Preparation of Novel 1,2,4-Thiadiazoles by Cyclization With 4-Methylbenzenesulfonyl Cyanide (Tosyl Cyanide) [1]

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The preparation of 1,2,4-thiadiazoles with a di-*tert*-butylphenol substituent at the thiadiazole 3-position is described. A thermally generated nitrile sulfide was reacted with tosyl cyanide in a 1,3-dipolar cyclization reaction to provide a thiadiazole intermediate containing a labile 5-tosyl substituent.

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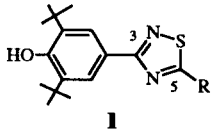
Derivatives of 2,6-di-*tert*-butylphenol are of interest as potential nonsteroidal antiinflammatory drugs. In some examples [3-7], a heterocyclic ring is directly attached, or linked by a carbon or heteroatom chain to the phenol 4-position.

As part of an antiinflammatory drug discovery program, we envisioned the preparation of a series of 1,2,4-thiadiazoles **1** containing a di-*tert*-butylphenol substituent at the thiadiazole 3-position.



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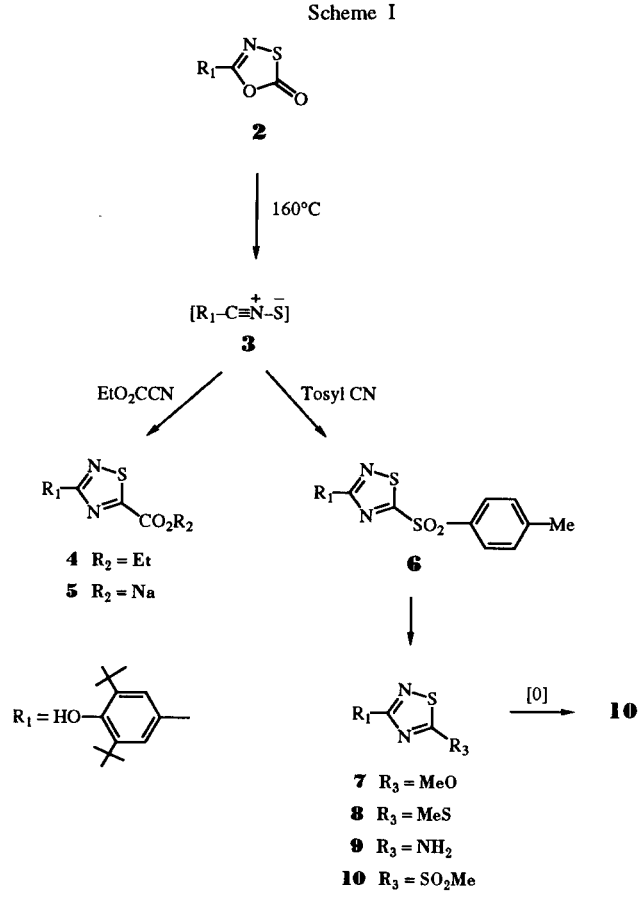
We required a method of synthesis that would permit functional variation at the thiadiazole 5-position. Our initial efforts by traditional methods of thiadiazole synthesis [8,9] employing amidine and benzamideoxime starting materials were unsuccessful. The target compounds were ultimately prepared by the 1,3-dipolar cycloaddition [10,11] of a nitrile sulfide **3** (Scheme I) with an appropriate dipolarophile. The nitrile sulfide was generated *in situ* by thermal decarboxylation of a 1,3,4-oxathiazol-2-one **2** [12].

Reaction of **3** with ethyl cyanoformate gave the desired thiadiazole ester **4** in moderate yield. The nitrile [13] derived from **3** by loss of elemental sulfur was formed as a side product and removed by chromatography. Saponification of **4** gave the corresponding carboxylic acid salt **5**.

When the dipolarophile for the cycloaddition reaction was changed from ethyl cyanoformate to 4-methylbenzenesulfonyl cyanide (tosyl cyanide), a versatile thiadiazole intermediate **6** was formed in high yield. The 5-tosyl substituent of **6** was readily displaced by methoxide, thiomethoxide, and ammonia to yield analogs **7**, **8**, and **9**, respectively. A sulfone **10** was prepared by oxidation of thioether **8**.

