Synthesis and characterization of chloromaleimidobenzenesulfonylhydrazones

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Abstract

This paper describes the synthesis of a new series of imidosulfonylhydrazones in a search for antibactericidal and/or antinociceptive lead compounds.Cyclic imides comprise an important family of organic compounds with therapeutic potential, including the sulfonylhydrazones. 3,4-Dichloro-1-phenyl-1*H*-pyrrole-2,5-dione **(1)** was obtained from the reaction between aniline and dichloromaleic anhydride in acetic acid. Reaction of (**1**) with pyrrolidine gave 3-chloro-1-phenyl-4-pyrrolidin-1-yl-1*H*-pyrrole-2,5-dione (**2**). 4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)benzenesulfonyl chloride **(3)** was obtained from the chlorosulfonation of compound (**2**). The reaction of (**3**) with hydrazine hydrate produced 4-(3-chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)benzenesulfonohydrazide (**4**), which was characterized through condensation with aldehydes to yield the imidosulfonylhydrazones (**5-12**).

Keywords: Chloromaleimidobenzenesulfonylhydrazones, sulfonylhydrazones, synthesis

Introduction

The synthesis of sulfonylhydrazones is of great interest since these compounds have shown anti-inflammatory, analgesic[1-3], anti-pyretic[4], and antibacterial activities[5]. The antineoplastic activity of some sulfonylhydrazones has also been reported[6]. Studies carried out by Barreiro *et al.* have shown that sulfonylhydrazone derivatives of safrole have potent analgesic action, exceeding and/or equalling the potency observed under the same conditions for either dypirone or indomethacin[7]. This paper describes the synthesis of chloro-maleimidobenzenesulfonylhydrazones, in a search for antibactericidal and/or antinociceptive lead compounds.

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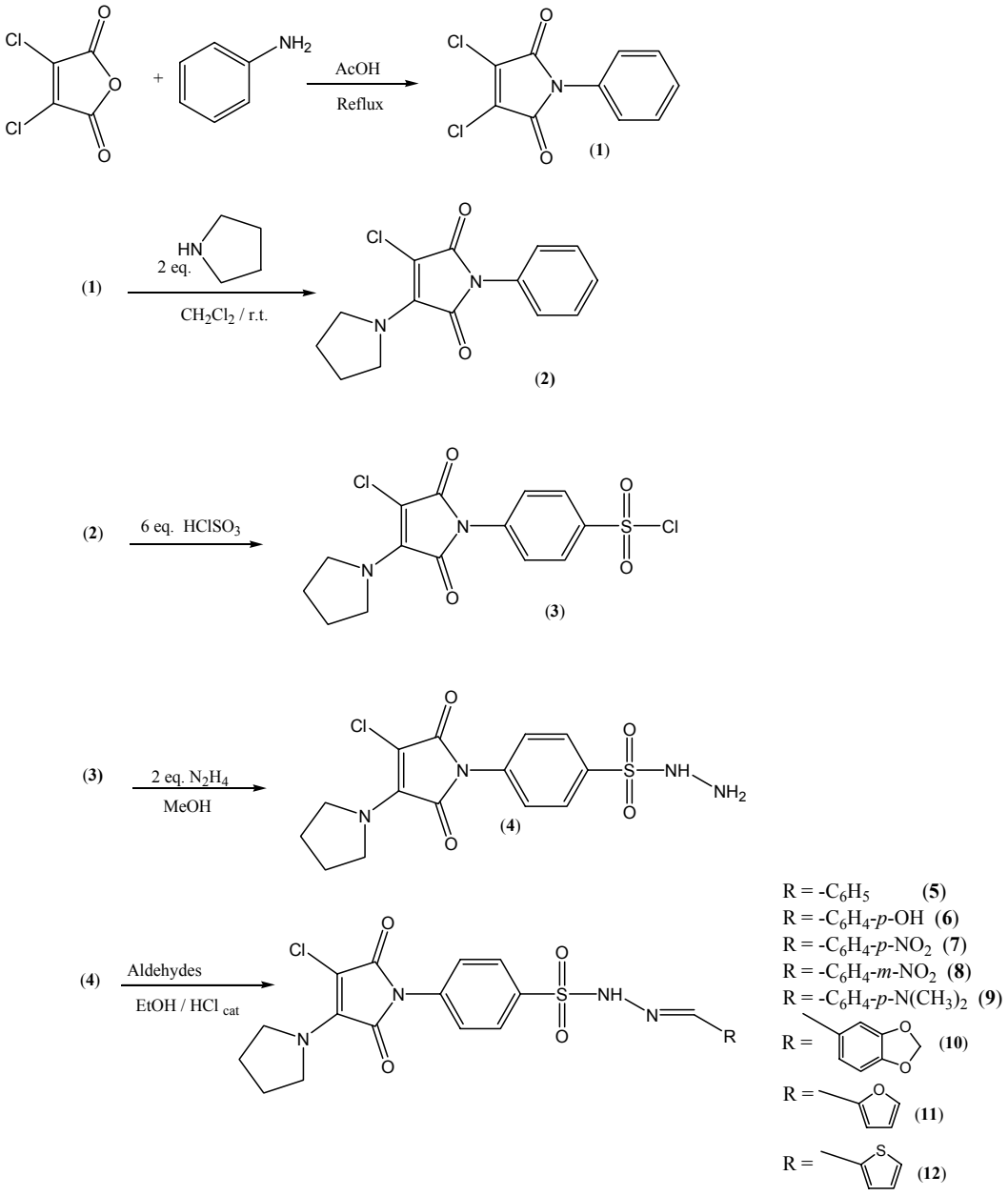
Results and Discussion

