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Several trifluoromethyl-substituted aromatic and heteroaromatic amines have been obtained by the reactions of the corresponding amines with the title reagent system. Computational results provide rationalization for the observed regioselectivities and support a mechanism in which the electrophilic trifluoromethyl radicals interact with the aromatic ring at the sites with the greatest electron density of the HOMO orbitals, and then the resultant adducts are oxidized to cations. The products obtained are potential building blocks for a number of heterocyclic systems.

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The trifluoromethyl group at the *ortho* or *para* position in aromatic and heteroaromatic amines exhibits unusual reactivity under basic conditions that cause ionization of the amino function [1,2]. Recently, the anionically activated trifluoromethyl group has emerged as a valuable synthon for substituted dihydro-1*H*-imidazoles [3], 1,4,5,6-tetrahydropyrimidines [3-5], benzothiazoles [6], and benzoxazoles [6]. The *ortho*-aminotrifluoromethyl functionality is a novel building block for fused pyridines [4,5,7-9] and pyrimidines [10]. Many substrates for these transformations are available commercially [11] and others can be prepared by trifluoromethylation of aromatic and heteroaromatic amines. In general, these reactions involve a trifluoromethyl radical which can be generated by chemical, photochemical or electrochemical methods [12-15].

In this paper we have investigated introduction of a trifluoromethyl group into aromatic and heteroaromatic amines by the redox system of trifluoroiodomethane-zinc-sulfur dioxide in *N,N*-dimethylformamide [16]. The reactions with trifluoroiodomethane are conveniently conducted in a standard glassware under an atmospheric pressure of nitrogen. The procedure is experimentally simpler than a similar method described previously with the use of bromotrifluoromethane in pressure equipment [12-14]. Another modification is the use of excess zinc as an acid scavenger. More importantly, we present a simple computational approach that can be applied for predicting, albeit qualitatively, the major products of the trifluoromethylation reaction.

A likely mechanism is illustrated in Figure 1 for the particular reaction of 3-aminopyridine (**1**), which gave 3-amino-2-(trifluoromethyl)pyridine (**6**) and the isomer **7** in the respective yields of 20% and 9% [17]. It is suggested that a reversible addition [18] of trifluoromethyl radicals with **1** produces intermediate radicals **2** and **3** which then

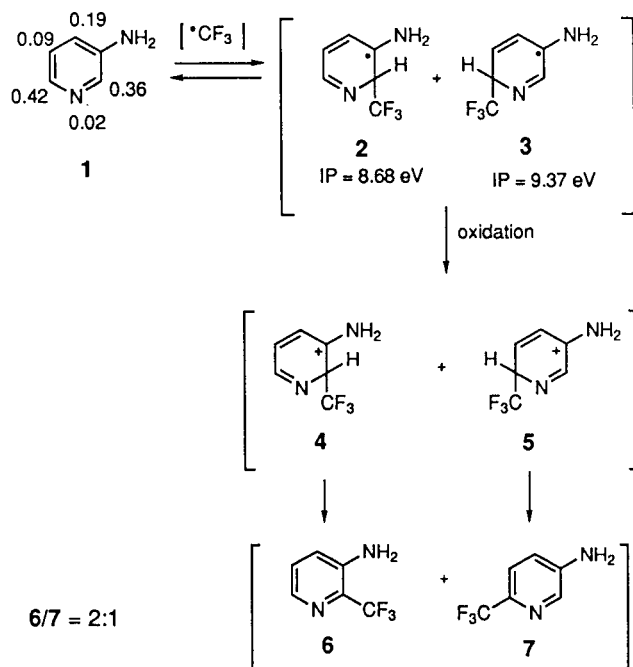


Figure 1. A proposed mechanism for trifluoromethylation of 3-aminopyridine (**1**) by the $\text{CF}_3\text{I}/\text{Zn}/\text{SO}_2$ system. Electron densities for the highest occupied molecular orbitals (HOMO) at ring atoms of **1** and ionization potentials (IP) for the presumed intermediate radicals **2** and **3**, as obtained by ampac computations, are shown.

undergo oxidation [12] to the respective cations **4** and **5**, a process generally accepted for other homolytic aromatic substitutions [19]. The cations **4** and **5** are direct precursors to the observed products **6** and **7**.

