AN ACTIVATED TRIFLUOROMETHYL GROUP AS A SYNTHON FOR 2-SUBSTITUTED BENZOTHIAZOLE AND BENZOXAZOLE

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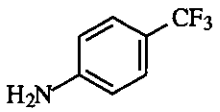
Abstract - Dianions derived from 2-mercaptoaniline and 2-hydroxyaniline are cyclized to 2-substituted benzothiazole and benzoxazole, respectively, in the reaction with ortho or para trifluoromethyl-substituted anilines and quinolinamines that involves the CF_3 group. The carbon atom of the CF_3 group becomes C-2 of the five-membered ring system. Synthesis of 3-trifluoromethylquinoline-4-amine and 5-trifluoromethylquinoline-6-amine is also reported.

The trifluoromethyl group shows an unusually high reactivity when activated by an ortho or para amino substituent in aromatic compounds or an appropriately positioned ring NH function in heterocyclic compounds.[1] These observations have been developed in our laboratories into practical syntheses of quinolines,[2] fused quinolines,[3] quinazolines,[4] and cyclic amidines.[5] Closely related heterocyclic syntheses have also been reported by others.[1,6] The continuous interest in the chemistry of the trifluoromethyl group is being stimulated by ready availability of trifluoromethyl substituted anilines and analogs. Many reagents such as **1**-**4** are available commercially and inexpensive, and others can conveniently be prepared by trifluoromethylation of aromatic and heteroaromatic amines.[1] For example, in this work the treatment of quinoline-3-amine with trifluoroiodomethane in the presence of zinc and sulfur dioxide under conditions similar to those described for trifluoromethylation of aniline[7] gave 4-trifluoromethylquinoline-3-amine (**5**) as a sole low molecular weight product. The high



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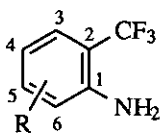
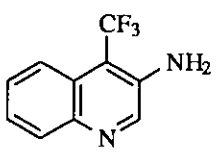


2: R = H
3: R = 4-Cl
4: R = 5-CF_3



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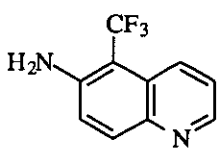

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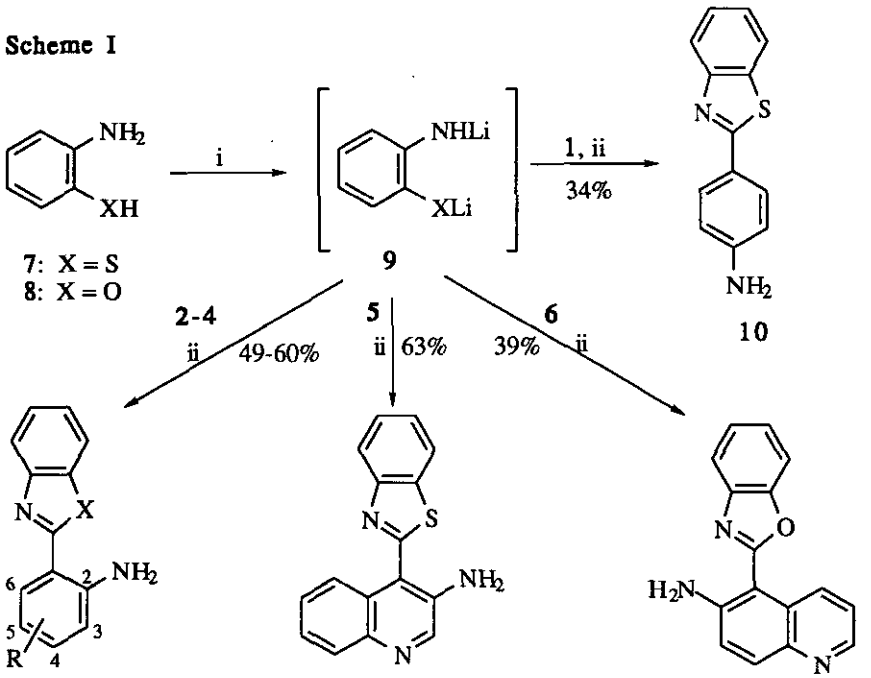
regioselectivity was also observed in a similar reaction with quinoline-6-amine,[8] which yielded 5-trifluoromethylquinoline-6-amine (**6**). The unambiguous structure assignments for **5** and **6** were obtained by ^{1}H nmr by extensive decoupling and nOe experiments.

