Synthesis and Transformations of 2,6-Bis(1,1-dimethylethyl)-4-[2-(thiazolyl)ethenyl]phenols

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(Thiazolylethenyl)phenols were prepared as potential antiinflammatories by reaction of thiazole 4- and 5-acetic acid derivatives with 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde. Alternatively, an arylethenyl methyl ketone was brominated and the bromoketone product reacted with methyl dithiocarbamate, ammonium dithiocarbamate, or thiourea.

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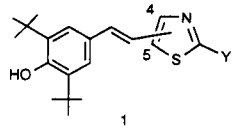
A variety of compounds containing the 2,6-di-*tert*-butylphenol substructure are of interest as potential nonsteroidal antiinflammatory drugs (NSAIDS). In some examples [1,2] a heterocyclic ring is linked by an olefinic group to the 4-position of the phenol. Antiinflammatory activity has also been found in a series of di-*tert*-butylphenols containing a directly attached thiazole ring [3]. Based on these precedents, we decided to prepare a novel series of (thiazolylethenyl)phenols **1**.



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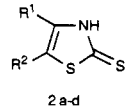


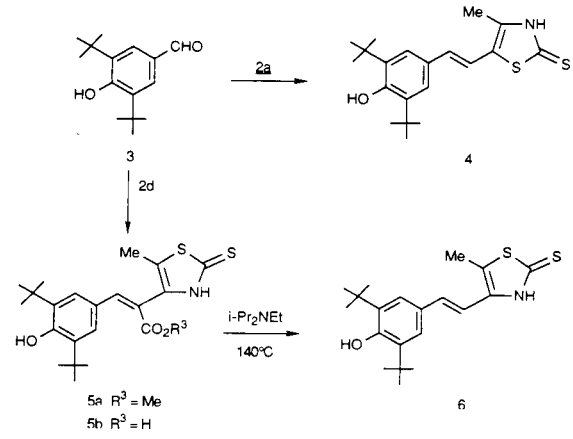
2 a-d

2	R^1	R^2
a	Me	CO_2H
b	CO_2H	H
c	CO_2H	Me
d	CO_2Me	Me

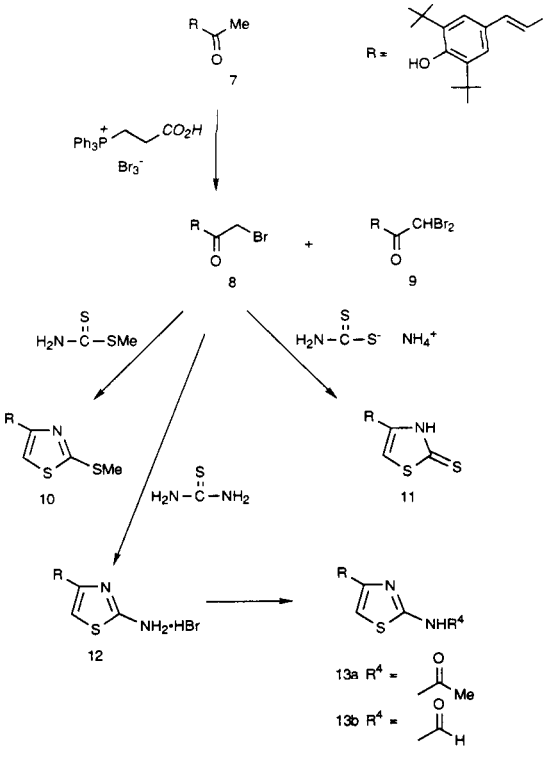
Styrylthiazoles in which the olefinic linkage is at the 4- or 5-position of the thiazole ring were first described by Southwick [4]. Since then a few scattered additional examples have appeared, primarily in the patent literature [5-7].

