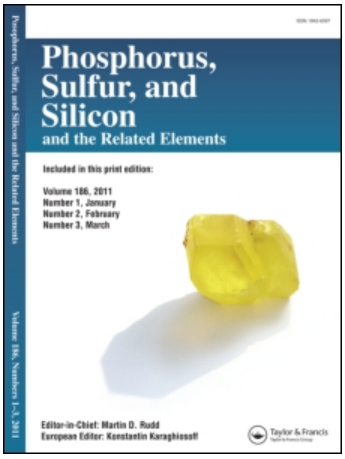

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF 4'-NITROPHENYL-2-AMINOBENZTHIAZOL-6-YL SULFIDES AND 4'-NITROPHENYL-2-AMINOBENZTHIAZOL-6-YL SULFONES CONTAINING DITHIOCARBAMATE

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To cite this Article Kandeel, Maymona M.(1990) 'SYNTHESIS OF 4'-NITROPHENYL-2-AMINOBENZTHIAZOL-6-YL SULFIDES AND 4'-NITROPHENYL-2-AMINOBENZTHIAZOL-6-YL SULFONES CONTAINING DITHIOCARBAMATE', Phosphorus, Sulfur, and Silicon and the Related Elements, 48: 1, 149 — 155
To link to this Article: DOI: 10.1080/10426509008045891
URL: http://dx.doi.org/10.1080/10426509008045891

Phosphorus, Sulfur, and Silicon, 1990, Vol. 48, pp. 149–155
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Printed in the United Kingdom

SYNTHESIS OF 4′-NITROPHENYL-2-AMINOBENZTHIAZOL-6-YL SULFIDES AND 4′-NITROPHENYL-2-AMINOBENZTHIAZOL-6-YL SULFONES CONTAINING DITHIOCARBAMATE

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(Received August 3, 1989; in final form September 29, 1989)

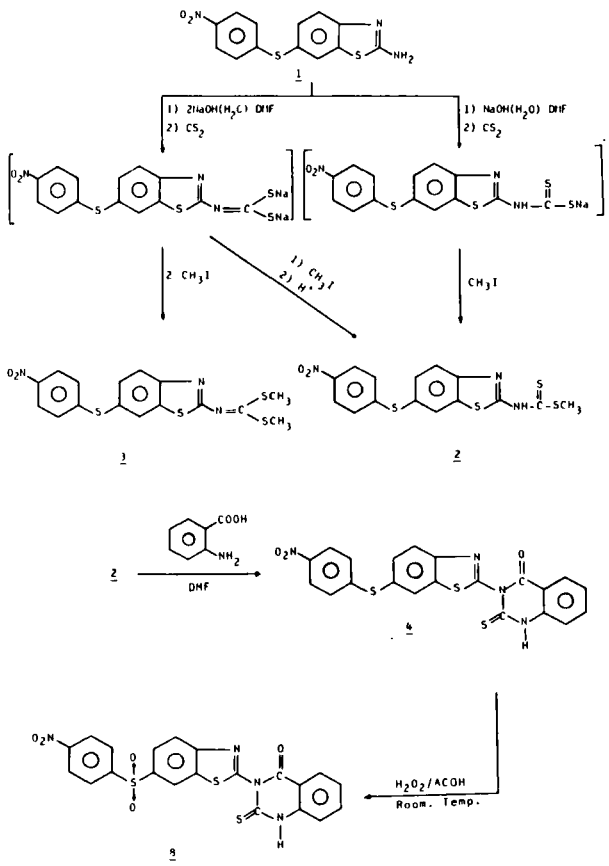
2-Amino-6-[(*p*-nitrophenyl)thio]benzthiazol (**1**) reacted with carbon disulfide in the presence of concentrated aqueous sodium hydroxide and with *N,N*-dimethylformamide as solvent, to form the sodium salt of dithiocarbonimidic acid. This compound was reacted without further purification with one mole of methyl iodide to give monoalkylated product (**2**). Reaction with two moles of methyl iodide gave the dialkylated product (**3**). Reaction of (**2**) with anthranilic acid yielded 2-(2,3-dihydro-2-thioxo-4(1H) quinoxa linon-3-yl)-6-[(*p*-nitrophenyl)thio]benzthiazol (**4**). Reaction of (**3**) with o-phenylene diamine gave 2-(2-benzimidazolylamino)-6-[(*p*-nitrophenyl)thio]-benzthiazole (**5**), and reaction of (**3**) with potassium salt of anthranilic acid gave 2-(2-imino benzoxazine)-6-[(*p*-nitrophenyl)thio]benzthiazol (**6**). (**6**) was condensed with a range of aromatic amine to form the 3-aryl quinazolinones ($\mathbf{7}_{a-d}$). Oxidation of compounds (**4–7**) using H_2O_2 in glacial acetic acid afforded the corresponding diaryl sulfones (**8–11**).