Tosyl cyanide has been employed in a variety of cyclization reactions [14-17]. We have now demonstrated the use of tosyl cyanide in the preparation of 3,5-disubstituted-1,2,4-thiadiazoles. Additional utility of **4** and **6**, as well as

Scheme I



the biological activity of all of these compounds, has been described elsewhere [18].

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover or Electrothermal capillary apparatus and are uncorrected. Elemental analyses were performed by the Analytical Chemistry staff of Parke-Davis (Ann Arbor, MI). The ir spectra were recorded as potassium bromide disks on a Nicolet MX-1 FTIR spectrometer. The ^{1}H nmr spectra were recorded on a Bruker AM 250 spectrometer, with chemical shifts reported in ppm relative to inter-

nal tetramethylsilane. Reactions were usually run under a nitrogen atmosphere, and organic solutions were concentrated at aspirator pressure on a rotary evaporator. Flash chromatography was performed with E. Merck silica gel 60, 230-400 mesh ASTM, according to the method of Still [19].

Ethyl 3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,2,4-thiadiazole-5-carboxylate (**4**).

A solution of ethyl cyanoformate (49.5 g, 0.50 mole) in 1,2-dichlorobenzene (500 ml) was heated to 155-160°. Solid **2** [12] (30.7 g, 0.10 mole) was added in portions over 1 hour. The mixture was heated for an additional hour, then cooled and added to a large flash chromatography column. Elution with 10% ether in hexane gave 26.5 g (73%) of **4**. A sample recrystallized from ether/hexane had mp 118-120°; ir: ν 3606, 1758, 1395, 1238 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.48 (t, 3H, CH_3), 1.51 (s, 18H, *t*-Bu), 4.53 (q, 2H, CH_2), 5.55 (s, 1H, OH), 8.18 (s, 2H, ArH).

Anal. Calcd. for $C_{19}H_{26}N_2O_3S$: C, 62.95; H, 7.23; N, 7.73. Found: C, 62.89; H, 7.19; N, 7.64.

Sodium 3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,2,4-thiadiazole-5-carboxylate (**5**).

A mixture of **4** (0.30 g, 0.83 mmoles) in ethanol (0.25 ml) and 1.0 *N* sodium hydroxide (1.5 ml) was stirred at reflux for 2 hours. The cooled mixture was diluted with ether, and the organic layer was decanted and discarded. Ethanol was added to the aqueous phase, and the mixture was evaporated to dryness. The residue was again treated with ethanol and evaporated. The final residue solidified to a white powder which was washed with ether to yield 0.20 g (69%) of **5**, mp > 300°; ir: ν 3481, 2956, 1635, 1400 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.44 (s, 18H, *t*-Bu), 7.39 (s, 1H, OH), 8.02 (s, 2H, ArH).

Anal. Calcd. for $C_{17}H_{21}N_2O_3SNa \cdot H_2O$: C, 54.53; H, 6.19; N, 7.48. Found: C, 54.65; H, 6.14; N, 7.43.

2,6-Bis(1,1-dimethylethyl)phenyl-4-[[(4-methylphenyl)sulfonyl]-1,2,4-thiazol-3-yl]-phenol (**6**).

Prepared from **2** [12] (30.7 g, 0.10 mole) and 4-methylbenzenesulfonyl cyanide (27.0 g, 0.15 mole) in 1,2-dichlorobenzene (100 ml) by the procedure described for the preparation of **4**. Flash chromatography of the crude reaction mixture gave 37.7 g (85%) of **6**. A sample recrystallized from ether/hexane had mp 136-138°; ir: ν 3629, 1598, 1388, 1158 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.47 (s, 18H, *t*-Bu), 2.45 (s, 3H, CH_3), 5.56 (s, 1H, OH), 7.40 (d, 2H, ArH), 8.05 (s, 2H, ArH), 8.05 (d, 2H, ArH).

Anal. Calcd. for $C_{23}H_{28}N_2O_3S_2$: C, 62.13; H, 6.35; N, 6.30. Found: C, 62.13; H, 6.46; N, 6.14.

2,6-Bis(1,1-dimethylethyl)-4-(5-methoxy-1,2,4-thiadiazol-3-yl)-phenol (**7**).

