Trifluoromethyl-Substituted Anilines with Oxime and Hydrazone Dianions

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5-(2-Aminophenyl)isoxazoles are obtained in good yields by the reaction of 2-(trifluoromethyl)aniline with dilithio derivatives of oximes of acetone, 3-pentanone, propiophenone, and cyclohexanone. An analogous synthesis of a substituted isoxazole from 4-(trifluoromethyl)aniline and 3-pentanone oxime and the synthesis of a substituted pyrazole from 2-(trifluoromethyl)aniline and 3-pentanone hydrazone are less efficient.

2-(Trifluoromethyl)aniline (**1** in Scheme 1) and its *para* isomer **13** (equation 1), but not the *meta* isomer, exhibit high reactivity under strongly basic conditions that cause ionization of the amino function. In particular, the ionization of **1** is followed by elimination of fluoride ion from the resultant anion **3** to generate an intermediate product **4**, as shown in Scheme 1. The subsequent cyclization of **4** by the reaction with a variety of two-carbon components has been developed into a practical synthetic route to quinolines [1-6]. Alternatively, the cyclization with a four-atom component may involve only the difluoromethylene function of **4**, but these reactions leading to five-membered ring systems have received less attention [6-9]. In this paper we report that dianions derived from ketone oximes can be successfully used as the four-atom components in cyclization with the trifluoromethyl group of **1**, **2** or **13** to give the isoxazole ring system. Cyclizations of such dianions with other one-carbon units are known [10,11]. We also describe briefly an analogous reaction of a dianion derived from cyclohexanone hydrazone which leads to a pyrazole.

Oximes are deprotonated quickly at the hydroxy group and then slowly at the carbon atom by the reaction with *n*-butyllithium. The reaction is regioselective in that it generates conformationally stable Z-dianions [12]. The dilithiation is also accomplished in the presence of lithium diisopropylamide. We have found, however, that the best yields of isoxazoles **8-12** and **14** are obtained for the reaction of **1**, **2**, **13** with the corresponding dilithio derivatives of oximes generated from the oximes in the presence of an equimolar mixture of *n*-butyllithium and lithium diisopropylamide. This mixture is conveniently obtained by treatment of one molar equivalent of diisopropylamine with two equivalents of *n*-butyllithium. Substitution of 2,2,6,6-tetramethylpiperidine for diisopropylamine provides equally good results.

Under optimized conditions the yields of 5-(2-aminophenyl)isoxazoles **8-12** were in the range of 45-

63%, and the efficiency of an analogous synthesis of a 5-(4-aminophenyl)isoxazole from **13** and 3-pentanone oxime was only 17%. In contrast to the successful preparation of **12** from **1** and cyclohexanone oxime (yield 50%), the attempted reactions of **1** with dilithio derivatives of cyclopentanone or camphor oximes failed to produce an isoxazole. These results are fully consistent with the proposed mechanism of cyclization (Scheme 1).