We initially prepared a group of known thiazoleacetic acid derivatives **2a-d** for use in Knoevenagel-type condensation reactions with aldehydes **3** (Scheme I). Thiazole acid **2a** [8] was condensed with **3** to provide the olefin **4** in low yield, but similar reactions with **2b** [9] and **2c** [10] yielded only complex mixtures. However, ester **2d** [10] reacted with **3** to provide an intermediate olefinic ester **5a**, which was saponified to acid **5b**. Thermal decarboxylation of **5b** yielded the target **6**.

Scheme I



Scheme II



Scheme II illustrates an alternate route to compounds of type **1**. An arylethenyl methyl ketone **7** [11] was brominated with 2-carboxyethyltriphenylphosphonium perbromide [12] to provide α-bromoketone **8** plus a minor amount of dibromide **9**. Reaction of **8** with methyl dithiocarbamate [13], ammonium dithiocarbamate [14], or thiourea gave the desired thiazoles **10**, **11**, and **12**, respectively. Acetyl **13a** and formyl **13b** derivatives of **12** were also prepared. The magnitude of the ^{1}H nmr coupling constants (J = 16 Hz) for the olefinic protons of the products indicated the *E* configuration for the compounds [15].

Compound **13a** was found to be an inhibitor of inflammation (IC_{40} = 14.9 mg/kg) when dosed orally in the rat mycobacterium footpad edema test [16]. Unfortunately, additional testing showed **13a** to be ulcerogenic.

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 Brüker AM 250 spectrometer, with chemical shifts reported in ppm relative to internal 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 [17].

(*E*)-5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-4-methyl-2(3*H*)-thiazolethione (**4**).

A mixture of **2a** [8] (4.1 g, 22 mmoles), **3** (5.1 g, 22 mmoles) and piperidine (4.5 ml, 3.9 g, 46 mmoles) in pyridine (50 ml) plus toluene (75 ml) was stirred at reflux with the use of a Dean-Stark trap for 28 hours. The cooled mixture was evaporated and the residue partitioned between ethyl acetate (350 ml) and 1.2*N* hydrochloric acid (150 ml). The organic layer was washed several additional times with dilute acid and water, then stirred with anhydrous sodium sulfate and Celite filter-aid. The dried solution was filtered and evaporated and the residue stirred with hexane (200 ml). The precipitated solid was recrystallized from aqueous acetonitrile to yield 2.2 g (28%) of **4**. An additional recrystallization from aqueous acetonitrile/*N*,*N*-dimethylformamide provided an analytical sample, mp 270° dec; ir: ν 3631, 1424, 1261, 1073 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.39 (s, 18H, *t*-Bu), 2.26 (s, 3H, CH_3), 6.43 (d, 1H, J = 16 Hz, olefinic), 6.94 (d, 1H, J = 16 Hz, olefinic), 7.11 (s, 1H, OH), 7.26 (s, 2H, ArH), 13.11 (br s, 1H, NH).

Anal. Calcd. for $C_{20}H_{27}NOS_2$: C, 66.43; H, 7.53; N, 3.87. Found: C, 66.23; H, 7.38; N, 3.61.

(*E*)-Methyl α-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,3-dihydro-5-methyl-2-thioxo-4-thiazoleacetate (**5a**).

A mixture of **2d** [10] (12.6 g, 60 mmoles), **3** (14.0 g, 60 mmoles), piperidine (6.0 ml, 5.2 g, 61 mmoles), and *p*-toluenesulfonic acid monohydrate (0.25 g, 5.3 mmoles) in methanol (150 ml) was stirred at reflux for 42 hours. The cooled mixture was concentrated to one-half of the original volume and added to a mixture of ice and 1.2*N* hydrochloric acid (800 ml). The precipitated solid was filtered and washed with water. The crude product was purified by flash chromatography (8-16% *tert*-butyl methyl ether in toluene) to yield 18.6 g (74%) of **5a**, mp 200-204°. Recrystallization of a sample from toluene/hexane raised the mp to 203° dec; ir: ν 3561, 1702, 1598, 1435 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.38 (s, 18H, *t*-Bu), 1.91 (s, 3H, CCH_3), 3.82 (s, 3H, OCH_3), 5.64 (s, 1H, OH), 7.21 (s, 2H, ArH), 7.97 (s, 1H, olefinic), 10.00 (br s, 1H, NH).

