Synthesis of Ethyl 2-[(1-Aryl-1*H*-1,2,4-triazol-3-yl)oxy]propionates and Related Derivatives

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Received March 7, 1988

Alkylation of 1-aryl-1*H*-1,2,4-triazol-3-ols with ethyl 2-bromopropionate under basic conditions resulted in the formation of 2-[(1-aryl-1*H*-1,2,4-triazol-3-yl)oxy]propionic acid, ethyl esters. No *N*-alkylated products were detected. Similar alkylation of 2-oxo-5-phenyl-1,3,4-thiazole and the corresponding 1,3,4-oxadiazole gave only *N*-alkylated derivatives. With 4-hydroxy-6-phenylpyrimidine and 2-oxo-4-phenylthiazole, both *O*- and *N*-alkylation occurred. Structure assignments were based on ir and ^{13}C nmr spectral data.

J. Heterocyclic Chem., **25**, 1467 (1988).

Alkylation of nitrogen heterocycles containing hydroxy or oxo functionality is ordinarily unpredictable. Alkylation can occur at either nitrogen or oxygen, and mixtures of the two products are often obtained. We wish to report the syntheses of 2-[(1-aryl-1*H*-1,2,4-triazol-3-yl)oxy]propionic acid, ethyl esters **2a-g** by alkylation of 1-aryl-1*H*-1,2,4-triazol-3-ols **1a-g** with ethyl 2-bromopropionate under basic conditions. These esters and their derived carboxylic acids were found to be plant growth regulators [1]. We will also describe similar alkylations with related nitrogen heterocycles containing hydroxy/oxo functionality.

The precursors **1a-g** were prepared in high yield (Table I) by heating the appropriate 1-arylsemicarbazide in triethyl orthoformate with *p*-toluenesulfonic acid as catalyst. This is a slight modification of a procedure originally described by Whitehead and Traverso [2]. The 1-arylsemicarbazides were synthesized by the method of Hewitt [3], which involved the reaction of an aryl hydrazine, hydrochloride salt, with potassium cyanate in water.

Table I

1-Aryl-1*H*-1,2,4-triazol-3-ols

Compound	X	Yield, %	Mp °C	Calcd. % (Found) C	H	N
1a	H	91	277-280 [a]	59.62 (59.35	4.38 4.25	26.07 25.86)
1b	2-Cl	80	168-170 [b]	49.12 (49.10	3.09 2.90	21.48 21.31)
1c	3-Cl	79	305-308 [c]	49.12 (49.35	3.09 2.84	21.48 21.41)
1d	4-Cl	86	>300 [d]	49.12 (49.03	3.09 2.80	21.48 21.58)
1e	3-CF_3	91	263-265	47.17 (47.40	2.64 2.87	18.34 18.32)
1f	2,4-diCl	81	236-238	41.77 (41.90	2.19 2.02	18.27 18.24)
1g	3,4-diCl	95	302-304	41.77 (41.76	2.19 2.31	18.27 18.03)

[a] Lit [2] mp 273-274°. [b] Lit [11] mp 168-171°. [c] Lit [11] mp 310° dec. [d] Lit [11] mp 322° dec.

The only example in the literature dealing with alkylation of 1-aryl-1*H*-1,2,4-triazol-3-ols was reported by Atkinson and coworkers [4], who treated **1a** with dimethyl sulfate in aqueous sodium hydroxide, and assigned the structure of the product as the corresponding 2-methyl-3-one derivative. Our conditions involved treatment of **1a-g** with one equivalent of sodium methoxide [5] in methanol-dimethyl sulfoxide solution. This mixture was heated at 100° for one hour to insure salt formation. Ethyl 2-bromopropionate (one equivalent) was added to the hot solution, and heating was continued for four hours to yield **2a-g** (Table II) with yields in the range of 55-95%.