Scheme 1

No	R^1	R^2	R^3
8	H	H	Me
9	H	Me	Et
10	Cl	Me	Et
11	H	Me	Ph
12	H	$-(CH_2)_4-$	
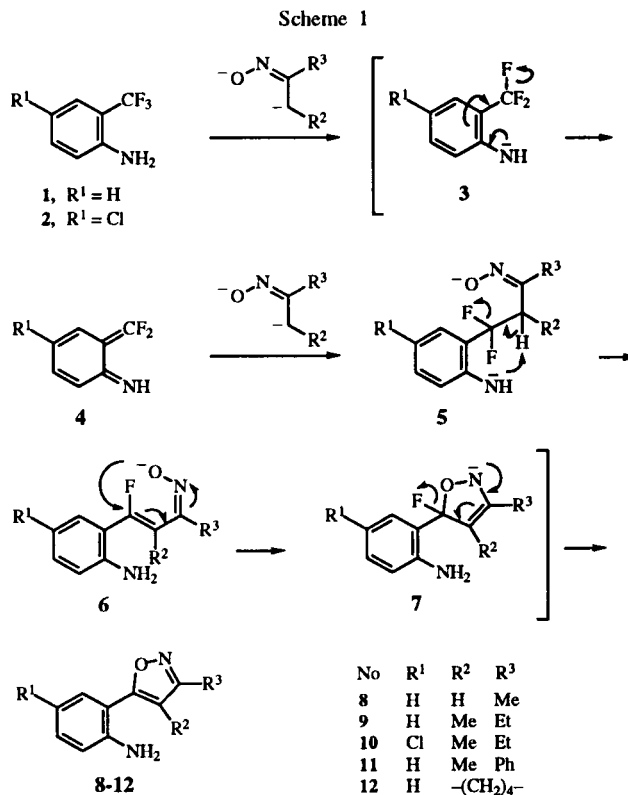
It can be suggested that isoxazoles **8-12** are produced by nucleophilic addition of the more nucleophilic carbon-centered anion of the oxime dianion to the intermediate product **4** followed by intramolecular (amide ion assisted)

elimination of fluoride from the resultant adduct **5** and then the self-explanatory pathway **5** → **8-12**. For steric reasons the short bridge R^2-R^3 in **6** derived from cyclopentanone or camphor may inhibit the intramolecular cyclization to **7**, and/or this cyclization may be reversible for such strained systems **7**. The low yield of **14** can be explained in terms of the lack of the intramolecular, amide ion-assisted deprotonation of the corresponding *para*-substituted analog of **5**. A competing reaction may involve elimination of fluoride ion by a pathway that is similar to that of **3→4**.

As an extension of this work, cyclohexanone hydrazone was lithiated with a mixture of one equivalent of *n*-butyllithium and one equivalent of lithium 2,2,6,6-tetramethylpiperidide, and then the presumed dilithio derivative was allowed to react with **1** (equation 2). The expected pyrazole **15** was obtained in a 28% yield under optimized conditions. Two tautomers for **15** are possible, and the given tentative structure is based on a likely, intramolecular hydrogen bonding between the amino group and the more basic N2 atom of the pyrazole. Due to the modest yield of **15** and difficulties in the preparation of unsubstituted hydrazones [13] this chemistry does not appear to provide a useful, general synthetic route to pyrazoles. This conclusion is further justified by our inability to obtain a pyrazole by attempted reactions of **1** with lithiated phenylhydrazone of cyclohexanone.

$$(1)$$

$$(2)$$

15 (or tautomer)
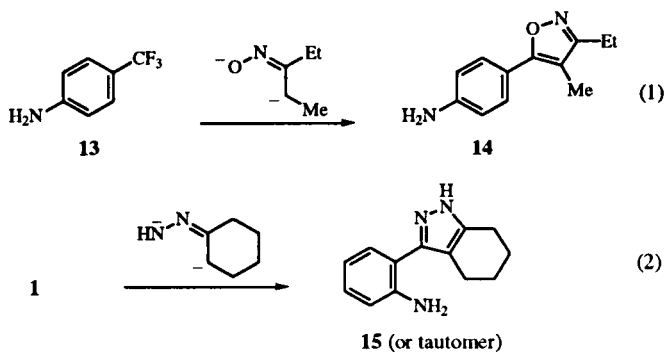
EXPERIMENTAL

Reagents were obtained and used as supplied from Aldrich. Oximes [14] and hydrazones [13] were synthesized by using the published procedures. The ^{1}H nmr and ^{13}C nmr spectra were recorded at 25° at 300 MHz and 75 MHz, respectively, in deuteriochloroform solutions containing tetramethylsilane as an internal reference. Proton-proton coupling constants smaller than 2 Hz are not reported. Progress of the reactions was monitored, purity of the samples was analyzed, and mass spectra of analytically pure products were recorded on a gc-ms instrument equipped with an on-column injector, a capillary column coated with poly(dimethylsiloxane), and a mass-selective detector oper-

ating at 70 eV. Microanalyses were obtained on a Perkin-Elmer series 4200 elemental analyzer.