In this paper we report that the activated trifluoromethyl group, such as in **1-6**, is a useful synthon for benzothiazoles and benzoxazoles in the reactions with dianions (**9**) derived from 2-mercaptoaniline (**7**) and 2-hydroxyaniline (**8**), respectively (Scheme I). Each fluorine of the CF_3 group is successfully eliminated by a series of internal nucleophilic processes, and the carbon atom of this group becomes C-2 of the five-membered ring system in the resultant products (**10-17**). The generation of highly basic anions (**9**) is essential for these syntheses. Attempted reactions of **1-6** with **7,8** or monoanions derived from **7,8** did not produce the corresponding products (**10-17**) under a variety of experimental conditions including prolonged heating of solutions in 2-aminoethanol to 170 °C.

Scheme I

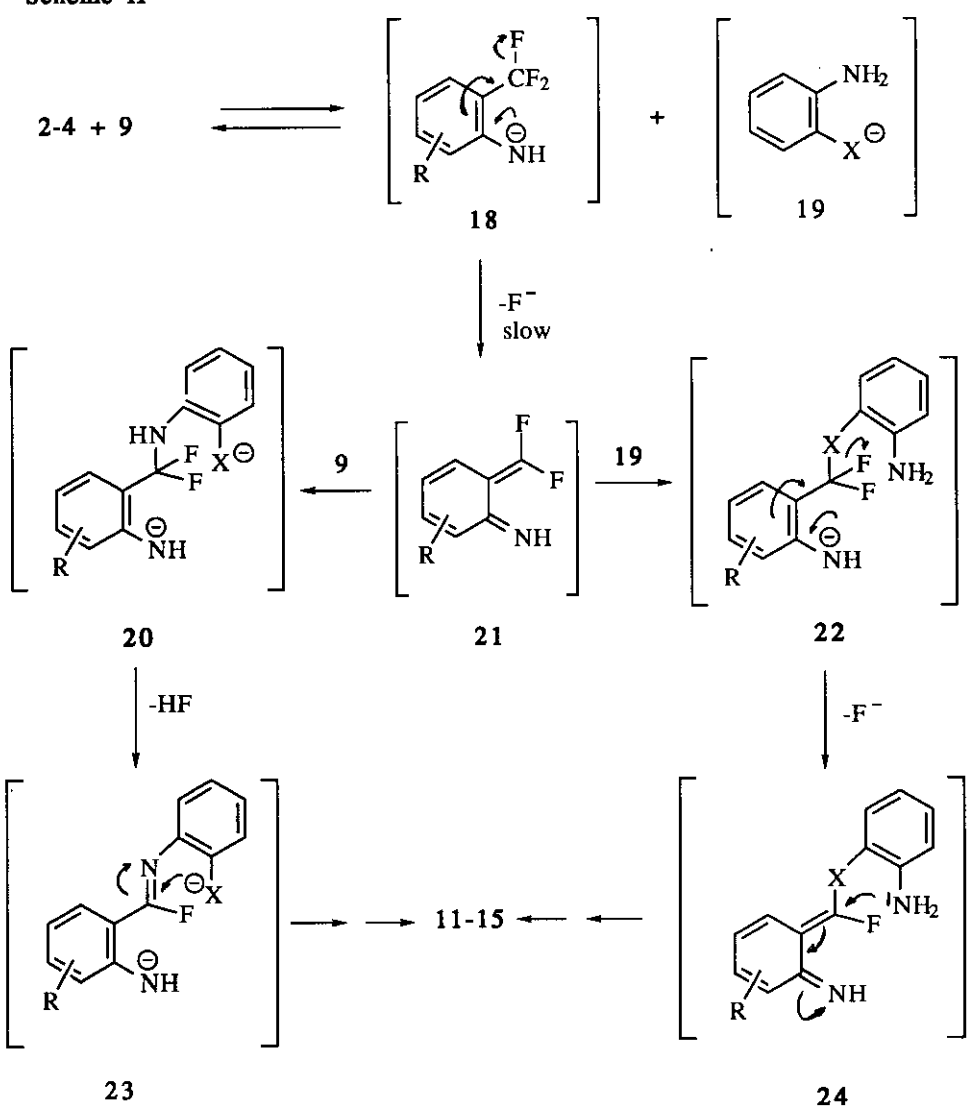


i: THF, 2 equiv. n-BuLi, 20 min at -78 °C.

ii: THF, -78 °C → 23 °C, 12 h at 23 °C; then H_2O.

The suggested mechanism is illustrated in Scheme II for the transformations of 2-trifluoromethylanilines (**2-4**). The strong base (**9**) is apparently necessary to cause ionization of **2-4**. There is growing evidence[1-6] that the resultant anion (**18**) undergoes a slow elimination of fluoride to generate an intermediate product (**21**). The major reaction pathway, especially at the initial stage of the reaction, may involve nucleophilic addition of **9** with **21** to give **20** and then base-mediated elimination of HF from **20** to generate another intermediate product (**23**). As the

Scheme II