Strong support for the suggested mechanism was obtained by computational studies. It was reasoned that the reaction of an electrophilic trifluoromethyl radical should take place at the positions of **1** with the greatest electron density of the highest occupied molecular orbitals (HOMO). As can be seen from Figure 1, this is exactly the case. Moreover, the observed ratio of **6** to **7**

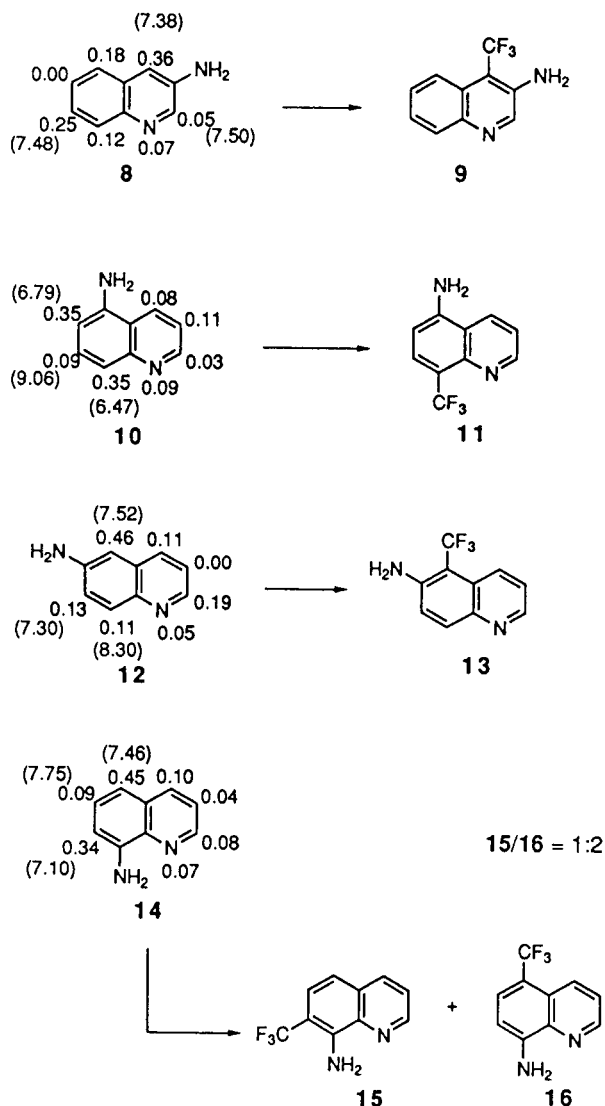


Figure 2. Trifluoromethylation reactions of aminoquinolines **8**, **10**, **12** and **14** by the $\text{CF}_3\text{I}/\text{Zn}/\text{SO}_2$ system. HOMO electron densities for the substrates and ionization potentials (eV, in parentheses) for the corresponding adducts of these substrates with a trifluoromethyl radical, as obtained by ampac computations, are shown.

can be explained by taking into consideration the reversibility of the first step and the relative ease of oxidation of the resultant radical intermediates **2** and **3**. On the basis of the HOMO electron densities along the radical **3** is expected to be present in a greater concentration than the radical **2**. On the other hand, **2** has a lower calculated ionization potential than **3**, which results in a more facile, irreversible oxidation [18] of **2** to cation **4** than the oxidation of **3** to **5**. As an overall result, **6** is the major observed product.

We have successfully applied this simple analysis to explain the observed outcome of the trifluoromethylation reactions of several commercially available aminoquinolines (Figure 2) and aminonaphthalenes (Figure 3). The

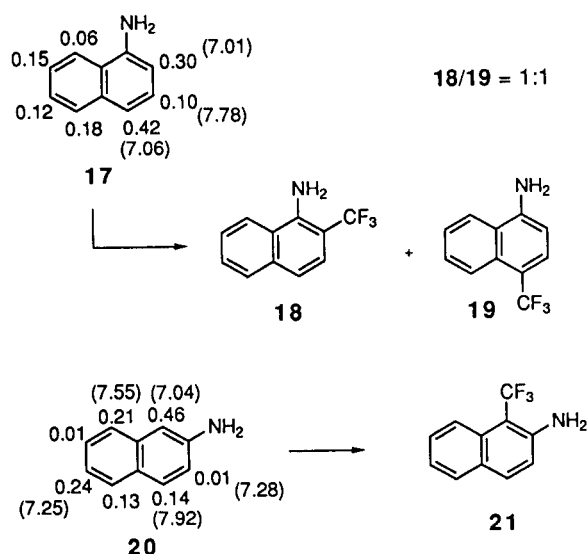


Figure 3. Trifluoromethylation reactions of aminonaphthalenes **17** and **20**. See Figure 2 for additional information.

results are statistically significant to suggest that this simple computational approach can be applied to predict the products of other trifluoromethylation reactions. Although more rigorous theoretical treatments are available [21], they are complicated and require a substantial amount of computational time.

