Figure 1. NOESY spectra of **7** (top) and **8** (bottom).

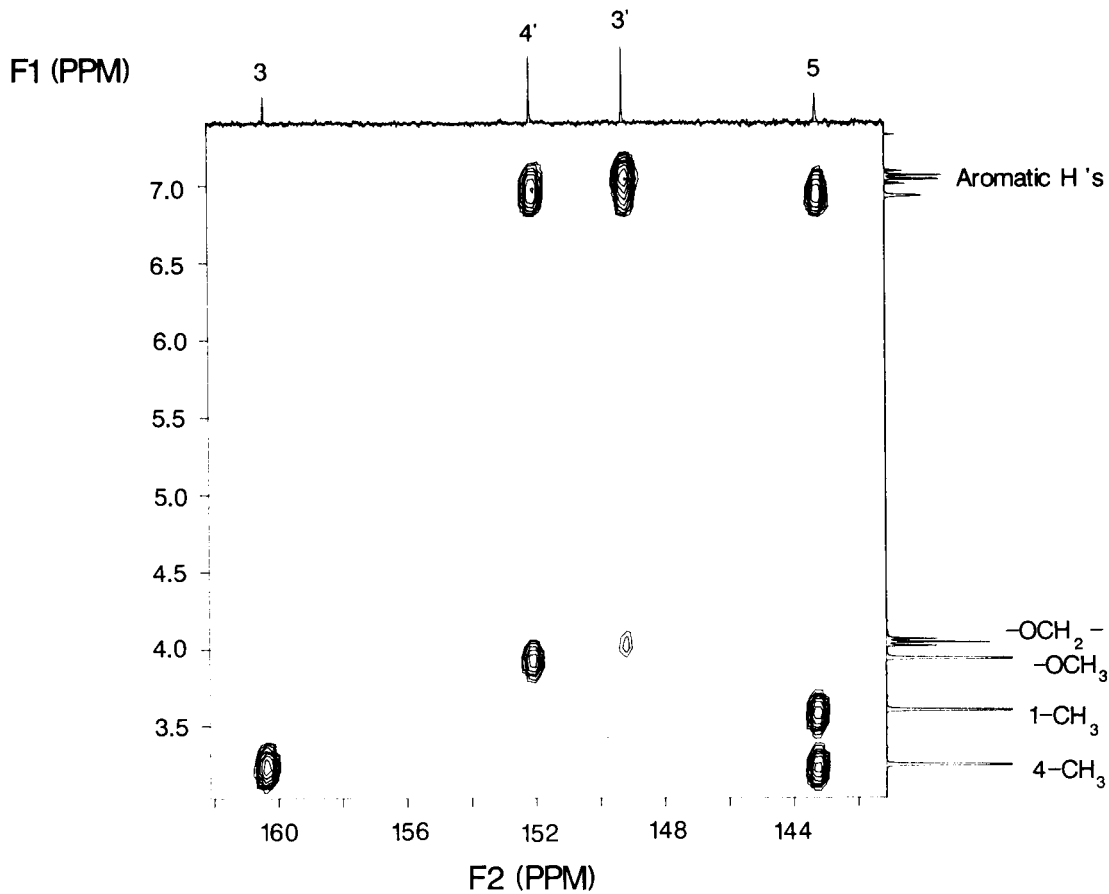