reaction progresses, the concentration of monoanion (**19**) increases and the nucleophilic addition of **19** with **21** may provide a second reaction pathway with the intermediacy of an adduct (**22**). It is suggested that **22** undergoes elimination of fluoride to generate **24** in a fashion similar to the formation of **21** from **18**. Both **23** and **24** are the suggested precursors to **11-15**, the observed products. The stability of the 5-trifluoromethyl substituent in **4** is fully consistent with the proposed mechanism.

In summary, we have described a method for the preparation of 2-substituted benzothiazoles and benzoxazoles, which appears to be general. It significantly expands known entries[9] to the target heterocyclic systems because the starting materials are readily available.[1] Products (**11-17**) and analogs may serve as building blocks for the construction of condensed heterocyclic systems.[10] Diverse pharmaceutical activities have also been noted for many similarly substituted benzothiazoles and benzoxazoles.[11]

EXPERIMENTAL

N,N-Dimethylformamide was dried with molecular sieves 3A, and tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use. The glassware was dried at 140 °C, assembled hot, and cooled under a nitrogen atmosphere. Melting points (Pyrex capillary) are not corrected. Unless otherwise stated ^{1}H nmr spectra (400 MHz, Varian VX-400) and ^{13}C nmr spectra (68 MHz, JEOL EX-270) were taken in deuteriochloroform solutions with tetramethylsilane as an internal standard. Mass spectra were obtained on an H-P 5890 Series II Gas Chromatograph equipped with an on-column injector, a poly(dimethylsiloxane)-coated capillary column (25 m x 0.32 mm), and a 5970 Mass Selective Detector operating at 70 eV.

4-(Trifluoromethyl)quinoline-3-amine (5)