EXPERIMENTAL

All reagents were obtained from Aldrich. Amines were stored over pellets of sodium hydroxide, and *N,N*-dimethylformamide was dried with molecular sieves 3A. Melting points (Pyrex capillary) are not corrected. The ^1H nmr (400 MHz) and ^{19}F nmr (377.4 MHz) spectra were obtained at 25° in deuteriochloroform solutions with tetramethylsilane and trichlorofluoromethane as the respective internal references. Chemical shift assignments for protons were obtained by using decoupling and nOe experiments. Coupling constants smaller than 2 Hz are not reported. Crude mixtures were analyzed and the purity of isolated products were tested on a gc-ms instrument equipped with an on-column injector, a poly(dimethylsiloxane)-coated column, and a mass selective detector.

General Procedure for Preparation of Trifluoromethyl Derivatives **6**, **7**, **9**, **11**, **13**, **15**, **16**, **18**, **19**, **21**.

N,N-Dimethylformamide (25 ml), an aromatic amine **1**, **8**, **10**, **12**, **14**, **17** or **20** (1.7 mmol), and zinc powder (0.17 g, 2.7 mmol) were placed in a flask equipped with a dry-ice condenser, and the mixture was stirred at -60° under a nitrogen atmosphere. Then sulfur dioxide (0.17 g, 2.7 mmol) and trifluoroiodomethane (5.2 g, 26 mmol) were liquified into the flask. The required amounts of these reagents were determined by weight differences of the small commercial cylinders containing the reagents. The resultant mixture was allowed to reach 23° within 4 hours and then stirred under a nitrogen atmosphere for

an additional 12 hours. Workup involved acidification with concentrated hydrochloric acid (2 ml, 2 mmoles), removal of *N,N*-dimethylformamide and water on a rotary evaporator, neutralization of the resultant slurry with solid sodium carbonate, and then extraction with diethyl ether (3 x 25 ml). Concentration of the extract was followed by silica gel chromatography with hexanes/ether (2:1) as an eluent. Solid products **6**, **9**, **11**, **13**, **15**, **18**, **19** were crystallized from hexanes or hexanes/ether.

All yields given below are for isolated products and are based on the starting amines. Non-consumed substrates constitute the balance material in all cases. A substantial amount of hexafluoroethane, resulting from coupling of trifluoromethyl radicals, was observed by a gc-ms analysis.

3-Amino-2-(trifluoromethyl)pyridine, **6**.

This compound was eluted first, mp 69-70°, yield 20%; ¹H nmr: δ 4.20 (br s, exchangeable with deuterium oxide, 2H, NH₂), 7.10 (d, J = 8 Hz, 1H, 4-H), 7.25 (dd, J = 4 and 8 Hz, 1H, 5-H), 8.08 (d, J = 4 Hz, 1H, 6-H); ¹⁹F nmr: δ -66.2; ms: m/z 115 (59), 142 (47), 162 (100, M⁺).

High resolution ms: Calcd. for C₆H₅F₃N₂ m/z 162.0405; observed m/z 162.0401.

5-Amino-2-(trifluoromethyl)pyridine, **7**.

Continuing elution gave this compound as an oil, yield 9%; ¹H nmr: δ 4.30 (br s, exchangeable with deuterium oxide, 2H, NH₂), 7.02 (dd, J = 3 and 8 Hz, 1H, 4-H), 7.45 (d, J = 8 Hz, 1H, 3-H), 8.13 (d, J = 3 Hz, 1H, 6-H); ¹⁹F nmr: δ -65.7; ms: m/z 115 (100), 142 (84), 162 (71, M⁺).

High resolution ms: Calcd. for C₆H₅F₃N₂ m/z 162.0405; observed m/z 162.0400.

3-Amino-4-(trifluoromethyl)quinoline, **9**.

This compound had mp 121-122°, yield 43%. Spectral data have been published previously [6].

5-Amino-8-(trifluoromethyl)quinoline, **11**.

This compound had mp 154-155°, yield 25%; ¹H nmr: δ 4.54 (br s, exchangeable with deuterium oxide, 2H, NH₂), 6.77 (d, J = 8 Hz, 1H, 6-H), 7.45 (dd, J = 4 and 8 Hz, 1H, 3-H), 7.87 (d, J = 8 Hz, 1H, 7-H), 8.18 (dd, J = 2 and 8 Hz, 1H, 4-H), 9.05 (dd, J = 2 and 4 Hz, 1H, 2-H); ¹⁹F nmr: δ -73.0; ms: m/z 162 (54), 193 (46), 212 (100, M⁺).

High resolution ms: Calcd. for C₁₀H₇F₃N₂ m/z 212.0561; observed m/z 212.0561.

6-Amino-5-(trifluoromethyl)quinoline, **13**.

This compound had mp 121-122°, yield 42%. Spectral data have been reported previously [6].

8-Amino-7-(trifluoromethyl)quinoline, **15**.