Table II

2-[(1-Aryl-1*H*-1,2,4-triazol-3-yl)oxy]propionic Acid, Ethyl Esters

Compound	X	Yield, %	Mp °C	Calcd. % (Found) C	H	N
2a	H	62	86-87	59.76 (59.91	5.79 5.82	16.08 16.29)
2b	2-Cl	93	-- [a]	52.80 (52.61	4.77 4.77	14.21 13.98)
2c	3-Cl	61	69-70	52.80 (52.51	4.77 4.59	14.21 14.05)
2d	4-Cl	56	61-63	52.80 (52.83	4.77 5.02	14.21 14.43)
2e	3-CF_3	78	104-106	51.07 (50.91	4.29 4.21	12.76 12.66)
2f	2,4-diCl	87	-- [a]	47.29 (47.09	3.97 4.06	12.73 12.48)
2g	3,4-diCl	65	84-86	47.29 (47.09	3.97 3.98	12.73 12.72)

[a] Oil.

Relevant spectral data are summarized in Table III. The ^1H nmr shifts of the methine and ring protons showed only slight variation for the seven compounds. Assignment of structure was based on the carbonyl absorptions in the infrared spectra. In each case, a single band was noted in the ester carbonyl region. *N*-Alkylation would have

resulted in a second carbonyl absorption. The infrared spectrum of **2g** in the solid state (potassium bromide or Nujol) did show two ester carbonyl bands at 1764 and 1743 cm^{-1}, but in the solution spectrum (chloroform), only one was seen at 1760 cm^{-1}. This anomaly can possibly be explained by influences in the nature of the unit cell [6] or, more likely, by the presence of different crystal forms in the sample.

Table III

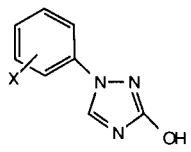
Relevant Spectral Data for Compounds **2a-g**

Compound	Methine Proton Shift (ppm)	Ring Proton Shift (ppm)	Carbonyl Region IR (cm^{-1})
2a	5.18	8.22	1757 [a]
2b	5.17	8.24	1760 [b]
2c	5.17	8.24	1720 [a]
2d	5.18	8.23	1748 [a]
2e	5.21	8.33	1753 [a]
2f	5.17	8.28	1720 [b]
2g	5.18	8.26	1764, 1743 [a] 1764, 1743 [c] 1760 [d]

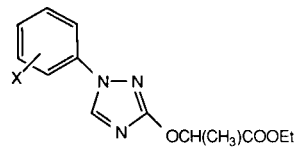
[a] Potassium bromide. [b] Neat. [c] Nujol. [d] Chloroform.

Under the same conditions used for the synthesis of **2a-g**, compound **1d** was allowed to react with ethyl bromoacetate. *O*-Alkylation occurred with the formation of **3** (70%). The infrared spectrum (potassium bromide) showed a single ester carbonyl band at 1748 cm^{-1}.

Alkylation with ethyl 2-bromopropionate was examined with related nitrogen heterocycles containing hydroxy/oxo functionality. Under similar reaction conditions used above, 2-oxo-5-phenyl-1,3,4-thiadiazole [7] and 2-oxo-5-phenyl-1,3,4-oxadiazole [8] were both alkylated exclusively on nitrogen, and led to the formation of **4** (60%) and **5** (51%), respectively. Relevant spectral data are summarized in Table IV. The ^1H nmr methine proton shifts were located at 5.14 and 4.86 ppm, respectively. The infrared spectra of **4** and **5** contained two carbonyl bands, indicating the presence of both ester the amide-like functionality. Similar treatment of 4-hydroxy-6-phenylpyrimidine [9] resulted in both *O*- and *N*-alkylation and led to the formation of **6** (14%) and **7** (72%), which were separated by chromatography. The methine proton shifts were essentially identical, but the infrared spectrum of **6** showed only one carbonyl band, whereas **7** showed two. Treatment of 2-oxo-4-phenylthiazole [10] also yielded *O*- and *N*-alkylated products with the formation of **8** (60%) and **9** (6%), which were separated by chromatography. In the ^1H nmr spectra of **8** and **9** the methine protons were widely separated and in the direction predicted. The infrared spectrum of **8** contained a single carbonyl band, and **9** showed both ester and amide carbonyl absorptions.