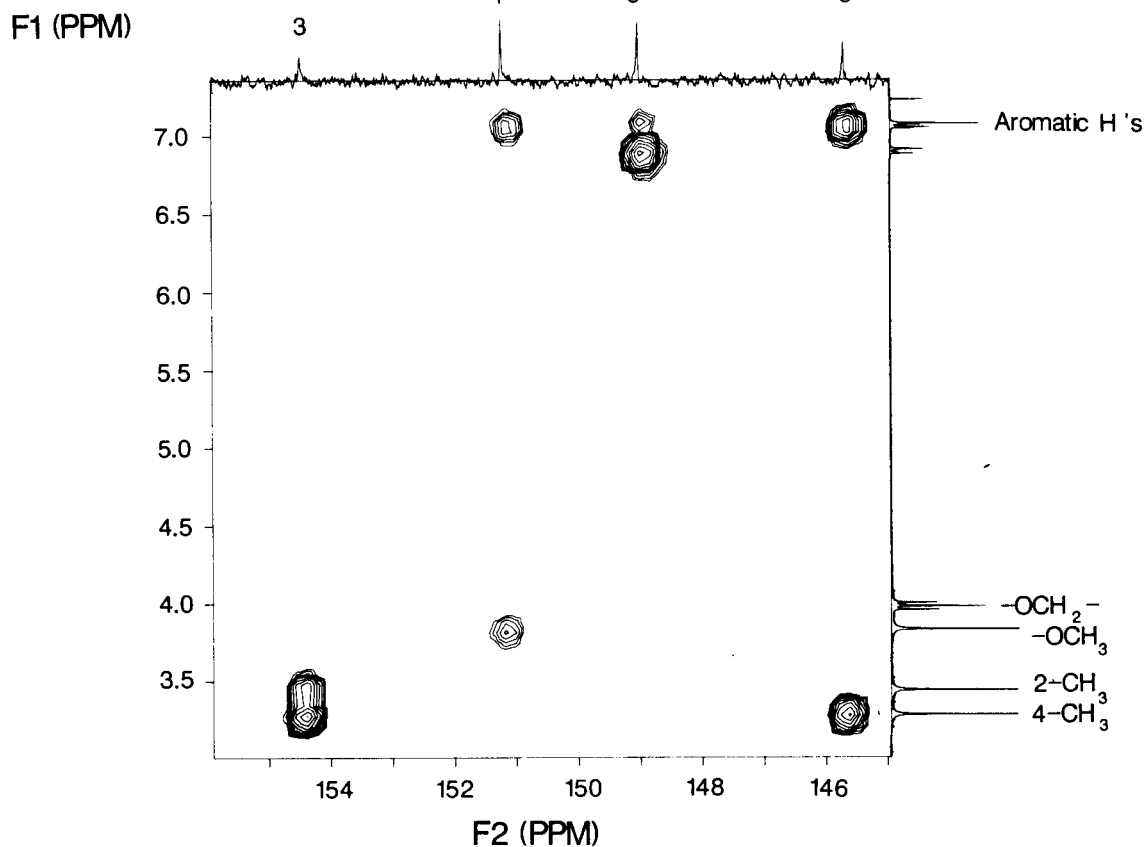
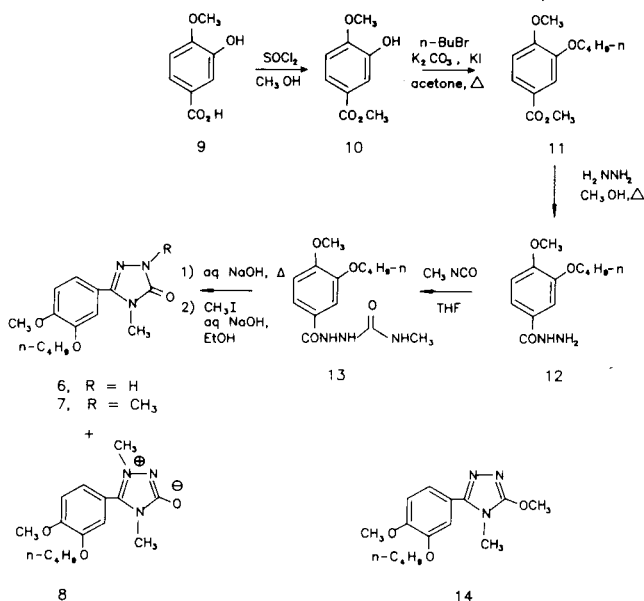