Key words: Synthesis, thiazolodiarylsulfides and diarylsulfones, arylthiobenzthiazol and dithiocarbamate.

It is thought that the fungicidal activity of many heterocyclic organo sulfur compounds may be attributed to the presence of an N–C–S linkage, as found in thiazoles and thiazolidinones.[1] Carbamates also show significant biological activity,[2] and have been used as biocides, insecticides and fungicides. Hence, it was of interest to incorporate these functional moieties into the well known antimicrobial diarylsulfides and diarylsulfones, which have found wide application in the therapy of functional diseases as antileprotics and antituberclouses.[3–6] With this in mind and, as a continuation of our previous work,[7–10] we have synthesized some heterocyclic compounds containing diarylsulfides, diarylsulfones and thiazole moieties in the hope that they may have a useful biological application.

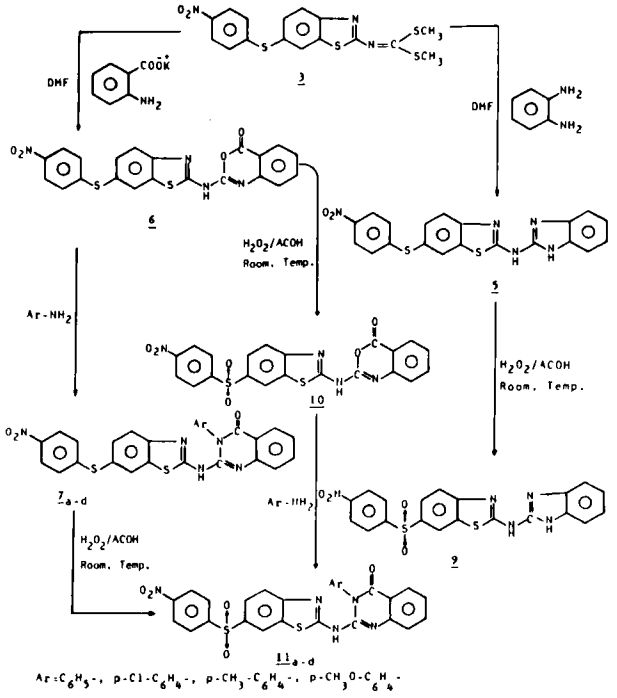
Thus 2-amino-6-[(*p*-nitrophenyl)thio]benzthiazol (**1**) was prepared by thiocyanation of 4-amino-4′-nitrodiphenylsulfide as reported previously.[11] Compound (**1**) was allowed to react with carbon disulfide in concentrated aqueous sodium hydroxide and *N,N*-dimethylformamide, the strong basic medium causing poorly nucleophilic amide to react with carbon disulfide.[12] When a 2:1 molar ratio of base to (**1**) was used the dithiocarbonimidic acid which was obtained was alkylated, without isolation, with one mole of methyliodide, to give the mono methyl derivative (**2**). Using two moles of methyliodide gave the dimethyl derivative (**3**).

The structure of methyldithiocarbamate (**2**) and dimethyldithiocarbamate (**3**) was in agreement with the supposed structures.



The 2-(methyl dithiocarbamate)-6-[(*p*-nitrophenyl)thio]-benzthiazol (**2**) reacted readily with anthranilic acid affording 2-(2,3-dihydro-2-thioxo-4(1H)quinazolinon-3-yl)-6-[(*p*-nitrophenyl)thio]benzthiazol (**4**).