1a-g



2a-g

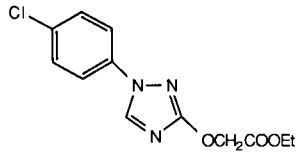


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Table IV

Relevant Spectral Data for Compounds **4-9**

Compound	Methine Proton Shift (ppm)	Carbonyl Region IR (cm^{-1})
4	5.14	1710, 1650 [a]
5	4.86	1790, 1725 [b]
6	5.44	1720 [b]
7	5.42	1746, 1658 [b]
8	5.42	1758 [b]
9	4.42	1750, 1670 [a]

[a] Neat. [b] Potassium bromide.

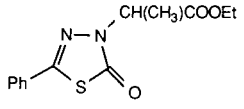
Table V summarizes the ^{13}C nmr data for seven compounds from the two classes of regiostructure represented in this study. There are three *O*-alkylated (**2a, 6** and **8**) and four *N*-alkylated (**4, 5, 7** and **9**) examples. Three parameters were found to correlate with the particular regiostructure represented. They were (1) the chemical shift of the *alpha*-methyl carbon, (2) the chemical shift of the

Table V

Relevant ^{13}C NMR Data for Compounds **2a** and **4-9**

	α-Methyl Carbon Shift (ppm)		Methine Carbon Shift (ppm)		J_{CH} (Hz)	
Compound	NCMe	OCMe	NCH	OCH	NCH	OCH
2a	–	17.7	–	73.6	–	151.6
4	15.8	–	54.9	–	140.6	–
5	15.2	–	53.9	–	139.7	–
6	–	17.4	–	70.4	–	162.3
7	16.7	–	52.5	–	142.1	–
8	–	17.1	–	75.1	–	153.7
9	14.9	–	53.7	–	134.5	–
Mean	15.7	17.4	53.7	73.0	139.2	155.9
Deviation	0.9	0.3	1.0	0.7	3.8	5.4

methine carbon and (3) the one-bond heteronuclear coupling constant (^1J) between the methine carbon and its attached proton.



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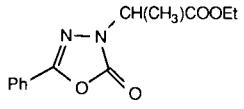

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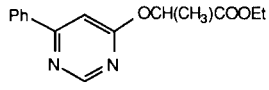

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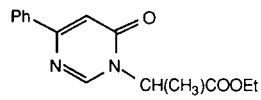

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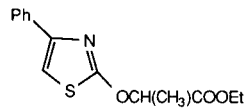

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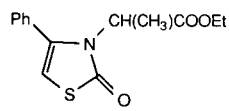

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As shown in Table V, the methyl resonance appeared at 15.7 (± 0.9) ppm for *N*-alkylated species, whereas the corresponding value for *O*-alkylated derivatives was 17.4 (± 0.3) ppm. This may be attributed to the difference in electronegativity between nitrogen and oxygen (3.0 versus 3.5 on the Pauling scale) [12] since, except for the pyrimidine compounds, there was little chemical shift variation with respect to the parent ring.

The difference in electronegativity was extended to the methine carbon as well. *N*-Alkylated species showed this resonance at 53.7 (± 1.0) ppm as opposed to the *O*-alkylated derivatives where the resonance appeared at 73.0 (± 0.7) ppm. This alone would be sufficient proof of the alkylation site, but further correlation was found in the one-bond C-H coupling within the methine fragment. For the *N*-alkylated derivatives, the value was 139.2 (± 3.8) Hz, and for the *O*-alkylated compounds, the corresponding value was nearly 17 Hz greater at 155.9 (± 5.4) Hz. This latter correlation is well documented [13a-b].

The carbon nmr data are entirely consistent with the findings from ir and, unlike proton nmr, offer an excellent alternate means of identifying the alkylation site in the series studied. Moreover, the generality of the method could probably be extended to many other heterocyclic systems as well.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Woelm 04530 silica gel and an FMI (RP SY) standard pump were used in all chromatographic separations (hplc). All ^1H nmr spectra were determined in deuteriochloroform solution.