Anal. Calcd. for $C_{22}H_{29}NO_3S_2$: C, 62.97; H, 6.97; N, 3.34. Found: C, 63.36; H, 6.96; N, 3.21.

(*E*)-α-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,3-dihydro-5-methyl-2-thioxo-4-thiazoleacetic Acid (**5b**).

A suspension of **5a** (9.5 g, 23 mmoles) in 95% ethanol (100 ml) was treated with a solution of 50% aqueous sodium hydroxide (9.0 g, 113 mmoles) diluted to 80 ml with water. The mixture was stirred at reflux for 3 hours, then concentrated to one-half of the original volume. The residue was partitioned between ether (200 ml) and ice water (600 ml). The aqueous layer was washed several times with fresh ether, then clarified with Celite filter-aid and acidified with 4.0*N* hydrochloric acid. The precipitated solid was washed with water to yield 4.3 g (47%) of **5b**. A sample recrystallized from aqueous acetonitrile had mp 225° dec; ir: ν 3626, 1686, 1428, 1208 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.33 (s, 18H, *t*-Bu), 2.08 (s, 3H, CH_3), 7.20 (s, 2H, ArH), 7.64 (s, 1H, OH or olefinic), 7.86 (s, 1H, OH or olefinic), 12.72 (br s, 1H, CO_2H), 13.03 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{27}NO_3S_2 \cdot 0.5CH_3CN$: C, 62.01; H, 6.74; N, 4.93. Found: C, 61.88; H, 6.85; N, 5.02.

(*E*)-4-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-5-methyl-2(3*H*)-thiazolethione (**6**).

A suspension of **5b** (4.1 g, 10 mmoles) in xylene (75 ml) was treated with *N*,*N*-diisopropylethylamine (5.2 ml, 3.9 g, 30 mmoles), and the mixture was stirred at reflux for 22 hours. The cooled mixture was added to ice and water (250 g) containing 10 ml of 50% aqueous sodium hydroxide. The aqueous layer was washed several times with ether, clarified with Celite filter-aid, and acidified with 4.0*N* hydrochloric acid. The precipitated solid was washed with water to yield 1.9 g (53%) of **6**. A sample recrystallized from ethyl acetate/hexane had mp 268° dec; ir: ν 3642, 1477, 1236, 1034 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.41 (s, 18H, *t*-Bu), 2.28 (s, 3H, CH_3), 6.69 (d, 1H, J = 16 Hz, olefinic), 7.20-7.30 (m, 4H, olefinic, OH, and ArH), 13.09 (s, 1H, NH).

Anal. Calcd. for $C_{20}H_{27}NOS_2$: C, 66.43; H, 7.53; N, 3.87. Found: C, 66.20; H, 7.60; N, 3.59.

(*E*)-4-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-bromo-3-buten-2-one (**8**) and (*E*)-4-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,1-dibromo-3-buten-2-one (**9**).

A solution of **7** [11] (12.0 g, 44 mmoles) in tetrahydrofuran (150 ml) was cooled in ice and treated dropwise with a solution of 2-carboxyethyltriphenylphosphonium perbromide [12] (25.2 g, 44 mmoles) in tetrahydrofuran (150 ml). The mixture was stirred at room temperature for an additional 16 hours, and the precipitated solid was filtered, washed with fresh tetrahydrofuran, and discarded. The combined filtrates were evaporated and the residue purified by flash chromatography (25% hexane in dichloromethane). The initial isolated product was the dibromide **9** (3.0 g, 16%). A sample recrystallized from hexane had mp 128-130°; ir: ν 3617, 1677, 1427, 1209 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ

1.47 (s, 18H, *t*-Bu), 5.67 (s, 1H, OH), 5.97 (s, 1H, $CHBr_2$), 7.06 (d, 1H, J = 16 Hz, olefinic), 7.45 (s, 2H, ArH), 7.95 (d, 1H, J = 16 Hz, olefinic).