A mixture of **6** (0.50 g, 1.1 mmoles) and sodium methoxide (0.070 g, 1.3 mmoles) in methanol (25 ml) was stirred at room temperature for 18 hours. The solvent was evaporated and the residue dissolved in ethyl acetate. The solution was washed with 1.0 *N* hydrochloric acid and brine, the dried (anhydrous sodium sulfate) and evaporated. Purification of the residue by flash chromatography (15% ether in hexane) gave 0.20 g (56%) of **7**, mp 103-104°; ir: ν 3633, 2932, 1540, 1236 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.49 (s, 18H, *t*-Bu), 4.23 (s, 3H, CH_3), 5.48 (s, 1H, OH), 8.04 (s, 2H, ArH).

Anal. Calcd. for $C_{17}H_{24}N_2O_2S$: C, 63.72; H, 7.55; N, 8.74. Found: C, 63.50; H, 7.55; N, 8.80.

2,6-Bis(1,1-dimethylethyl)-4-(5-methylthio)-1,2,4-thiadiazol-3-yl)-phenol (**8**).

Prepared from **6** (1.0 g, 2.2 mmoles) and sodium thiomethoxide (0.19 g, 2.7 mmoles) by the procedure described for the preparation of **7**. Recrystallization of the purified product after chromatography from ether/hexane gave 0.53 g (70%) of **8**, mp 120-121°; ir: ν 3629, 2956, 1411, 1294 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.50 (s, 18H, *t*-Bu), 2.77 (s, 3H, CH_3), 5.49 (s, 1H, OH), 8.11 (s, 2H, ArH).

Anal. Calcd. for $C_{17}H_{24}N_2OS_2$: C, 60.67; H, 7.19; N, 8.33. Found: C, 60.61; H, 6.97; N, 8.12.

4-(5-Amino-1,2,4-thiadiazol-3-yl)-2,6-bis(1,1-dimethylethyl)-phenol (**9**).

A solution of **6** (2.0 g, 4.5 mmoles) in ethanol (50 ml) was saturated with gaseous ammonia for 10 minutes, then heated in an oil bath at 60°. When the amber color of the reaction mixture had dissipated, the solution was cooled, again saturated with ammonia, and heated at 60° for 16 hours. The cooled reaction mixture was evaporated and the residue dissolved in ethyl acetate. The solution was washed with water, dried (anhydrous sodium sulfate), and evaporated. The crude product was purified by flash chromatography (20% ethyl acetate in hexane), then recrystallized from ethyl acetate/hexane to yield 1.1 g (78%) of **9**, mp 215-217°; ir: ν 3624, 1616, 1523, 1346 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.48 (s, 18H, *t*-Bu), 5.45 (s, 1H, OH), 5.68 (br s, 2H, NH_2), 7.99 (s, 2H, ArH).

Anal. Calcd. for $C_{16}H_{23}N_3OS$: C, 62.91; H, 7.59; N, 13.76. Found: C, 62.87; H, 7.58; N, 13.36.

2,6-Bis(1,1-dimethylethyl)-4-[5-(methylsulfonyl)-1,2,4-thiadiazol-3-yl]-phenol (**10**).

A solution of **8** (1.0 g, 3.0 mmoles) in ethanol (15 ml) was treated with a solution of magnesium monoperoxyphthalate hexahydrate (2.9 g, 5.9 mmoles) in water (10 ml). The mixture was stirred at room temperature for 18 hours, then evaporated and the residue dissolved in ethyl acetate. The solution was washed with 10% aqueous sodium bicarbonate and brine, then dried (anhydrous sodium sulfate) and evaporated. Recrystallization of the residue from ethyl acetate/hexane gave 0.45 g (41%) of **10**, mp 181-182°; ir: ν 3588, 1385, 1331, 1241 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.50 (s, 18H, *t*-Bu), 3.43 (s, 3H, CH_3), 5.62 (s, 1H, OH), 8.14 (s, 2H, ArH).

Anal. Calcd. for $C_{17}H_{24}N_2O_3S_2$: C, 55.40; H, 6.56; N, 7.60. Found: C, 55.44; H, 6.54; N, 7.28.

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