Figure 2. LR-HETCOR spectra of **7** (top) and **8** (bottom).

Kubota and Uda [6] gave the 2,4-dialkyl-3*H*-1,2,4-triazol-3-one **7** in 33% yield and an isomeric by-product which was isolated in 7.6% yield.



Literature precedent suggested that the structure of this product was probably that of mesoionic 1,2,4 triazole **8** [6]. The ¹H nmr spectrum of this product, however, did not permit conclusive differentiation between **8** and the isomeric *O*-methylated **14**. The ¹³C nmr spectrum on the other hand, appeared to rule out **14** as a possible structure since only one of the four methyl groups present in **14** occurred in the 50-60 ppm range that would be expected for a methyl ether. While the ¹³C chemical shifts were consistent with those expected for **8**, we desired a more definitive proof of structure without having to resort to an alternate synthesis.

This was accomplished by two separate approaches using 2D nmr spectroscopy. The first approach was two-dimensional nuclear Overhauser effect spectroscopy (NOESY). By this technique molecular structures are defined by the observation of crosspeaks between protons in close spatial proximity [7]. NOESY spectra for **7** and **8** are shown in Figure 1. For **7**, NOE crosspeaks are observed between the *ortho* aromatic protons and the protons of the 4-methyl group. No NOE crosspeaks are observed between the protons of the 2-methyl group and the aromatic protons. In contrast, for **8**, NOE crosspeaks are observed between both the protons of the 1- and 4-methyl groups and the *ortho* aromatic protons. These NOE crosspeaks establish the close spatial proximity of the protons of the 4-methyl group of **7** to the 5-aryl substituent and of both the 1- and 4-methyl substituents of **8** to the 5-aryl substituent. This permits definitive differentiation between the mesoionic **8** and the possible isomeric *O*-methylated product **14**.

The second approach, long-range heteronuclear correlated spectroscopy (LR-HETCOR), is used to define molecular structures based on the observation of scalar coupling between specific protons and carbons [8]. LR-HETCOR spectra of **7** and **8**, obtained with a pulse sequence optimized to observe typical three bond proton to carbon couplings, are shown in Figure 2. For **7**, the important crosspeaks observed are between the protons of the 4-methyl group and both C-3 and C-5, between the protons of the 2-methyl group and C-3, and between the *ortho* aromatic protons and C-5. For **8** crosspeaks are observed between the 1-methyl, 4-methyl and *ortho* aromatic protons and C-5. The protons of the 4-methyl substituent also exhibit a crosspeak to C-3. These crosspeaks define the methyl substitution patterns in **7** and **8** relative to the triazole carbons confirming the structures drawn.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas Hoover apparatus and are uncorrected. Mass spectra were obtained on a Finnigan MAT 4600 mass spectrometer. Nuclear magnetic resonance spectra were recorded on Varian FT-80A, VXR-300 and Gemini-300 spectrometers. The chemical shifts are given in parts per million from tetramethylsilane. The NOESY spectra were obtained using the Varian supplied pulse sequence by recording 256 increments over a spectral width of 2.5 kHz (1024 data points) in a phase sensitive mode. A mixing time of 1.7 seconds was used. The LR-HETCOR spectra were obtained in the absolute value mode using the Varian supplied pulse sequence with final delays set for 7 Hz proton-carbon couplings. The minimum sweep widths required to observe all proton and carbon resonances was used. The spectra were recorded with 128 time increments zero filled to give a final 256 by 2048 data matrix.

Methyl 3-Hydroxy-4-methoxybenzoate (**10**).

To a stirred, 0° suspension of 3-hydroxy-4-methoxybenzoic acid (16.8 g, 0.100 mole) and methanol (200 ml) was added dropwise thionyl chloride (8.0 ml, 0.11 mole). After being stirred at room temperature for 24 hours, the reaction was filtered and the methanol was evaporated at reduced pressure. The resultant oil was kugelrohr distilled (180°/0.02 mm) affording an oil which crystallized upon standing. Crystallization from ethyl acetate/hexane afforded 13.3 g (73%) of **10** as a colorless solid, mp 63-65°; ¹H nmr (deuteriochloroform): δ 3.94 (s, 3H), 3.88 (s, 3H), 5.75 (s, 1H), 6.87 (d, 1H, J = 8.1 Hz), 7.59-7.64 (m, 2H).

Anal. Calcd. for C₉H₁₀O₄: C, 59.34; H, 5.33. Found: C, 59.37; H, 5.51.