Anal. Calcd. for $C_{18}H_{24}Br_2O_2$: C, 50.02; H, 5.60; Br, 36.98. Found: C, 50.35; H, 5.65; Br, 36.69.

Additional column development provided 10.0 g (65%) of the main product **8**. A sample recrystallized from hexane had mp 126-127°; ir: ν 3620, 1648, 1426, 1214 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.46 (s, 18H, *t*-Bu), 4.11 (s, 2H, CH_2), 5.62 (s, 1H, OH), 6.78 (d, 1H, J = 16 Hz, olefinic), 7.42 (s, 2H, ArH), 7.67 (d, 1H, J = 16 Hz, olefinic).

Anal. Calcd. for $C_{18}H_{25}BrO_2$: C, 61.19; H, 7.13; Br, 22.62. Found: C, 61.15; H, 7.46; Br, 22.82.

(*E*)-2,6-Bis(1,1-dimethylethyl)-4-[2-[2-(methylthio)-4-thiazolyl]ethenyl]phenol (**10**).

A mixture of **8** (1.06 g, 3.0 mmoles) and methyl dithiocarbamate [13] (0.33 g, 3.1 mmoles) in absolute ethanol (10 ml) was heated on the steam bath for 45 minutes. The precipitated solid was filtered and washed with hexane to yield 0.60 g (56%) of **10**. A sample recrystallized from aqueous acetonitrile had mp 98-101°; ir: ν 3614, 1416, 1226, 1146 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.47 (s, 18H, *t*-Bu), 2.74 (s, 3H, CH_3), 5.29 (s, 1H, OH), 6.86 (d, 1H, J = 16 Hz, olefinic), 6.96 (s, 1H, CHS), 7.35 (s, 2H, ArH), 7.41 (d, 1H, J = 16 Hz, olefinic).

Anal. Calcd. for $C_{20}H_{27}NOS_2$: C, 66.43; H, 7.53; N, 3.87. Found: C, 66.65; H, 7.49; N, 3.79.

(*E*)-4-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-2(3*H*)-thiazolone (**11**).

A suspension of freshly-prepared ammonium dithiocarbamate [14] (2.3 g, 21 mmoles) in absolute ethanol (20 ml) was cooled in ice and treated in portions over 20 minutes with **8** (3.8 g, 11 mmoles). The mixture was stirred at room temperature for 48 hours. Water (150 ml) was added, and the mixture was extracted with ether. The combined organic layers were washed several times with brine, dried (anhydrous sodium sulfate), and evaporated. The residue was purified by flash chromatography (0.1% acetic acid in dichloromethane followed by 1% ethyl acetate) to yield 1.4 g (37%) of **11**. A sample recrystallized from ethyl acetate/hexane had mp 240-243°; ir: ν 3580, 1552, 1457, 1213 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.40 (s, 18H, *t*-Bu), 6.75 (d, 1H, J = 16 Hz, olefinic), 6.93 (s, 1H, CHS), 7.24 (s, 2H, ArH), 7.29 (d, 1H, J = 16 Hz, olefinic), 13.33 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{25}NOS_2$: C, 65.66; H, 7.25; N, 4.03. Found: C, 65.57; H, 7.17; N, 3.96.

(*E*)-4-[2-(2-Amino-4-thiazoyl)ethenyl]-2,6-bis(1,1-dimethylethyl)-phenol Monohydrobromide (**12**).

