **1a** must be ionized quickly and remain fully ionized in the presence of an amide reagent [9].

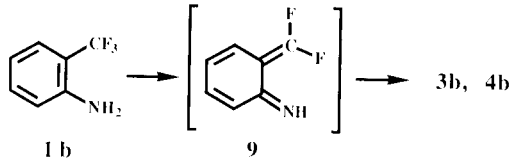
Scheme II



We believe that the resultant anion **5** then undergoes elimination of fluoride to give 4-(difluoromethylene)-2,5-cyclohexadien-1-imine **6** as an intermediate product. The addition reaction of the amide anion with **6** then produces **7**, which is followed by a base-induced elimination of hydrogen fluoride to give a fluoro imine **8**. In the sodium amide-mediated reaction the resultant **8** undergoes elimination of hydrogen fluoride to give 4-aminobenzonitrile **2a**, the observed product [5]. This elimination is not possible for aminoalkyl-substituted **8** which, instead, undergo cyclization followed by elimination of hydrogen fluoride to give respective products **3a** and **4a** after quenching the mixtures with water. Although it can be suggested that the intermediate products **7** and **8** can also undergo elimination of fluoride in a fashion similar to that for **5**, there is a good reason to believe that this possible mechanistic pathway is not important for the transformations of **7** and **8**. More specifically, the elimination of hydrogen fluoride from **7** and **8** are apparently much faster processes. This conclusion was reached after analysis of the reaction mixtures quenched before the maximum yields of **3a** and **4a** were obtained. It was found that **1a** was consumed slowly within 1.5 hours at −5° to give the respective **3a** or **4a**, and no other low molecular compounds, possible intermediates could be observed by tlc analysis conducted at low temperature immediately after the quenching. These results demonstrate that the decomposition of the anion **5**, apparently to give **6**, is relatively slow, and this decomposition is followed by fast processes to give final products **3a** or **4a**.

6-(Difluoromethylene)-2,4-cyclohexadien-1-imine **9** (Scheme III) is the suggested intermediate product in the synthesis of **3b** and **4b** from **1b**. The given mechanism is consistent with the lack of reactivity of **1c** which cannot form a similar conjugate intermediate product.

Scheme III



1b 9

It is interesting to note that the enimine-type intermediate products similar to **6** and **9** have been postulated in several other known transformations of the trifluoromethyl group. In these studies [4] the activation has been achieved by an anionic ring nitrogen, in addition to the exocyclic anionic nitrogen as in **5** [5]. It appears, therefore, that the chemistry described in this work may successfully be applied for the synthesis of a large variety of 2-substituted 4,5-dihydroimidazoles and 1,4,5,6-tetrahydropyrimidines, as determined by the position of an anionic center in the trifluoromethyl-substituted molecule [10-12].

EXPERIMENTAL

All reagents were obtained from Aldrich. Compounds **1a-c** were dried with molecular sieves 3A. 1,2-Ethanediamine and 1,3-propanediamine were stored over pellets of sodium hydroxide. Reactions with *n*-butyllithium (2.6 *M* in hexanes) were conducted in ether distilled from sodium benzophenone ketyl immediately before use and under static pressure of nitrogen. The glassware was dried at 140°, assembled hot and cooled in a stream of nitrogen. The liquids were transferred with syringes.

Melting points (Pyrex capillary) are uncorrected. Mass spectra (70 eV) were recorded on a Varian MAT spectrometer. The ^{1}H nmr spectra were obtained on a Varian VXR-400 (400 MHz) spectrometer at 25°. The spectra were taken in deuterium oxide solutions (0.05 *M*) with sodium 3-(trimethylsilyl)propionate as an internal standard. Elemental analyses (Atlantic Microlab, Inc.) of the oily free bases **3** and **4** showed a decreased content of carbon (up to −1.2%) and an increased content of hydrogen (up to +0.25%) in comparison to the calculated values, indicative of contamination of the samples with water. Similar problems with the elemental analyses for other amidines have been reported [13]. However, the hydrochloride salts of **3** and **4** gave excellent microanalysis results. The mass spectra reported for the free bases **3** and **4** were virtually identical with those obtained for the hydrochloride salts.

General Procedure for Preparation of Compounds **3a,b** and **4a,b**.