Reaction of 2-(dimethyldithio carbamate)-6-[(*p*-nitrophenyl)thio]benzthiazol (**3**) with o-phenylenediamine produced 2-(2-benzimidazolylamino)-6-[(*p*-nitrophenyl)thio]benzthiazol (**5**). It has been suggested[13] that this reaction proceeds through one step by the elimination of a molecule of methanethiol and subsequent rearrangement to afford (**5**). When (**3**) reacted with potassium salt of anthranilic acid 2-[(4H-3,1-benzoxazin-4-one-2-yl)imino]-6-[(*p*-nitrophenyl)thio]-benzthiazol (**6**) was formed. Compound (**6**) condensed with the appropriate aromatic amine to give 2-[(3-aryl-4H-3,1-quinazolin-4-one-2-yl)imino]-6-[(*p*-nitrophenyl)thio]benzthiazol ($\mathbf{7}_{a-d}$). Oxidation of compounds (**4–7**) was carried out using hydrogen peroxide in glacial acetic acid for 2–7 days, leading to the formation of the corresponding diaryl sulfones (**8–11**). The sulfones obtained were highly crystalline compounds with melting points that were higher than those of the corresponding sulfides, in most cases. The sulfones ($\mathbf{11}_{a-d}$) were also obtained by condensation of 2-[(4H-3,1-benzoxazin-4-one-2-yl)imino]-6-[(*p*-nitrophenyl)sulfono]benzthiazol (**10**) with the aromatic amines discussed before, to yield ($\mathbf{11}_{a-d}$). The resultant sulfones ($\mathbf{11}_{a-d}$) obtained by both routes are



identical, as was shown by melting point comparison, mixed melting point and i.r. determinations.

EXPERIMENTAL

The time allowed for the completion of the reaction and the purity of the prepared compounds were controlled by means of T.L.C. Melting points were determined on Fisher–Johns melting-point apparatus and were uncorrected. Elemental analyses were performed on a Perkin–Elmer 240 C elemental analyser. IR spectra were recorded on a Pye–Unicam infrared spectrophotometer, using the KBr wafer technique. ^{1}H NMR spectra were recroded on a 90 MHz-Varian NMR spectrophotometer, in a suitable deutrated solvent, using TMS as an internal standard.

2-Amino-6-[(p-nitrophenyl)thio]benzthiazol (**1**). This compound was prepared by thiocyanation of 4-amino-4′-nitrodiphenylsulfide, as reported previously.[11]

2-(Methyldithiocarbamate)-6-[(p-nitrophenyl)thio]benzthiazol (**2**). General procedure: To a well stirred, cooled (ice/water) solution of 2-amino-6-[(*p*-nitrophenyl)thio]benzthiazol (**1**) (0.05 mole, 15.15 gm) in dimethylformamide (50 ml) was successively added (a) aqueous 20 molar NaOH (2 ml), (b) carbondisulfide (6 ml); (c) aqueous 20 molar NaOH (3 ml) and after 30 minutes, methyl iodide (7.1 gm, 0.05 mole). The time between additions was 30-minutes in order to improve the yield. Stirring was continued for 2 hours. The mixture was poured into water (500 cc) and neutralized to litmus with 2 N hydrochloric acid. The solid obtained was filtered, washed with water and recrystallized from ethanol as yellow crystals in 84% yield. mp. 197°C.

Anal. Calcd. for: $C_{15}H_{11}N_3O_2S_4$: C, 45.80; H, 2.79; N, 10.68; S, 32.56%. Found: C, 46.28; H, 2.56; N, 10.92; S, 32.12%.

IR 3300 cm^{-1} (NH), 1580 cm^{-1} (C=N), 1540, 1340 cm^{-1} (NO_2) and 1510 cm^{-1} (N—C(=S)—). ^{1}H NMR in DMSO, d_6 at δ 2.60 (s) (3H of CH_3S), δ 3.32 (s) (1H of NH) and δ 7.15–8.20 (m) (7H of Ar—H).