Thiourea (0.22 g, 2.9 mmoles) was dissolved in absolute ethanol (5.0 ml) by heating briefly to reflux. To the warm solution was added dropwise a similarly warm solution of **8** (1.0 g, 2.8 mmoles) in ethanol (12 ml). The mixture was stirred at reflux for 2 hours, then cooled and evaporated. Trituration of the residue with a few ml of warm acetonitrile provided 0.65 g (56%) of **12**, mp 244° dec; ir: ν 3630, 1627, 1438, 1213 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.41 (s, 18H, *t*-Bu), 6.84 (d, 1H, J = 16 Hz, olefinic), 6.88 (s, 1H, CHS), 7.11 (d, 1H, J = 16 Hz, olefinic), 7.26 (s, 2H, ArH), 7.29 (br s, 1H, OH), 8.97 (br s, NH_2).

Anal. Calcd. for $C_{19}H_{26}N_2OS \cdot HBr$: C, 55.47; H, 6.62; N, 6.81. Found: C, 55.68; H, 6.73; N, 6.88.

(*E*)-*N*-[4-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-2-thiazolyl]acetamide (**13a**).

A suspension of **12** (2.1 g, 5.1 mmoles) in ether (75 ml) was cooled in ice and treated with triethylamine (1.0 ml, 0.73 g, 7.2 mmoles). The mixture was stirred for 2 hours, filtered and the filtrate evaporated. The residue was dissolved in toluene (75 ml) and treated with acetic anhydride (1.5 ml, 1.6 g, 16 mmoles). The mixture was stirred at reflux for 3 hours, then evaporated. Recrystallization of the residue from aqueous acetonitrile gave 1.6 g (86%) of **13a**, mp 120° dec; ir: ν 3630, 1685, 1550, 1437 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.41 (s, 18H, *t*-Bu), 2.15 (s, 3H, CH_3), 6.94 (d, 1H, J = 16 Hz, olefinic), 7.07 (s, 1H, CHS), 7.12 (s, 1H, OH), 7.19 (d, 1H, J = 16 Hz, olefinic), 7.24 (s, 2H, ArH), 12.13 (s, 1H, NH).

Anal. Calcd for $C_{21}H_{28}N_2O_2S$: C, 67.70; H, 7.58; N, 7.52. Found: C, 67.47; H, 7.56; N, 7.40.

(*E*)-*N*-[4-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-2-thiazolyl]formamide (**13b**).

In order to generate acetic formic anhydride, acetic anhydride (1.5 ml, 1.6 g, 16 mmoles) was cooled in ice and treated over 20 minutes with 99% formic acid (0.75 ml, 0.92 g, 20 mmoles). The mixture was heated at 50-60° for 2 hours, then cooled, and ether (5.0 ml) was added.

In a separate flask, **12** (2.3 g, 5.6 mmoles) was suspended in ether (75 ml), the mixture cooled in ice and treated with triethylamine (1.2 ml, 0.87 g, 8.6 mmoles). After stirring for 2 hours, the solid was filtered and discarded and the filtrate condensed to 15 ml. This ether solution was added to the above anhydride solution and the new mixture was stirred at room temperature for 16 hours. The precipitated solid was filtered and washed with hexane to yield 1.4 g (69%) of crude product. A sample was purified by flash chromatography (2% ethyl acetate in dichloromethane) followed by recrystallization from aqueous acetonitrile to yield **13b**, mp 217-219°; ir: ν 3631, 1695, 1560, 1280 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.47 (s, 18H, *t*-Bu), 5.35 (s, 1H, OH), 6.87 (s, 1H, CHS), 6.90 (d, 1H, J = 16 Hz, olefinic), 7.24 (d, 1H, J = 16 Hz, olefinic), 7.31 (s, 2H, ArH), 8.53 (s, 1H, CHO), 11.82 (br s, 1H, NH).

Anal. Calcd. for $C_{20}H_{26}N_2O_2S$: C, 67.00; H, 7.31; N, 7.82. Found: C, 66.83; H, 7.22; N, 7.86.

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