The cyclic imide (**1**) was obtained from the reaction between aniline and dichloromaleic anhydride with acetic acid under reflux, as previously described [8] (Scheme **1**). Compound (**2**) was obtained from the reaction of compound (**1**) (1 mol) and pyrrolidine (2 mol) in dichloromethane at room temperature[9]. Compound (**3**) was prepared by the reaction of compound (**2**) (1 mol) with chlorosulfonic acid (6 mol)[9]. The reaction of the sulfonylchloride with hydrazine hydrate gave the sulfonylhydrazide (**4**), which was characterized by condensation with aldehydes to yield the sulfonylhydrazones (5-12) (Scheme **1**).



Scheme 1

The configuration of the imino double bonds of (**5-12**) could not be determined by NMR data, where only one imino hydrogen was observed. However, a study of the relative stability of the *E/Z* diastereomers involved, employing the Hamiltonian PM3 molecular model and the work of Barreiro *et al.*[10], indicated that the *E* isomers may be preferentially formed. The structures were confirmed through ^{1}H NMR and ^{13} C NMR spectroscopic analysis and CNH elemental analysis.

Experimental Section

General Procedures. All compounds were characterised by ^{1}H NMR, ^{13}C NMR, IR, and microanalysis. The purity of these compounds was determined by thin layer chromatography (TLC). Infrared spectra were obtained with a Perkin Elmer 16PC spectrophotometer (Perkin Elmer, Wellesley, MA, USA). ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC-200F spectrometer (Rheinstetten, Germany) (at 200 MHz and 50 MHz, respectively). $CDCl_3$ and DMSO were used as solvents with tetramethylsilane (TMS) as the internal standard; chemical shifts (δ) are reported in parts per million. For the CHN analysis, a CHN elemental analyser PERKIN ELMER 2400 (Boston, MA, USA) was used. In the TLC, aluminium sheets with 60 F-254 silica gel and 0.2 mm thickness were utilised.

3,4-Dichloro-1-phenyl-1*H*-pyrrole-2,5-dione (1). Imide (**1**) was obtained as describe in the literature [8]. Yield: 82 %. mp 206-207 °C (Lit[8] m.p. 204-206°C).

