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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.

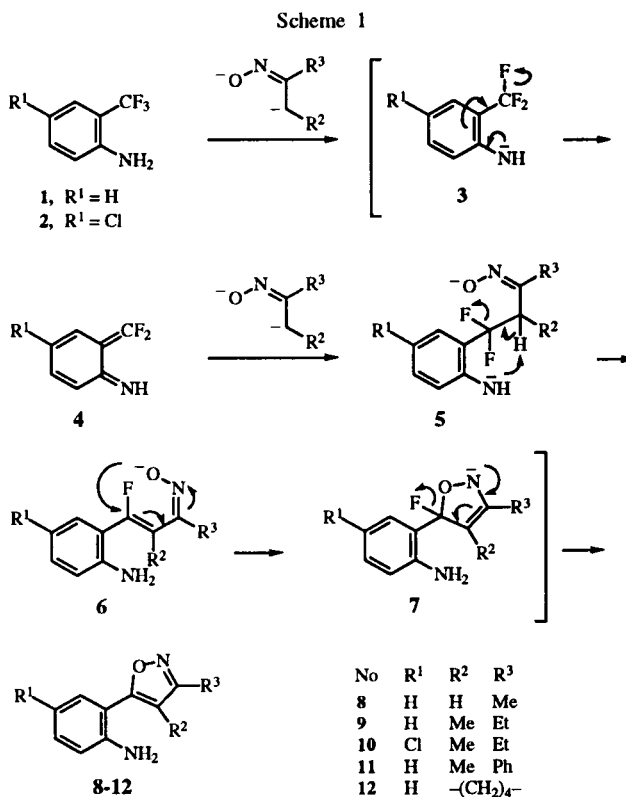
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2-(Trifluoromethyl)aniline (**1** in Scheme 1) and its *para* isomer **13** (equation 1), but not the *meta* isomer, exhibit high reactivity under strongly basic conditions that cause ionization of the amino function. In particular, the ionization 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-

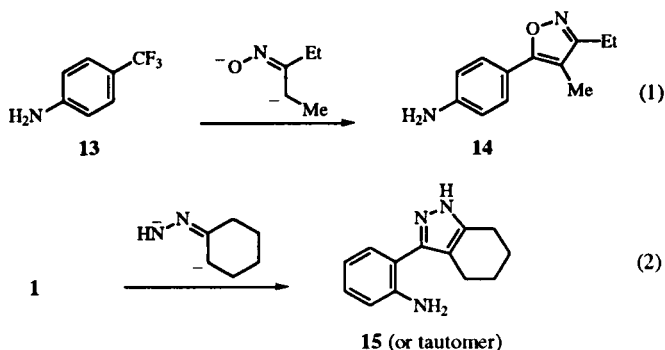
63%, and the efficiency of an analogous synthesis of a 5-(4-aminophenyl)isoxazole from **13** and 3-pentanone oxime was only 17%. In contrast to the successful preparation of **12** from **1** and cyclohexanone oxime (yield 50%), the attempted reactions of **1** with dilithio derivatives of cyclopentanone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



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 $5 \rightarrow 8-12$. 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 $3 \rightarrow 4$.

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.



EXPERIMENTAL

Reagents were obtained and used as supplied from Aldrich. Oximes [14] and hydrazones [13] were synthesized by using the published procedures. The ^1H 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; ^1H 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 $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}$: 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; ^1H 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 $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$: 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; ^1H 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 $\text{C}_{12}\text{H}_{13}\text{ClN}_2\text{O}$: 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; ^1H 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 $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}$: 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; ^1H 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 $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$: 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); ^1H 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); ^1H 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 $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$: 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; ^1H 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 $\text{C}_{13}\text{H}_{15}\text{N}_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.03; H, 7.15; N, 19.54.

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