Methyl 3-(*n*-Butoxy)-4-methoxybenzoate (**11**).

A stirred mixture of **10** (16.4 g, 90.2 mmoles), *n*-butyl bromide (13.6 g, 99.2 mmoles), potassium carbonate (13.7 g, 99.4 mmoles), potassium iodide (1.52 g, 9.16 mmoles), and acetone (250 ml) was refluxed for 48 hours. The solvent was evaporated at reduced pressure and the concentrate was dissolved in a two phase mixture of ethyl acetate and water. The ethyl acetate layer was separated and the aqueous layer was extracted two more times

with ethyl acetate. The ethyl acetate extracts were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was evaporated at reduced pressure leaving a solid. Purification by a combination of flash chromatography [9] (dichloromethane) and crystallization from cyclohexane afforded 15.7 g (73%) of **11** as colorless needles, mp 59-60°; ¹H nmr (deuteriochloroform): δ 0.99 (t, 3H, J = 7.4 Hz), 1.51 (m, 2H), 1.85 (m, 2H), 3.89 (s, 3H), 3.92 (s, 3H), 4.07 (t, 2H, J = 6.7 Hz), 6.88 (d, 1H, J = 8.4 Hz), 7.54 (d, 1H, J = 2.0 Hz), 7.66 (dd, 1H, J = 8.4, 2.0 Hz).

Anal. Calcd. for C₁₃H₁₈O₄: C, 65.53; H, 7.61. Found: C, 65.61; H, 7.70.

3-(*n*-Butoxy)-4-methoxybenzoic Acid Hydrazide (**12**).

A stirred mixture of **11** (10.0 g, 42.0 mmoles), anhydrous hydrazine (6.7 ml, 0.21 mole) and methanol (50 ml) was refluxed for 3 days. The methanol was evaporated at reduced pressure and the resulting solid was crystallized from ethanol yielding 9.6 g (96%) of **12** as colorless, matted needles, mp 124-125°; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 0.94 (t, 3H, J = 7.3 Hz), 1.44 (m, 2H), 1.71 (m, 2H), 3.80 (s, 3H), 3.98 (t, 2H, J = 6.7 Hz), 4.41 (s, 2H), 6.99 (d, 1H, J = 8.2 Hz), 7.41-7.46 (m, 2H), 9.61 (s, 1H); ms: 238 (M⁺, 15), 207 (100).

Anal. Calcd. for C₁₂H₁₈N₂O₃: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.40; H, 7.71; N, 11.82.

1-[3-(*n*-Butoxy)-4-methoxybenzoyl]-4-methylsemicarbazide (**13**).

A stirred mixture of **12** (0.3877 g, 1.627 mmoles) and dry tetrahydrofuran (5 ml) was warmed until a homogeneous solution was obtained. To this solution was added methyl isocyanate (0.11 ml, 1.9 mmoles). A precipitate soon formed. After being stirred 17 hours the reaction was diluted with ether and the precipitate was collected by filtration. Crystallization from ethanol gave 0.3976 g (83%) of **13** as a colorless solid, mp 195-197°; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 0.94 (t, 3H, J = 7.3 Hz), 1.44 (m, 2H), 1.71 (m, 2H), 2.57 (d, 3H, J = 4.5 Hz), 3.81 (s, 3H), 4.00 (t, 2H, J = 6.6 Hz), 6.40 (bq, 1H, J = 4.5 Hz), 7.03 (d, 1H, J = 8.4 Hz), 7.47-7.53 (m, 2H), 7.81 (bs, 1H), 9.97 (bs, 1H).

Anal. Calcd. for C₁₄H₂₁N₃O₄: C, 56.94; H, 7.17; N, 14.23. Found: C, 56.78; H, 7.19; N, 14.23.

5-[3-(*n*-Butoxy)-4-methoxyphenyl]-4-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**6**).