2-(Dimethyldithiocarbamate)-6-[(p-nitrophenyl)thio]benzthiazol (**3**). To a well stirred solution of (**1**)

TABLE I

Physical data of compounds **2–7**

Compound	M.P	% Yield	Molecular formula		Elemental analysis %C	%H	%N	%S	%Cl	IR spectra
2	197°C	84	$C_{15}H_{11}N_3O_2S_4$	Calc.	45.80	2.79	10.68	32.56		at 3300 cm^{-1} (NH), 1580 cm^{-1} (C═N), 1540, 1340 cm^{-1} (NO_2) and 1510 cm^{-1} (N—C═S).
				Found	46.28	2.56	10.92	32.12		
3	135°C	75	$C_{16}H_{13}N_3O_2S_4$	Calc.	47.17	3.19	10.31	31.44		at 3300 cm^{-1} (NH), 1580 cm^{-1} (C═N), 1545, 1340 cm^{-1} (NO_2) and 1500 cm^{-1} (N—C═S).
				Found	47.58	3.15	10.77	31.16		
4	148°C	62	$C_{21}H_{12}N_4O_3S_3$	Calc.	54.31	2.58	12.06	20.68		at 3400 cm^{-1} (NH), 1730 cm^{-1} (C═O), 1580 cm^{-1} (C═N), 1525, 1340 cm^{-1} (NO_2) and 1500 cm^{-1} (C═S).
				Found	54.72	2.19	11.83	20.29		
5	210°C	87	$C_{20}H_{13}N_5O_2S_2$	Calc.	57.27	3.10	16.70	15.27		at 3400 cm^{-1} (NH), 1630 cm^{-1} (C═N), 1600 cm^{-1} (C═N) and 1500, 1340 cm^{-1} (NO_2).
				Found	57.64	3.28	16.45	15.43		
6	142°C	85	$C_{21}H_{12}N_4O_4S_2$	Calc.	56.25	2.67	12.50	14.28		at 3400 cm^{-1} (NH), 1720 cm^{-1} (C═O), 1580 cm^{-1} (C═N) and 1530, 1340 cm^{-1} (NO_2).
				Found	56.34	2.79	12.65	14.39		
7_a	173°C	72	$C_{27}H_{17}N_5O_3S_2$	Calc.	61.95	3.25	13.38	12.23		at 3300 cm^{-1} (NH), 1720 cm^{-1} (C═O), 1650 cm^{-1}, 1580 cm^{-1} (C═N) and 1520, 1340 cm^{-1} (NO_2).
				Found	62.36	3.14	13.62	12.44		
7_b	155°C	79	$C_{27}H_{16}N_5O_3S_2Cl$	Calc.	58.11	2.86	12.55	11.47	6.36	at 3300 cm^{-1} (NH), 1720 (C═O), 1640 cm^{-1} (C═N) cm^{-1}, 1525, 1340 cm^{-1} (NO_2) and 750 cm^{-1} (C—Cl).
				Found	58.44	2.39	12.92	11.96	6.24	
7_c	135°C	77	$C_{28}H_{19}N_5O_3S_2$	Calc.	62.56	3.53	13.03	11.91		at 3300 cm^{-1} (NH), 1720 cm^{-1} (C═O), 1620 cm^{-1} (C═N), 1580 cm^{-1} (C═N) and 1525, 1340 cm^{-1} (NO_2).
				Found	62.23	3.42	12.97	11.84		
7_d	140°C	68	$C_{28}H_{19}N_5O_4S_2$	Calc.	60.75	3.43	12.65	11.57		at 3290 cm^{-1} (NH), 1720 cm^{-1} (C═O), 1640 cm^{-1}, 1580 cm^{-1} (C═N) and 1510, 1340 cm^{-1} (NO_2).
				Found	60.82	3.29	12.77	11.81		