3-Chloro-1-phenyl-4-pyrrolidin-1-yl-1*H*-pyrrole-2,5-dione (2). Imide (**2**) was obtained as describe in the literature [9]. Yield: 80 %. mp 134-135 °C (Lit[9] m.p. 135-136°C).

4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)benzenesulfonyl chloride (3). Chloride (**3**) was obtained as described in the literature [9]. Yield: 89 %. mp 121-123 °C (Lit[9] m.p. 122-123°C).

4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)benzenesulfono hydrazide (4). Hydrazine hydrate (51.3 mg, 1.60 mmol) was added to a mixture of 4-(3-chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)benzenesulfonyl chloride (3) (0.3 g, 0.80 mmol) in methanol (30 mL) at 0 °C. The mixture was allowed to warm to room temperature for 30 minutes and was then poured onto ice-water. The solid formed was obtained through filtration with suction. The product was crystallized from hexane-chloroform (1:2). Yield: 89 %. mp 178.1-179.0 °C. *IR*(KBr) ν_{Max}: 3383, 3192, 2963, 1777, 1708, 1387, 1193, 1173, 837.

4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*'-[(1*E*)phenyl-methylene]benzenesulfonohydrazide (5). Benzaldehyde (28.6 mg, 0.27 mmol) was added to a mixture of 4-(3-chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)benzenesulfono hydrazide (4) (0.10 g, 0.27 mmol) in ethanol (10 mL), along with a drop of hydrochloric acid as the catalyst. The reaction was left under stirring at room temperature for 1 ½ hours. The solid formed was obtained through filtration with suction. The product was crystallized from ethanol-ethyl acetate (2:1) as light yellow colored crystals. Yield: 73 %. mp

189.2-190.5 °C. *IR*(KBr)ν_{Max} 3210, 2970, 1770, 1704, 1635, 1493, 1386, 1167, 1232. Anal. Calcd. for $C_{21}H_{19}ClN_4O_4S$: C, 54.96; H, 4.17; Cl, 7.73; N, 12.21; S, 6.99. Found: C, 54.49; H, 4.30; N, 12.10; S, 6.94. ^{1}H NMR δ ppm, DMSO-*d*^{6}: 11.58 (s, 1H: -NH-N=); 7.98 and 7.94 (2d, 2H: ArH J= 8.2 Hz); 7.93 (s, 1H: -N=CH-) 7.55 (m, 2H: ArH); 7.40 (m, 5H: ArH); 3.88- (s, 4H: CH_2-N-CH_2); 1.87 (s, 4H: CH_2-CH_2). ^{13}C NMR δ ppm, DMSO-*d*^{6}: 25.31 ($\underline{C}H_2$-$\underline{C}H_2$-CH_2-N); 51.11(CH_2-N-CH_2-); 89.87 (Cl-$\underline{C}$=C); 127.23, 127.54; 128.57; 129.50; 130.88; 134.25 (CH Ar); 136.39 (-Cl-C=$\underline{C}$-); 137.81 (-C Ar-SO_2); 141.72 (-C Ar-N-), 148.20 (-N=C-); 163.45 (C=O), 165.57 (C=O).

Using this procedure the following sulfonylhydrazones were prepared:

4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*'-[(1*E*)-(4-hydroxy-phenyl)methylene]benzenesulfonohydrazide (6). Yield: 71 %. Dec.: 200 °C. *IR*(KBr) ν_{Max}: 3452, 3156, 2995, 1759, 1706, 1626, 1499, 1389, 1174, 1232. Anal. Calcd. for $C_{21}H_{19}ClN_4O_5S$: C, 53.11; H, 4.03; Cl, 7.47; N, 11.80; S, 6.75. Found: C, 52.87; H, 4.18; N, 11.74; S, 6.71. ^{1}H NMR δ ppm, DMSO-*d*^{6}: 11.27 (s, 1H: -NH-N=); 9.91 (s, 1H: OH); 7.95 and 7.91 (2d, 2H: ArH; J= 8.0 Hz); 7.82 (s, 1H: -N=CH-); 7.60 and 7.56 (2d, 2H: ArH; J= 8.0 Hz); 7.42 and 7.38 (2d, 2H: ArH; J= 8.0 Hz); 6.78 and 6.74 (2d, 2H: ArH; J= 8.0 Hz); 3.88 (s, 4H: -CH_2-N-CH_2-); 1.87 (s, 4H: -CH_2-CH_2-). ^{13}C NMR δ ppm, DMSO-*d*^{6}: 24.70 ($\underline{C}H_2$-$\underline{C}H_2$-CH_2-N); 50.51 (CH_2-N-CH_2-); 109.26 (Cl-$\underline{C}$=C); 115.71; 124.66; 126.61; 127.96; 128.72 (CH Ar); 135.65 (-Cl-C=$\underline{C}$-); 137.29 (-C Ar-SO_2); 141.12 (-C Ar-N); 148.14 (-N=C-); 159.51 (-HC-OH Ar); 162.86 (C=O); 165.00 (C=O).

4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*'-[(1*E*)-(4-nitrophenyl)methylene]benzenesulfonohydrazide (7). Yield: 80 %. mp 201.0-202.7 °C. *IR*(KBr) ν_{Max}: 3240, 2990, 1759, 1706, 1630, 1495, 1522, 1348, 1385, 1168, 1226, 852. Anal. Calcd. for $C_{21}H_{18}ClN_5O_6S$: C, 50.05; H, 3.60; Cl, 7.04; N, 13.90; S, 6.36. Found: C, 49.76; H, 3.83; N, 13.85; S, 6.22. ^{1}H NMR δ ppm, DMSO-*d*^{6}: 11.96 (s, 1H: -NH-N=); 8.26 and 8.22 (2d, 2H: ArH, J= 8.2 Hz); 7.99 (s, 1H: -N=CH-) 7.96 (m, 4H: ArH); 7.59 (m, 2H: ArH); 3.89 (s, 4H: -CH_2-N-CH_2-); 1.86 (s, 4H: -CH_2-CH_2-). ^{13}C NMR δ ppm, DMSO-*d*^{6}: 25.32 ($\underline{C}H_2$-$\underline{C}H_2$-CH_2-N); 51.11 (CH_2-N-CH_2-); 85.56 (Cl-$\underline{C}$=C); 124.73, 127.33; 128.53 (CH Ar); 136.56 (-Cl-C=$\underline{C}$-); 140.42 (-C Ar-SO_2); 141.75 (-C Ar-N); 145.60- (CH-NO_2 Ar), 148.60 (-N=C-); 163.43 (C=O); 165.54 (C=O).

4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*'-[(1*E*)-(3-nitrophenyl)methylene]benzenesulfonohydrazide (8). Yield: 88 %. mp 199.6-201.4 °C. *IR*(KBr) ν_{Max}: 3208, 2985, 1764, 1706, 1633, 1500, 1543, 1348, 1372, 1166, 1241, 869. Anal. Calcd. for $C_{21}H_{18}ClN_5O_6S$: C, 50.05; H, 3.60; Cl, 7.04; N, 13.90; S, 6.36. Found: C, 49.96; H, 3.74; N, 13.77; S, 6.24. ^{1}H NMR δ ppm, DMSO-*d*^{6}: 11.97 (s, 1H: -NH-N=); 8.38 (m, 2H: ArH); 8.24 and 8.20 (2d, 2H: ArH, J = 8.0 Hz); 8.15- (s, 1H: N=CH-) 8.04 (m, 2H: ArH); 7.61 (2d, 2H: ArH J = 8,1); 3.90 (s, 4H: -CH_2-N-CH_2-); 1.87 (s, 4H: -CH_2-CH_2-). ^{13}C NMR δ ppm, DMSO-*d*^{6}: 25.30 ($\underline{C}H_2$-$\underline{C}H_2$-CH_2-N); 51.11 (CH_2-N-CH_2-); 88.98 (Cl-$\underline{C}$=C); 121.91, 125.12; 127.30, 128.53, 131.13, 133.41, 136.05 (CH Ar); 136.52 (-Cl-C=$\underline{C}$-); 137.70 (-C Ar-SO_2); 141.72 (-C Ar-N); 145.84 (-C Ar-NO_2), 148.84 (-N=C-); 163.43 (C=O), 165.70 (C=O).