A stirred mixture of **13** (23.5 g, 79.6 mmoles) and 1 molar aqueous sodium hydroxide (135 ml, 0.135 mole) was refluxed for 6 hours. The reaction was allowed to cool to room temperature where it was stirred for 17 hours. The reaction was then acidified by the dropwise addition of 4 molar aqueous hydrochloric acid (36 ml, 0.14 mole). The reaction was transferred to a separatory funnel where it was extracted several times with ethyl acetate. The ethyl acetate extracts were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was evaporated at reduced pressure leaving an oil which solidified upon standing. Two crystallizations from ethyl acetate/hexane gave 15.5 g (70%) of **6** as colorless plates, mp 96-98°; ¹H nmr (deuteriochloroform): δ 0.98 (t, 3H, J = 7.3 Hz),

1.41 (m, 2H), 1.72 (m, 2H), 3.82 (s, 3H), 3.88 (s, 3H), 4.02 (t, 2H, J = 6.8 Hz), 6.94 (d, 1H, J = 8.2 Hz), 7.00-7.19 (m, 2H), 10.83 (bs, 1H).

Anal. Calcd. for C₁₄H₁₉N₃O₃: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.34; H, 6.93; N, 15.21.

5-[3-(*n*-Butoxy)-4-methoxyphenyl]-2,4-dimethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**7**) and Anhydro-5-[3-(*n*-butoxy)-4-methoxyphenyl]-1,4-dimethyl-3-hydroxy-1,2,4-triazolium Hydroxide (**8**).

Methyl iodide (4.9 ml, 79 mmoles) was added to a stirred solution of **6** (18.0 g, 64.9 mmoles), 1 molar aqueous sodium hydroxide (78 ml, 78 mmoles) and ethanol (13 ml). After being stirred at room temperature for 17 hours, the reaction was transferred to a separatory funnel where it was extracted several times with ethyl acetate. The ethyl acetate extracts were combined, washed with saturated sodium chloride, and dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was evaporated at reduced pressure leaving an oil which solidified upon standing. Flash chromatography (70% ethyl acetate/dichloromethane) afforded a higher R_f material which after crystallization from ethyl acetate/hexane gave 6.2 g (33%) of **7** as colorless, matted needles, mp 112-114°; ¹H nmr (deuteriochloroform): δ 0.99 (t, 3H, J = 7.4 Hz), 1.51 (m, 2H), 1.84 (m, 2H), 3.38 (s, 3H), 3.53 (s, 3H), 3.92 (s, 3H), 4.06 (t, 2H, J = 6.8 Hz), 6.95 (d, 1H, J = 8.7 Hz), 7.09-7.13 (m, 2H); ¹³C nmr (deuteriochloroform): 13.84, 19.17, 29.46, 31.14, 32.43, 56.04, 68.90, 111.37, 112.25, 119.34, 120.49, 145.73, 148.97, 151.16, 154.45 ppm; ms: 291 (M⁺, 100), 235 (86), 220 (69).

Anal. Calcd. for C₁₅H₂₁N₃O₃: C, 61.84; H, 7.27; N, 14.42. Found: C, 62.18; H, 7.37; N, 14.23.

Also isolated was a lower R_f material which after crystallization from ethyl acetate/hexane gave 1.43 g (7.6%) of **8** as a colorless solid, mp 164-165°; ¹H nmr (deuteriochloroform): δ 1.00 (t, 3H, J = 7.3 Hz), 1.53 (m, 2H), 1.87 (m, 2H), 3.28 (s, 3H), 3.63 (s, 3H), 3.96 (s, 3H), 4.08 (t, 2H, J = 6.6 Hz), 6.96 (d, 1H, J = 1.7 Hz), 7.03 (dd, 1H, J = 8.3, 1.7 Hz), 7.09 (d, 1H, J = 8.3 Hz); ¹³C nmr (deuteriochloroform): 13.69, 19.02, 28.49, 30.92, 36.54, 56.00, 69.08, 111.85, 112.81, 113.96, 122.34, 143.32, 149.21, 152.06, 160.35 ppm; ms: 291 (M⁺, 72), 220 (100).

Anal. Calcd. for C₁₅H₂₁N₃O₃: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.77; H, 7.42; N, 14.33.

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