TABLE II

Physical data of compounds **8–11**

Compound	M.P	% Yield	Reaction time (days)	Molecular formula		Elemental analysis %C	%H	%N	%S	%Cl	IR spectra
8	162°C	63	4	$C_{21}H_{12}N_4O_5S_3$	Calc.	51.85	2.46	11.52	19.75		at 3300 cm^{-1} (NH), 1720 cm^{-1} (C=O), 1610 cm^{-1} (C=N), 1500 cm^{-1} (C=S), 1530, 1330 cm^{-1} (NO_2) and 1350, 1165 cm^{-1} (SO_2).
					Found	51.69	2.27	11.42	19.36		
9	222°C	68	5	$C_{20}H_{13}N_5O_4S_2$	Calc.	53.21	28.82	15.52	14.19		at 3300 cm^{-1} (NH), 1640 cm^{-1} (C=N), 1600 cm^{-1} (C=N), 1530, 1320 cm^{-1} (NO_2) and 1350, 1160 cm^{-1} (SO_2).
					Found	53.32	29.14	15.37	14.42		
10	165°C	76	2	$C_{21}H_{12}N_4O_6S_2$	Calc.	52.50	2.50	11.66	13.33		at 3250 cm^{-1} (NH), 1720 cm^{-1} (C=O), 1600 cm^{-1} (C=N), 1530, 1310 cm^{-1} (NO_2) and 1350, 1165 cm^{-1} (SO_2).
					Found	52.12	2.43	11.82	13.75		
11$_a$	212°C	59	2	$C_{27}H_{17}N_5O_5S_2$	Calc.	58.37	3.06	12.61	11.53		at 3300 cm^{-1} (NH), 1720 cm^{-1} (C=O), 1600 cm^{-1} (C=N), 1540, 1320 cm^{-1} (NO_2) and 1360, 1175 cm^{-1} (SO_2).
					Found	58.23	2.91	12.50	11.47		
11$_b$	192°C	64	7	$C_{27}H_{16}N_5O_5S_2Cl$	Calc.	54.96	2.71	11.87	10.85	6.02	at 3300 cm^{-1} (NH), 1720 cm^{-1} (C=O), 1600 cm^{-1} (C=N), 1535, 1320 cm^{-1} (NO_2), 1350, 1160 cm^{-1} (SO_2) and 750 cm^{-1} (C—Cl).
					Found	55.24	2.55	11.43	10.96	5.66	
11$_c$	185°C	61	3	$C_{28}H_{19}N_5O_5S_2$	Calc.	59.05	3.33	12.30	11.24		at 3290 cm^{-1} (NH), 1720 cm^{-1} (C=O), 1605 cm^{-1} (C=N), 1540, 1305 cm^{-1} (NO_2) and 1350, 1165 cm^{-1} (SO_2).
					Found	59.18	3.49	12.74	11.53		
11$_d$	196°C	67	2	$C_{28}H_{19}N_5O_6S_2$	Calc.	57.43	3.24	11.96	10.94		at 3290 cm^{-1} (NH), 1720 cm^{-1} (C=O), 1610 cm^{-1} (C=N), 1530, 1310 cm^{-1} (NO_2) and 1350, 1170 cm^{-1} (SO_2).
					Found	57.70	3.52	12.29	10.78		

(0.05 mole) in dimethyl formamide (50 ml) in an ice/water bath, was added (a), (b), (c) as mentioned above. After 30 minutes, methyl iodide (15 gm, 0.1 mole) was added and stirring continued for 2 hours. The mixture was poured into 500 cc water, filtered and the obtained solid washed with water and recrystallized from ethanol to give (**3**) as yellow crystals in 75% yield mp. 135°C.

Anal. Calcd. for: $C_{16}H_{13}N_3S_4O_2$: C, 47.17; H, 3.19; N, 10.32; S, 31.44%. Found: C, 47.58; H, 3.15; N, 10.77; S, 31.16%.

IR, 1580 cm^{-1} (C=N), 1545, 1340 cm^{-1} (NO_2) and 1500 cm^{-1} (N—C=S). ^1H NMR in DMSO, d_6 at δ 2.60 (s) $\left(6H \text{ of } S\langle^{CH_3}_{CH_3}\right)$ and δ 7.15–8.20 (m) (7H of Ar—H).

2-(2,3-Dihydro-2-thioxo-4(1H)quinoxalinon-3-yl)-6-[(p-nitrophenyl)thio]benzthiazol (**4**). A mixture of 2-(methyldithiocarbamate)-6-[(*p*-nitrophenyl)thio]benzthiazol 2 (0.1 mole) and anthranilic acid (0.1 mole) in dimethylformamide (20 ml) was heated at reflux for 4 hours. The precipitate was filtered, washed with water, dried and crystallized from ethanol to afford 2-(2,3-dihydro-2-thioxo-4-(1H)quinoxalinon-3-yl)-6-[(*p*-nitrophenyl)thio]benzthiazol (**4**) as yellowish green crystals mp. 148°C.