A mixture of quinoline-3-amine (2.5 g, 17 mmol) and zinc powder (0.17 g, 2.7 mmol) in *N,N*-dimethylformamide (25 ml) was cooled to -78 °C under a nitrogen atmosphere and treated with sulfur dioxide (0.17 g, 2.7 mmol) and then with trifluoroiodomethane (5.2 g, 26 mmol). The temperature was raised to -30 °C, and the mixture was stirred under a nitrogen atmosphere for 4 h. Workup included extraction with ether, washing of the extract with water, and drying with sodium sulfate. Silica gel chromatography with a mixture of hexanes and ether (4:6) as an eluent gave compound (**5**) in the first fractions. Crystallization from a mixture of hexanes and ether (7:3) afforded 1.54 g (43%) of **5**, mp 121-122 °C. Anal. Calcd for $C_{10}H_7N_2F_3$: C, 56.60; H, 3.33; N, 13.20. Found: C, 56.84; H, 3.39; N, 13.15. ^{1}H Nmr: δ 4.75 (br s, exchangeable with D_2O, 2H, NH_2), 7.55 (m, 2H, H-5 and H-8), 8.00 (m, 2H, H-6 and H-7), 8.45 (s, 1H, H-2). Ms: m/z 165 (65), 212 (100, M^+).

5-Trifluoromethylquinoline-6-amine (6)

Substitution of quinoline-6-amine for quinoline-3-amine in the procedure described above afforded 1.50 g (42%) of compound (**6**), mp 121-122 °C. Anal. Calcd for $C_{10}H_7N_2F_3$: C, 56.60; H, 3.33; N, 13.20. Found: C, 56.79; H, 3.38; N, 13.16. ^{1}H Nmr: δ 4.81 (br s, exchangeable with D_2O, 2H, NH_2), 7.05 (d, J_{7-8} = 9.4 Hz, 1H, H-7), 7.38 (dd, J_{3-4} = 8.8 Hz and J_{2-3} = 4.0 Hz, 1H, H-3), 7.97 (d, J_{7-8} = 9.4 Hz, 1H, H-8), 8.30 (d, J_{3-4} = 8.8 Hz, 1H, H-4), 8.68 (d, J_{2-3} = 4.0 Hz, 1H, H-2). Ms: m/z 165 (36), 173 (19), 192 (54), 212 (100, M^+).

General procedure for the preparation of compounds 10-17

A solution of 2-mercaptoaniline (**7**, 1.25 g, 10 mmol) or 2-hydroxyaniline (**8**, 1.09 g, 10 mmol) in tetrahydrofuran (5 ml) was added dropwise to a stirred solution of n-butyllithium (2.5 M in hexanes, 8 ml, 20 mmol) in tetrahydrofuran (15 ml) at -78 °C under a nitrogen atmosphere. The mixture was stirred at -78 °C for 20 min and then treated with a solution of a trifluoromethyl-substituted aniline (**1-4**) or a quinolinamine (**5,6**) (2.5 mmol) in tetrahydrofuran (5 ml). The resulting yellow solution was stirred at -78 °C for 1 h and then at 23 °C for 12 h. Quenching with water (1 ml) was followed by concentration on a rotary evaporator, extraction with dichloromethane (3 x 15 ml), and drying of the extract with magnesium sulfate. Products were purified by silica gel chromatography with hexanes as an eluent. Solid products (**10-16**) were additionally crystallized from ethanol.

2-(4-Aminophenyl)benzothiazole (10)

Compound **10** (34%) was obtained from **1** and **7**, mp 156-157 °C (lit.,[12] mp 156.2-156.7 °C).

2-(2-Aminophenyl)benzothiazole (11)

Compound **11** (55%) was obtained from **2** and **7**, mp 127-128 °C (lit.,[13] mp 126.7-127.7 °C).

2-(2-Amino-5-chlorophenyl)benzothiazole (12)

Compound **12** (57%) was obtained from **3** and **7**, mp 145-146 °C. Anal. Calcd for $C_{13}H_9N_2OCl$: C, 59.88; H, 3.48. Found: C, 59.64; H, 3.55. ^{1}H Nmr: δ 6.18 (br s, exchangeable with D_2O, 2H), 6.75 (d, J = 8.8 Hz, 1H), 7.21 (dd, J = 8.8 Hz, J = 2.6 Hz, 1H), 7.37 (m, 2H), 7.54-7.78 (m, 2H), 8.26 (d, J = 2.6 Hz, 1H). ^{13}C Nmr: δ 116.07, 118.04, 121.24, 122.54, 125.17, 126.19, 129.24, 131.30, 141.05, 141.11, 145.23, 153.49, 167.66. Ms: m/z 69 (28), 198 (15), 224 (14), 260 (100, M^+).