This compound was eluted first, an oil, yield 17%; ¹H nmr: δ 5.80 (br s, exchangeable with deuterium oxide, 2H, NH₂), 7.12 (d, J = 9 Hz, 1H, 5-H), 7.49 (dd, J = 4 and 8 Hz, 1H, 3-H), 7.51 (d, J = 9 Hz, 1H, 6-H), 8.10 (dd, J = 2 and 8 Hz, 1H, 4H), 8.81 (dd, J = 2 and 4 Hz, 1H, 2-H); ¹⁹F nmr: δ -70.8; ms: m/z 173 (75), 192 (27), 212 (100, M⁺).

High resolution ms: Calcd. for C₁₀H₇F₃N₂ m/z 212.0561; observed m/z 212.0564.

8-Amino-5-(trifluoromethyl)quinoline, **16**.

Continuing elution gave this compound in a 37% yield, mp

83-84°; ¹H nmr: δ 5.40 (br s, exchangeable with deuterium oxide, 2H, NH₂), 6.85 (d, J = 8 Hz, 1H, 7-H), 7.52 (dd, J = 4 and 8 Hz, 1H, 3-H), 7.70 (d, J = 8 Hz, 6-H), 8.20 (m, 1H, 4-H), 8.82 (dd, J = 2 and 4 Hz, 1H, 2-H); ¹⁹F nmr: δ -74.4; ms: m/z 162 (55), 193 (25), 212 (100, M⁺).

High resolution ms: Calcd. for C₁₀H₇F₃N₂ m/z 212.0561; observed m/z 212.0562.

1-Amino-2-(trifluoromethyl)naphthalene, **18**.

This compound was eluted first, mp 102-103°, yield 20%; ¹H nmr: δ 4.84 (br s, exchangeable with deuterium oxide, 2H, NH₂), 7.27 (d, J = 9 Hz, 1H, 4-H), 7.47 (dd, J = 9 Hz, 1H, 3-H), 7.52 (t, J = 8 Hz, 1H, 7-H), 7.57 (t, J = 8 Hz, 1H, 6-H), 7.81 (d, J = 8 Hz, 1H, 8-H), 7.89 (d, J = 8 Hz, 1H, 5-H); ¹⁹F nmr: δ -62.0; ms: m/z 164 (37), 191 (100), 211 (100, M⁺).

Anal. Calcd. for C₁₁H₈F₃N: C, 62.56; H, 3.82; N, 6.63. Found: C, 62.71; H, 3.88; N, 6.70.

1-Amino-4-(trifluoromethyl)naphthalene, **19**.

Continuing elution gave this compound in a 20% yield, mp 83-84°; ¹H nmr: δ 4.46 (br s, exchangeable with deuterium oxide, 2H, NH₂), 6.72 (d, J = 8 Hz, 1H, 2-H), 7.53 (t, J = 8 Hz, 1H, 7-H), 7.60 (t, J = 8 Hz, 1H, 6-H), 7.67 (d, J = 8 Hz, 1H, 3-H), 7.85 (d, J = 8 Hz, 1H, 8-H), 8.15 (d, J = 8 Hz, 1H, 5-H); ¹⁹F nmr: δ -59.0; ms: m/z 161 (33), 192 (20), 211 (100, M⁺).

Anal. Calcd. for C₁₁H₈F₃N: C, 62.56; H, 3.82; N, 6.63. Found: C, 62.67; H, 3.87; N, 6.55.

2-Amino-1-(trifluoromethyl)naphthalene, **21**.

This compound was obtained as an oil, yield 40%; ¹H nmr: δ 4.60 (br s, exchangeable with deuterium oxide, 2H, NH₂), 6.78 (d, J = 9 Hz, 1H, 3-H), 7.28 (t, J = 8 Hz, 1H, 6-H), 7.48 (t, J = 8 Hz, 1H, 7-H), 7.66 (d, J = 8 Hz, 1H, 5-H), 7.68 (d, J = 9 Hz, 1H, 4-H), 7.98 (d, J = 8 Hz, 1H, 8-H); ¹⁹F nmr: δ -80.3; ms: m/z 164 (81), 191 (75), 211 (100, M⁺).

Anal. Calcd. for C₁₁H₈F₃N: C, 62.56; H, 3.82; N, 6.63. Found: C, 62.77; H, 3.72; N, 6.58.

Computations.

Computations of the HOMO electron densities for aromatic amines **1**, **8**, **10**, **12**, **14**, **17**, **20** and the ionization potentials of the adducts of a trifluoromethyl radical with these amines were run on a Silicon Graphics 4d/380s computer and a Silicon Graphics Iris workstation. The computations were conducted with the program ampac 2.1 (QCPE Program 506, Indiana University) and by using the AM1 Hamiltonian for fully optimized geometries. Preliminary geometry optimizations were conducted in the program PCMODEL by using the mmx force field (a modified mm2 force field). In both the molecular mechanics and semi-empirical operations the geometry optimization was stopped when the gradient was below 0.2 cal·mol⁻¹·Å⁻¹.

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