Anal. Calcd. for: $C_{21}H_{12}N_4O_3S_3$: C, 54.31; H, 2.58; N, 12.06; S, 20.68. Found: C, 54.72; H, 2.19; N, 11.83; S, 20.29%.

IR, 3400 cm^{-1} (NH), 1730 cm^{-1} (C=O), 1580 cm^{-1} (C=N), 1500 cm^{-1} (C=S) and 1525, 1340 cm^{-1} (NO_2). ^1H NMR, in DMSO, D_6 at δ 3.50 (s) (1H of NH), δ 7.15–8.10 (m) (11H of Ar—H).

2-(2-Benzimidazolylamino)-6-[(p-nitrorophenyl)thio]benzthiazol (**5**). A suspension of compound **3** (0.14 mole) and *o*-phenylene diamine (0.14 mole) in dimethylformamide (100 ml) was heated at reflux for 5 hours. The reaction mixture was concentrated and cooled to room temperature. The solid product was filtered off and crystallized from ethanol to afford yellow crystals of compound (**5**) in 87% yield, mp. 210°C.

Anal. Calcd. for: $C_{20}H_{13}N_5O_2S_2$: C, 57.27; H, 3.10; N, 16.70; S, 15.27%. Found: C, 57.64; H, 3.28; N, 16.45; S, 15.43%.

IR, at 3400 cm^{-1} (NH), 1630 cm^{-1}, 1600 cm^{-1} (C=N) and 1500, 1340 cm^{-1} (NO_2). ^1H NMR, in DMSO, D_6 δ 3.35 (s) (1H of NH) and δ 7.18–8.15 (m) (11H of Ar—H).

2-(4H-3,1-benzoxazin-4-on-2-yl)imino-6-[(p-nitrophenyl)thio]benzthiazol (**6**). A mixture of compound **3** (0.01 mole), anthranilic acid (0.01 mole) in dimethylformamide (20 ml) and potassium hydroxide (0.01 mole) in water (2 ml) was heated at reflux for 5 hours. After cooling the product was filtered, washed with water, air-dried and crystallized from ethanol–water (1:1) to give 2-[(4H-3,1-benzoxazin-4-on-2-yl)imino]-6-[(*p*-nitrophenyl)thio]benzthiazol (**6**) as yellow crystals in 85% yield. mp. 142°C.

Anal. Calcd. for: $C_{21}H_{12}N_4O_4S_2$: C, 56.25; H, 2.74; N, 12.50; S, 14.26%. Found: C, 56.34; H, 2.74; N, 12.65; S, 14.39%.

IR: at 3400 cm^{-1} (NH), 1720 cm^{-1} (C=O), 1650 cm^{-1}, 1580 cm^{-1} (C=N) and 1530, 1340 cm^{-1} (NO_2). ^1H NMR, in DMSO, d_6 δ 3.00 (s) (1H of NH) and δ 7.15–8.15 (m) (11H of Ar—H).

2-[(3-Aryl-4H-3,1-quinazolin-4-on-2-yl)imino]-6-[(p-nitrophenyl)thio]benzthiazol ($\mathbf{7}_{a-d}$). A mixture of compound **6** (0.01 mole) and the appropriate aromatic amine (0.01 mole) was heated at 155–160°C in an oil-bath for 30 minutes. The mixture was cooled, washed with dilute hydrochloric acid and then several times with water. The crude product was filtered, dried and crystallized from chloroform–petroleum ether (60–80°C) to give ($\mathbf{7}_{a-d}$). The physical constants and IR spectral data of compounds ($\mathbf{7}_{a-d}$) were represented in Table I.

Oxidation of compounds (**4–7**) *to their corresponding sulfones* (**8–11**). General procedure: The sulfide (**4–7**) (0.02 mole) was dissolved in glacial acetic acid (20 ml). Hydrogen peroxide (30%, 20 ml) was added and the mixture was left at room temperature for 2–7 days. The deposited diaryl sulfone (**8–11**) was collected and purified as usual. The physical properites and IR spectral data were represented in Table II. ^1H NMR of compound $\mathbf{11}_d$ in DMSO, d_d: δ 3.45 (s) (1H of NH), δ 3.70 (s) (3H of CH_3—O) and δ 7.70–8.70 (m) (15H of Ar—H).

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