4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*'-{(1*E*)-[4-(dimethylamino)phenyl]methylene}benzenesulfonohydrazide (9). Yield: 71 %. Dec. 170 °C. *IR*(KBr) ν_{Max}: 3126, 2978, 1770, 1717, 1634, 1495, 1365, 1163, 1232.Anal. Calcd. for $C_{23}H_{24}ClN_5O_4S$: C, 55.03; H, 4.82; Cl, 7.06; N, 13.95; S, 6.39. Found: C, 54.83; H, 4.98; N, 13.82; S, 6.26. ^{1}H NMR δ ppm, DMSO-d^6: 11.32 (s, 1H: -NH-N=); 7.97 and 7.93 (2d, 2H: ArH, J= 8.0 Hz); 7.83 (s, 1H: -N=CH-); 7.59 and 7.55 (2d, 2H: ArH, J= 8.0 Hz); 7.45 and 7.41 (2d, 2H: ArH, J= 8.0 Hz); 6.91 and 6.87 (2d, 2H: ArH, J= 8.0 Hz); 3.89 (s, 4H: -CH_2-N-CH_2-); 2.97 (s, 6H: -N-$(CH_3)_2$); 1.88 (s, 4H -CH_2-CH_2-:). ^{13}C NMR δ ppm, DMSO-d^6: 24.68 ($\underline{C}H_2$-$\underline{C}H_2$-CH_2-N); 41.13 (-N-$(CH_3)_2$); 50.47 (CH_2-N-CH_2-); 110.53 (Cl-$\underline{C}$=C); 114.09, 126.55, 127.95, 128.26 (CH Ar); 135.61 (-Cl-C=$\underline{C}$-); 137.29 (-C Ar-SO_2); 141.07 (-C Ar-N); 148.09 (-CH-N$(CH_3)_2$), 149.86 (-N=C-); 162.81 (C=O), 164.96 (C=O).

4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*'-[(1*E*)-1,3-benzodioxol-5-ylmethylene]benzenesulfonohydrazide (10). Yield: 69 %. mp 217.5 – 218.1 °C. *IR*(KBr) ν_{Max}: 3157, 2976, 1764, 1706, 1632, 1500, 1372, 1163, 1258. Anal. Calcd. for $C_{22}H_{19}ClN_4O_6S$: C, 52.54; H, 3.81; Cl, 7.05; N, 11.14; S, 6.38. Found: C, 52.25; H, 3.90; N, 11.03; S, 6.15. ^{1}H NMR δ ppm, DMSO-d^6: 11.36 (s, 1H: -NH-N=); 7.98 and 7.94 (2d, 2H: ArH, J= 8.4 Hz); 7.83 (s, 1H: -N=CH-); 7.61 and 7.57 (2d, 2H: ArH, J= 8.4 Hz); 7.03 (m, 3H: ArH); 6.05 (s, 2H: O-CH_2-O); 3.90 (s, 4H: -CH_2-N-CH_2-); 1.89 (s, 4H: -CH_2-CH_2-). ^{13}C NMR δ ppm, DMSO-d^6: 24.68 ($\underline{C}H_2$-$\underline{C}H_2$-CH_2-N); 50.47 (CH_2-N-CH_2-); 101.60 (O-CH_2-O); 104.98 (Cl-$\underline{C}$=C); 108.45, 123.24, 126.58, 127.97, 147.45, 147.99 (CH Ar); 135.70 (-Cl-C=$\underline{C}$); 137.11 (-C Ar-SO_2); 141.08 (-C Ar-N); 149.18 (-N=C-); 162.81 (C=O); 164,96 (C=O).