2-[2-Amino-4-(trifluoromethyl)phenyl]benzothiazole (13)

Compound **13** (60%) was obtained from **4** and **7**, mp 183-183.5 °C. Anal. Calcd for $C_{14}H_9N_2SF_3$: C, 57.13; H, 3.08; N, 9.52. Found: C, 57.20; H, 3.11; N, 9.46. ^{1}H Nmr: δ 6.63 (br s, exchangeable with D_2O, 2H), 6.95 (d, J = 8.0 Hz, 1H), 7.03 (s, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H). ^{13}C Nmr: δ 113.00 (q, $^3J_{CCCF}$ = 3 Hz), 113.51 (q, $^3H_{CCCF}$ = 3 Hz), 119.50 (q, $^1J_{CF}$ = 275 Hz), 121.32 , 122.82, 125.47, 126.35, 130.83, 133.00 (q, $^2J_{CCF}$ = 40 Hz), 140.84, 140.89, 146.63, 153.53, 167.85. Ms: m/z 69 (12), 108 (14), 247 (13), 294 (100, M^+).

2-(2-Aminophenyl)benzoxazole (14)

Compound **14** (49%) was obtained from **2** and **8**, mp 106-107 °C (lit.,[14] mp 106-107 °C).

2-(2-Amino-5-chlorophenyl)benzoxazole (15)

Compound **15** (52%) was obtained from **3** and **8**, mp 146-147 °C. Anal. Calcd for $C_{13}H_9N_2OCl$: C, 63.81, H, 3.71. Found: C, 63.56; H, 3.83. ^{1}H Nmr (DMSO-d_6): δ 6.95 (d, J = 8.8 Hz, 1H), 7.26 (br s, exchangeable with D_2O, 2H), 7.31 (dd, J = 8.8 Hz, J = 2.6 Hz, 1H), 7.42 (m, 2H), 7.79 (m, 2H), 7.88 (d, J = 2.6 Hz, 1H). ^{13}C Nmr (DMSO-d_6): δ 109.44, 110.31, 117.47, 119.45, 121.22, 124.45, 125.03, 127.78, 132.15, 141.58, 146.26, 149.13, 161.79. Ms: m/z 63 (15), 215 (27), 244 (100, M^+).

4-(Benzoxazol-2-yl)quinoline-3-amine (16)

Compound **16** (63%) was obtained from **5** and **7**, mp 187-187.5 °C. Anal. Calcd for $C_{16}H_{11}N_3S$: C, 69.29; H, 4.00. Found: C, 69.01; H, 4.11. ^{1}H Nmr (DMSO-d_6): δ 5.66 (br s, exchangeable with D_2O, 2H), 7.35-7.65 (m, 4H), 7.92 (d, J = 6.7 Hz, 1H), 8.08 (m, 1H), 8.14 (d, J = 6.7 Hz, 1H), 8.36 (m, 1H), 8.62 (s, 1H). ^{13}C Nmr (DMSO-d_6): δ 113.71, 121.37, 122.84, 123.14, 125.32, 125.66, 126.42, 128.06, 130.13, 135.21, 138.60, 140.76, 142.35, 144.45, 152.71, 163.01. Ms: m/z 69 (11), 138 (10), 249 (14), 277 (100, M^+).