General Procedure for Preparation of Isoxazoles **8-12, 14**.

A solution of *n*-butyllithium (2 *M* in cyclohexane, 20 ml, 40 mmoles) was added dropwise to a stirred solution of diisopropylamine (2.8 ml, 20 mmoles) in tetrahydrofuran (20 ml) at -40° under a nitrogen atmosphere. The solution was stirred at -20° for 30 minutes, cooled to -50°, and then treated dropwise with a solution of a ketone oxime (20 mmoles) in tetrahydrofuran (5 ml). The mixture was stirred at 0° for 30 minutes and then cooled to -50° before the addition of **1, 2** or **13** (4 mmoles) dissolved in tetrahydrofuran (2 ml). The final mixture was stirred at -50° for 1 hour, at 0° for 2 hours, and then quenched with water (0.5 ml). Concentration under reduced pressure followed by extraction of the residue with ether (2 x 25 ml), then concentration of the extract and chromatography on silica gel eluting with pentanes/ether (1:1) gave **8-12, 14**.

5-(2-Aminophenyl)-3-methylisoxazole (**8**, from **1** and Acetone Oxime).

This compound was obtained in a 45% yield, an oil; ^{1}H nmr: δ 2.36 (s, 3 H), 4.57 (br, exchangeable with deuterium oxide, 2 H), 6.28 (s, 1 H), 6.76 (m, 2 H), 7.20 (t, J = 8 Hz, 1 H), 7.46 (d, J = 8 Hz, 1 H); ^{13}C nmr: δ 11.3, 101.0, 112.1, 116.9, 118.0, 128.6, 131.1, 144.5, 159.9, 170.1; ms: m/z 104 (60), 174 (100, M$^+$).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.73; H, 5.82; N, 15.98.

5-(2-Aminophenyl)-3-ethyl-4-methylisoxazole (**9**, from **1** and 3-Pentanone Oxime).

This compound was obtained in a 58% yield, an oil; ^{1}H nmr: δ 1.34 (t, J = 7 Hz, 3 H), 2.05 (s, 3 H), 2.70 (q, J = 7 Hz, 2 H), 4.28 (br, exchangeable with deuterium oxide, 2 H), 6.79 (m, 2 H), 7.23 (m, 2 H); ^{13}C nmr: δ 7.8, 11.8, 18.8, 109.9, 113.2, 116.3, 117.8, 129.7, 130.7, 145.3, 164.8, 165.2; ms: m/z 146 (90), 173 (60), 202 (100, M$^+$).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.25; H, 6.98; N, 13.85. Found: C, 71.00; H, 7.08; N, 13.80.

5-(2-Amino-5-chlorophenyl)-3-ethyl-4-methylisoxazole (**10**, from **2** and 3-Pentanone Oxime).

This compound was obtained in a 63% yield, an oil; ^{1}H nmr: δ 1.34 (t, J = 7 Hz, 3 H), 2.06 (s, 3 H), 2.69 (q, J = 7 Hz, 2 H), 4.31 (br, exchangeable with deuterium oxide, 2 H), 6.70 (d, J = 8 Hz, 1 H), 7.18 (m, 2 H); ^{13}C nmr: δ 7.8, 11.8, 18.8, 110.5, 114.3, 117.5, 122.3, 129.0, 130.6, 143.9, 163.4, 165.3; ms: m/z 180 (100), 207 (50), 236 (100, M$^+$), 238 (30, M$^+$).

Anal. Calcd. for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; N, 11.83. Found: C, 60.82; H, 5.57; N, 11.80.

5-(2-Aminophenyl)-4-methyl-3-phenylisoxazole (**11**, from **1** and Propiophenone Oxime).