The ^{13}C nmr spectra were run in 10% or greater concentration solutions with the solvent deuteriochloroform serving as a secondary reference, namely 77.0 ppm. A Bruker WM-250 FT NMR spectrometer was used to acquire and plot both the broad-band and gated decoupled spectra for which the spectrometer frequency was 62.89 MHz. Several thousand scans were accumulated and Fourier transformed into 16K data points for each experiment. The pulse width was 3.0 μsec corresponding to a 45 degree flip angle. The ^1H coupled ^{13}C nmr spectra were acquired in the gated mode with the proton decoupler turned on during the acquisition time to allow nOe build-up, and turned off during the pulse to permit retention of coupling information.

Assignment of the key ^{13}C nmr peaks was achieved by chemical shift considerations and/or coupling with the directly attached proton(s). Chemical shifts are accurate to ± 0.1 ppm, while coupling constants are accurate to ± 0.1 Hz.

General Synthesis of 1-Aryl-1*H*-1,2,4-triazol-3-ols **1a-g**.

A solution containing 0.08 mole of the appropriate 1-arylsemicarbazide [3] and 100 mg of *p*-toluenesulfonic acid in 200 ml of triethyl orthoformate was stirred and heated at steam bath temperature for 16 hours. The solvent was removed *in vacuo*. Compounds **1a**, **1d** and **1g** were crystallized from acetic acid, and **1b**, **1c**, **1e** and **1f** were crystallized from ethanol (Table I).

General Synthesis of 2-[(1-Aryl-1*H*-1,2,4-triazol-3-yl)oxy]propionic Acid, Ethyl Esters **2a-g**.

Sodium methoxide was prepared from 0.05 mole of sodium dissolved in 30 ml of methanol [5] and added to a solution containing 0.05 mole of the appropriate **1** in 100 ml of dimethyl sulfoxide. The mixture was stirred and heated at steam bath temperature for 1 hour. Ethyl 2-bromopropionate (0.05 mole) was added to the hot solution, and stirring and heating were continued for 4 hours. The mixture was poured into ice-water. In the cases of **2a**, **2c**, **2d**, **2e** and **2g**, the solids were collected and crystallized from ethanol (**2e** and **2g**), toluene (**2a** and **2c**) or toluene-hexane (**2d**). In the cases of **2b** and **2f**, the aqueous mixture was extracted with diethyl ether. The organic layer was washed with water and saturated brine solution and dried with anhydrous sodium sulfate. Removal of the solvent *in vacuo* yielded **2b** and **2f** as analytically pure oils. See Table II for yields, mp and microanalytical data; ^1H nmr: **2a**, δ 8.22 (s, 1H), 7.3-7.65 (m, 5H), 5.18 (q, 1H), 4.22 (q, 2H), 1.66 (d, 3H), 1.24 (t, 3H); **2b**, 8.24 (s, 1H), 7.3-7.6 (m, 4H), 5.17 (q, 1H), 4.21 (q, 2H), 1.66 (d, 3H), 1.28 (t, 3H); **2c**, 8.24 (s, 1H), 7.62 (s, 1H), 7.25-7.5 (m, 3H), 5.17 (q, 1H), 4.22 (q, 2H), 1.66 (d, 3H), 1.26 (t, 3H); **2d**, 8.23 (s, 1H), 7.56 (d, 2H), 7.42 (d, 2H), 5.18 (q, 1H), 4.25 (q, 2H), 1.66 (d, 3H), 1.25 (t, 3H); **2e**, 8.33 (s, 1H), 7.55-7.9 (m, 4H), 5.21 (q, 1H), 4.25 (q, 2H), 1.70 (d, 3H), 1.32 (t, 3H); **2f**, 8.28 (s, 1H), 7.3-7.6 (m, 3H), 5.17 (q, 1H), 4.21 (q, 2H), 1.64 (d, 3H), 1.26 (t, 3H); **2g**, 8.26 (s, 1H), 7.77 (s, 1H), 7.4-7.6 (m, 2H), 5.18 (q, 1H), 4.25 (q, 2H), 1.68 (d, 3H), 1.29 (t, 3H); ^{13}C nmr: **2a** δ 171.2, 168.2, 139.7, 137.0, 129.6, 127.5, 119.0, 73.7, 61.1, 17.8, 14.1.