5-(Benzoxazol-2-yl)quinoline-6-amine (17)

Compound **17** (39%) was obtained from **6** and **8**, an oil. Anal. Calcd for $C_{16}H_{11}N_3O$: C, 73.57; H, 4.20. Found: C, 73.39; H, 4.29. ^{1}H Nmr (DMSO-d_6): δ 7.46 (m, 2H), 7.58 (d, J = 9.2 Hz, 1H), 7.70 (m, 1H), 7.86 (m, 2H), 8.01 (d, J = 9.2 Hz, 2H), 8.71 (d, J = 4.4 Hz, 1H), 9.31 (d, J = 9.2 Hz, 1H). ^{13}C Nmr (DMSO-d_6): δ 96.38, 111.08, 119.25, 123.18, 124.87, 125.11, 125.33, 128.28, 131.25, 140.23, 140.27, 140.46, 143.19, 143.21, 148.93, 150.00 Ms: m/z 103 (8), 232 (11), 261 (100, M^+).

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REFERENCES AND NOTES

1. For reviews, see: M.A. McClinton and D.A. McClinton, *Tetrahedron*, 1992, **48**, 6555; Y. Kobayashi and I. Kumadaki, *Acc. Chem. Res.*, 1978, 11, 197.
2. L. Strekowski, S.E. Patterson, L. Janda, R.L. Wydra, D.B. Harden, M. Lipowska, and M.T. Cegla, *J. Org. Chem.*, 1992, **57**, 196.
3. L. Strekowski, R.L. Wydra, D.B. Harden, and V.A. Honkan, *Heterocycles*, 1990, **31**, 1565.
4. S.E. Patterson, L. Janda, and L. Strekowski, *J. Heterocycl. Chem.*, 1992, **29**, 703.
5. R.L. Wydra, S.E. Patterson, and L. Strekowski, *J. Heterocycl.Chem.*, 1990, **27**, 803.
6. R.D. Chambers, M.J. Silvester, M. Tamura, and D.E. Wood, *J. Chem. Soc., Chem. Commun.*, 1982, 1412; J.F. Bunnett and C. Galli, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2515.
7. C. Wakselman and M. Tordeux, *J. Chem. Soc., Chem. Commun.*, 1987, 1701; M. Tordeux, B. Langlois, and C. Wakselman, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2293.
8. These reactions apparently involve the intermediary of a highly electrophilic trifluoromethyl radical, as suggested in references (7) above. Consistent with this suggestion our AMPAC computations gave the highest HOMO electron density in **5** and **6** at the sites of the regioselective trifluoromethylation.
9. For reviews, see: G.V. Boyd, 'Comprehensive Heterocyclic Chemistry,' Vol. 6, ed. by A.R. Katritzky, C.W. Rees, and K.T. Potts, Pergamon Press, Inc., Oxford, 1984, pp. 216-223; J.V. Metzger, 'Comprehensive Heterocyclic Chemistry,' Vol. 6, ed. by A.R. Katritzky, C.W. Rees, and K.T. Potts, Pergamon Press, Inc., Oxford, 1984, pp. 321-326.
10. M. Davis and F.G. Mann, *J. Chem. Soc.*, 1962, 945; C.S. Davis, *J. Pharm. Sci.*, 1962, **51**, 1111; E. Barni and G. DiModica, *Ann. Chim.*, 1973, **63**, 373.
11. K. Nagarajan, A.N. Goud, R.V. Rao, R.K. Shah, H.G. Sen, and B.N. Deb, *Indian J. Pharm. Sci.*, 1986, **48**, 53; L.W. Wattenberg, M.A. Page, and J.L. Leong, *Cancer Res.*, 1968, **28**, 2539; T.H. Haskell, F.E Petersen, D. Watson, N.R. Plessas, and T. Culbertson, *J. Med. Chem.*, 1970, **13**, 697.
12. M.T. Bogert and H.B. Corbitt, *J. Am. Chem. Soc.*, 1926, **48**, 783.

13. D.W. Hein, R.J. Alheim, and J.J. Leavitt, *J. Am. Chem. Soc.*, 1957, **79**, 427.

14. T. Nagai, Y. Fukushima, T. Kuroda, H. Shimizu, S. Sekiguchi, and K. Matsui, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 2600.

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