This compound was obtained in a 47% yield, an oil; ^{1}H nmr: δ 2.20 (s, 3 H), 4.28 (br, exchangeable with deuterium oxide, 2 H), 6.82 (m, 2 H), 7.28 (m, 2 H), 7.50 (m, 3 H), 7.72 (m, 2 H); ^{13}C nmr: δ 9.3, 110.0, 113.0, 116.5, 118.0, 128.3, 128.8, 129.5, 129.7, 130.0, 131.1, 145.4, 163.3, 166.3; ms: m/z 249 (90), 250 (100, M$^+$).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.62; H, 5.70; N, 11.10.

7-(2-Aminophenyl)-3,4,5,6-tetrahydrobenzo[c]isoxazole (12, from 1 and Cyclohexanone Oxime).

This compound was obtained in a 50% yield, an oil; ^{1}H nmr: δ 1.78 (m, 2 H), 1.84 (m, 2 H), 2.67 (t, J = 6 Hz, 2 H), 2.81 (t, J = 6 Hz, 2 H), 4.56 (br, exchangeable with deuterium oxide, 2 H), 6.75 (d, J = 8 Hz, 1 H), 6.77 (t, J = 8 Hz, 1 H), 7.19 (t, J = 8 Hz, 1 H), 7.30 (d, J = 8 Hz, 1 H); ^{13}C nmr: δ 21.2, 21.8, 22.2, 22.9, 111.3, 113.2, 116.6, 117.7, 128.7, 130.6, 145.1, 161.3, 163.6; ms: m/z 145 (100), 171 (70), 214 (70, M$^+$).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.88; H, 6.59; N, 13.07. Found: C, 72.80; H, 6.62; N, 13.01.

5-(4-Aminophenyl)-3-ethyl-4-methylisoxazole (14, from 13 and 3-Pentanone Oxime).

This compound was obtained in a 17% yield, mp 88-89° (from ether/hexanes, 1:1); ^{1}H nmr: δ 1.31 (t, J = 7 Hz, 3 H), 2.13 (s, 3 H), 2.66 (q, J = 7 Hz, 2 H), 3.85 (br, exchangeable with deuterium oxide, 2 H), 6.74 (d, J = 8 Hz, 2 H), 7.50 (d, J = 8 Hz, 2 H); [1]H nOe experiment: irradiation at δ 2.13 (CH$_3$) gave signals at δ 2.66 (CH$_2$) and δ 7.50 (2-H/6-H of the phenyl); ^{13}C nmr: δ 8.0, 12.0, 18.6, 106.4, 114.7, 119.0, 127.9, 147.4, 164.8, 165.3; ms: m/z 120 (95), 202 (100, M$^+$).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.25; H, 6.98; N, 13.85. Found: C, 71.29; H, 7.02; N, 13.70.

3-(2-Aminophenyl)-4,5,6,7-1H-benzo[d]pyrazole (15 or Isomer).

The procedure given above was followed with the modification that 2,2,6,6-tetramethylpiperidine and cyclohexanone hydrazone were substituted for diisopropylamine and cyclohexanone oxime, respectively, yield 28%, an oil; ^{1}H nmr: δ 1.77 (m, 2 H), 1.85 (m, 2 H), 2.64 (t, J = 6 Hz, 2 H), 2.68 (t, J = 6 Hz, 2 H), 4.40 (br, exchangeable with deuterium oxide, 3 H), 6.75 (m, 2 H), 7.12 (t, J = 8 Hz, 1 H), 7.33 (d, J = 8 Hz, 1 H); ^{13}C nmr: δ 21.7, 22.2, 22.5, 23.5, 113.9, 116.0, 117.3, 117.7, 128.3, 129.3, 141.7, 145.0, 146.0; ms: m/z 184 (40), 212 (30), 213 (100, M$^+$).

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.03; H, 7.15; N, 19.54.

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