[[1-(4-Chlorophenyl)-1*H*-1,2,4-triazol-3-yl]oxy]acetic Acid, Ethyl Ester (**3**).

Sodium methoxide was prepared by dissolving 1.2 g (0.052 mole) of sodium in 20 ml of methanol and added to a solution containing 10.0 g (0.051 mole) of **1d** in 100 ml of dimethyl sulfoxide. The mixture was stirred and heated at steam bath temperature for 2 hours. Ethyl bromoacetate (8.5 g, 0.051 mole) was added and heating was continued for 2 hours. The mixture was poured into ice-water. The solid was collected and crystallized from ethanol to yield 10.0 g (70%) of **3**, mp 143-145°; ir (potassium bromide): 1748 cm^{-1}; ^1H nmr: δ 8.23 (s, 1H), 7.56 (d, 2H), 7.46 (d, 2H), 4.91 (s, 2H), 4.26 (q, 2H), 1.28 (t, 3H).

Anal. Calcd. for $C_{12}H_{12}ClN_3O_3$: C, 51.17; H, 4.29; N, 14.92. Found: C, 50.94; H, 4.02; N, 15.04.

2-[2-Oxo-5-phenyl-1,3,4-thiadiazol-3(2*H*)-yl]propionic Acid, Ethyl Ester (**4**).

Sodium ethoxide was prepared from 0.35 g (15.2 mmoles) of sodium in 20 ml of absolute ethanol and added to a solution containing 2.7 g (15.2 mmoles) of 2-oxo-5-phenyl-1,3,4-thiadiazole [7] in 25 ml of dimethyl sulfoxide. The mixture was stirred and heated at steam bath temperature for 30 minutes. Ethyl 2-bromopropionate (2.7 g, 14.9 mmoles) was added and

heating was continued for 2 hours. The mixture was poured into ice-water, which was extracted with ethyl acetate. The organic layer was washed with water and saturated brine solution and dried with magnesium sulfate. The solvent was removed *in vacuo* to yield 2.5 g (60%) of **4** as an oil; ^{1}H nmr: δ 7.6-7.7 (m, 2H), 7.35-7.5 (m, 3H), 5.14 (q, 1H), 4.21 (q, 2H), 1.74 (d, 3H), 1.24 (t, 3H); ^{13}C nmr: δ 169.7, 169.5, 150.1, 130.7, 128.9, 126.0, 61.8, 54.5, 15.8, 14.0; ms: m/e 278 (M^+).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06. Found: C, 55.75; H, 5.50; N, 10.37.

2-[2-Oxo-5-phenyl-1,3,4-oxadiazol-3(2*H*)-yl]propionic Acid, Ethyl Ester (**5**).

Sodium ethoxide was prepared from 0.92 g (40.0 mmoles) of sodium in 25 ml of absolute ethanol and added to a solution containing 5.6 g (38.4 mmoles) of 2-oxo-5-phenyl-1,3,4-oxadiazole [8] in 50 ml of dimethyl sulfoxide. The mixture was stirred and heated at 85° for one hour. Ethyl 2-bromopropionate (7.25 g, 40.1 mmoles) was added and heating at 85° was continued for 3 hours. The mixture was poured into ice-water. The solid was collected and crystallized from ethanol to yield 5.1 g (51%) of **5**, mp 65-67°; ^{1}H nmr: δ 7.8-7.9 (m, 2H), 7.4-7.55 (m, 3H), 4.86 (q, 1H), 4.25 (q, 2H), 1.75 (d, 3H), 1.28 (t, 3H); ^{13}C nmr: δ 170.0, 153.6, 131.6, 128.9, 125.9, 123.8, 62.1, 53.9, 15.2, 14.0.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.59; H, 5.38; N, 10.68. Found: C, 59.41; H, 5.15; N, 10.58.