4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*'-[(1*E*)-2-furylmethylene]benzenesulfonohydrazide (11). Yield: 64 %. Dec.: 195.0° C. *IR*(KBr) ν_{Max}: 3147, 2995, 1759, 1701, 1638, 1506, 1378, 1168, 1240. Anal. Calcd. for $C_{19}H_{17}ClN_4O_5S$: C, 50.84; H, 3.82; Cl, 7.90; N, 12.48; S, 7.14. Found: C, 50.67; H, 3.86; N, 12.43; S, 7.01. ^{1}H NMR δ ppm, DMSO-d^6: 11.57 (s, 1H: -NH-N=); 7.95 (s, 1H: -N=CH-) 7.85 (m, 2H: ArH); 7.60 (m, 2H: ArH); 6.81 (m, 2H: -O-C$\underline{H}$=CH-C$\underline{H}$); 6.56 (s, 1H: -O-C$\underline{H}$=CH); 3.88 (s, 4H: -CH_2-N-CH_2-); 1.87 (s, 4H: -CH_2-CH_2-). ^{13}C NMR δ ppm, DMSO-d^6: 28.73 ($\underline{C}H_2$-$\underline{C}H_2$-CH_2-N); 54.55 (CH_2-N-CH_2-); 109.33 (Cl-$\underline{C}$=C); 113.54 (-O-CH=$\underline{C}$H-CH), 125.32 (-O-CH=CH-$\underline{C}$H), 130.68; 131.95; 135.55 (CH Ar); 133.05 (-Cl-C=$\underline{C}$-); 137.17 (-C Ar-N- and -O-$\underline{C}$H=CH-CH); 145.19 (-N=C- and HC=$\underline{C}$-O-); 163.75 (C=O); 165.96 (C=O).

4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*'-[(1*E*)-thien-2-ylmethylene]benzenesulfonohydrazide (12). Yield: 66 %. Dec. 209 °C. *IR*(KBr) ν_{Max}: 3152, 2986, 1759, 1706, 1631, 1506, 1387, 1168, 1233. Anal. Calcd. for $C_{19}H_{17}ClN_4O_4S_2$: C, 49.08; H, 3.69; Cl, 7.63; N, 12.05; S, 13.79. Found: C, 48.97; H, 3.89; N, 11.98; S, 13.66. ^{1}H NMR δ ppm, DMSO-d^6: 11.52 (s, 1H: -NH-N=); 8.12 (s, 1H: -N=CH-); 7.94 and 7.90 (2d, 2H: ArH, J= 8.0 Hz); 7.62 and 7.57 (2d, 2H: ArH, J= 8.0 Hz); 7.20 (m, 3H: -S-C$\underline{H}$=C$\underline{H}$-C$\underline{H}$); 3.89 (s, 4H: -CH_2-N-CH_2-); 1.88 (s, 4H: -CH_2-CH_2-). ^{13}C NMR δ ppm, DMSO-d^6: 24.69 ($\underline{C}H_2$-$\underline{C}H_2$-CH_2-N); 50.50 (CH_2-N-CH_2-); 112.12 (Cl-$\underline{C}$H=CH); 114.34; 120.12; 126.72; 127.58 (CH Ar); 127.90 (-

Cl-C=C-); 135.75 (-C Ar-N), 137.49 (-S-CH=CH-CH); 145.28 (-N=C-), 151.96 (HC=C-S-); 161.89 (C=O); 163.91 (C=O).

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