A solution of 1,2-ethanediamine (0.60 ml, 9 mmoles) or 1,3-propanediamine (0.75 ml, 9 mmoles) in ether (25 ml) was treated with *n*-butyllithium (8 mmoles) at −5°. The mixture was stirred for 10 minutes, then treated with a solution of **1a** or **1b** (0.32 g, 2 mmoles) in ether (5 ml) and stirred for additional 1.5 hours at −5°. Quenching of the mixture with water (0.18 ml, 10 mmoles) was followed by removal of ether and excess of diamine under reduced pressure. Distillation of the residue on a Kugelrohr (100°/0.05 mm Hg) gave the respective **3** or **4**. Alternatively, the residue after removal of the diamine was dissolved in methanol (5 ml). The solution was treated with a mixture of concentrated hydrochloric acid and methanol (1:9, 4 ml, 4 mmoles of hydrochloric acid) and then with ether (10 ml). The resultant precipitate was crystallized from methanol/ether to give a hydrochloride salt of the respective **3** or **4**.

2-(4-Aminophenyl)-4,5-dihydro-1*H*-imidazole, **3a**.

This compound was obtained as an oil, yield 55%; ms: m/e 43 (27), 57 (11), 65 (13), 92 (13), 131 (14), 132 (100), 133 (11), 149 (11), 160 (32), 161 (64, M^+).

2-(4-Aminophenyl)-4,5-dihydro-1*H*-imidazole Hydrochloride Hemihydrate, **3a·HCl·0.5H$_2$O**.

This compound had mp 261-263°, yield 68%; ^{1}H nmr: δ 4.00 (s, 4H), 6.88 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H).

Anal. Calcd. for $C_9H_{11}N_3 \cdot HCl \cdot 0.5H_2O$: C, 52.30; H, 6.34; N, 20.33. Found: C, 52.35; H, 6.32; N, 20.21.

2-(2-Aminophenyl)-4,5-dihydro-1*H*-imidazole, **3b**.

This compound was obtained as an oil, yield 62%; ms: m/e 41 (13), 43 (25), 44 (24), 104 (12), 118 (28), 131 (84), 132 (17), 160 (20), 161 (100, M^+), 162 (10).

2-(2-Aminophenyl)-4,5-dihydro-1*H*-imidazole Hydrochloride, **3b•HCl**.

This compound had mp 211-213°, yield 71%; ^{1}H nmr: δ 4.07 (s, 4H), 6.91 (m, 1H), 6.96 (m, 1H), 7.42 (m, 1H), 7.46 (m, 1H).

Anal. Calcd. for $C_9H_{11}N_3$·HCl: C, 54.68; H, 6.12; N, 21.26. Found: C, 54.39; H, 6.06; N, 21.16.

2-(4-Aminophenyl)-1,4,5,6-tetrahydropyrimidine, **4a**.

This compound was obtained as an oil, yield 72%; ms: m/e 65 (13), 91 (12), 92 (14), 118 (40), 119 (66), 120 (10), 145 (20), 174 (100), 175 (85, M$^+$), 176 (20).

2-(4-Aminophenyl)-1,4,5,6-tetrahydropyrimidine hydrochloride, **4a•HCl**.

This compound had mp 311-313°, yield 78%; ^{1}H nmr: δ 2.07 (pent, J = 5.6 Hz, 2H), 3.54 (t, J = 5.6 Hz, 4H), 6.89 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H).

Anal. Calcd. for $C_{10}H_{13}N_3$·HCl: C, 56.74; H, 6.67; N, 19.85. Found: C, 56.86; H, 6.66; N, 19.77.

2-(2-Aminophenyl)-1,4,5,6-tetrahydropyrimidine, **4b**.

This compound was obtained as an oil, yield 82%; ms: m/e 56 (13), 58 (15), 91 (13), 92 (10), 118 (44), 119 (21), 146 (24), 174 (57), 175 (100, M$^+$), 176 (19).

2-(2-Aminophenyl)-1,4,5,6-tetrahydropyrimidine hydrochloride, **4b•HCl**.

This compound had mp 244-246°, yield 85%; ^{1}H nmr: δ 2.11 (pent, J = 5.6 Hz, 2H), 3.57 (t, J = 5.6 Hz, 4H), 6.91 (m, 2H), 7.28 (m, 1H), 7.40 (m, 1H).

Anal. Calcd. for $C_{10}H_{13}N_3$·HCl: C, 56.74; H, 6.67; N, 19.85. Found: C, 56.66; H, 6.71; N, 19.74.

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