2-[(6-Phenyl-4-pyrimidinyl)oxy]propionic Acid, Ethyl Ester (**6**) and 2-[6-Oxo-4-phenyl-1(6*H*)-pyrimidinyl]propionic Acid, Ethyl Ester (**7**).

Sodium ethoxide was prepared from 0.6 g (26.1 mmoles) of sodium in 10 ml of absolute ethanol and added to a solution containing 4.4 g (25.6 mmoles) of 4-hydroxy-6-phenylpyrimidine [9] in 25 ml of dimethyl sulfoxide. The mixture was stirred and heated at 40° for 1 hour. Ethyl 2-bromopropionate (4.6 g, 25.4 mmoles) was added and the mixture was stirred at ambient temperature for 2 hours and at 50° for 2 hours. The mixture was poured into ice-water. The solid was collected and chromatographed (hplc) with hexane-ethyl acetate (2:1) as eluent. The faster moving component was collected to yield 1.0 g (14%) of **6** as an oil; ^{1}H nmr: δ 8.81 (s, 1H), 8.0-8.1 (m, 2H), 7.45-7.55 (m, 3H), 7.21 (s, 1H), 5.44 (q, 1H), 4.23 (q, 2H), 1.67 (d, 3H), 1.26 (t, 3H); ^{13}C nmr: δ 171.4, 169.1, 165.3, 158.0, 136.8, 130.7, 128.9, 127.1, 103.6, 70.5, 61.2, 17.4, 14.4.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.32; H, 5.67; N, 10.10.

The second component was collected to yield 5.0 g (72%) of **7**, mp 76-78°; ^{1}H nmr: δ 8.25 (s, 1H), 7.9-8.05 (m, 2H), 7.4-7.6 (m, 3H), 6.88 (s, 1H), 5.42 (q, 1H), 4.25 (q, 2H), 1.75 (d, 3H), 1.29 (t, 3H); ^{13}C nmr: δ 170.0, 161.1, 160.8, 148.7, 130.7, 128.8, 126.9, 109.2, 62.2, 52.5, 16.7, 14.0.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.37; H, 5.76; N, 10.12.

2-[(4-Phenyl-2-thiazolyl)oxy]propionic Acid, Ethyl Ester (**8**) and 2-[2-Oxo-4-phenyl-3(2*H*)-thiazolyl]propionic Acid, Ethyl Ester (**9**).

Sodium ethoxide was prepared from 0.65 g (28.3 mmoles) of sodium in 20 ml of absolute ethanol and added to a solution containing 4.7 g (28.4 mmoles) of 2-oxo-4-phenylthiazole [10] in 50 ml of dimethyl sulfoxide. The mixture was stirred and heated at steam bath temperature for 1 hour. Ethyl 2-bromopropionate (5.2 g, 28.7 mmoles) was added and heating was continued for 2 hours. The mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with 1*N* sodium hydroxide and saturated brine solutions and dried with anhydrous sodium sulfate. The solvent was removed *in vacuo* and the crude product was chromatographed (hplc) with hexane-ethyl acetate (4:1) as eluent. The faster moving component was collected to yield 4.7 g (60%) of **8**, mp 74-76°; ^{1}H nmr: δ 7.7-7.8 (m, 2H), 7.2-7.45 (m, 3H), 6.87 (s, 1H), 5.42 (q, 1H), 4.22 (q, 2H), 1.64 (d, 3H), 1.22 (t, 3H); ^{13}C nmr: δ 172.5, 170.8, 148.7, 134.4, 128.5, 127.8, 125.7, 105.1, 75.1, 61.2, 17.4, 14.1.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.88; H, 5.22; N, 4.91.

The second component was collected to yield 0.5 g (6%) of **9** as an oil; ^{1}H nmr: δ 7.2-7.5 (m, 5H), 5.93 (s, 1H), 4.42 (q, 1H), 4.15 (q, 2H), 1.58 (d, 3H), 1.29 (t, 3H); ^{13}C nmr: δ 171.9, 169.6, 137.3, 131.3, 129.7, 129.1, 128.9, 99.2, 61.7, 53.7, 14.9, 14.1.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.53; H, 5.54; N, 5.10.

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