Synthesis of Benzisochalcogenol and -azole Derivatives via ortho Metalation of Isophthalamides

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The syntheses of benzofused isochalcogenazole derivatives via ortho-lithiation of isophthalamides is reported. N,N'-Dialkyl-isophthalamides, C₆H₄-1,3-(CONHR)₂, bearing R = tPr or tBu substituents are readily ortho metalated by using 3.3 equiv. of n-BuLi/TMEDA. The organo lithium compounds react with S, Se, or Te to give 2-chalcogenol-isophthalamides, C₆H₄-1,3-(CONHR)₂-2-XH (X = S, Se, Te). Oxidation of the chalcogenols affords dichalcogenides under acidic and benzisochalcogenazoles under basic conditions, respectively. The formation of the five-membered heterocycles proceeds by disproportionation of the dichalcogenides. Oxidation of the benzisothiazoles by hydrogen peroxide gives access to substituted sulfin- and sulfonamides.

Introduction

Ortho-lithio benzamides (I) are useful reagents in organic syntheses since they undergo reactions with a variety of electrophiles [1]. They are also valuable synths for the preparation of sulfur heterocycles such as saccharine [2 - 4] and benzisothiazole derivatives [5]. The ortho position in isophthalamides, C₆H₄-1,3-(CONHR)₂ (II), is expected to be even more activated towards C-H deprotonation, however, only few studies on the preparation and reactivity of o-lithio isophthalamides have appeared in the literature [6, 7]. This is true in particular for o-lithio isophthalamides of primary amines and their reactions with elemental sulfur, selenium [8], and tellurium [9].

![Fig. 1. o-Lithio benzamides and o-lithio isophthalamides.](image)

In the present study we describe i) the conditions required for successful metalation of N,N'-di-alkylisophthalamides, ii) the regioselectivity of the metalations, and iii) reactions of sulfur, selenium, and tellurium with the aryl lithium compounds. The preparation and characterization of some oxidation products of the initially obtained chalcogenol compounds are also described.

Results and Discussion

Syntheses

o-Lithiation of the readily available N,N'-di-alkylisophthalamides 1a,b (R = tPr, tBu) proceeded in good yields by using three equivalents of n-butyllithium/TMEDA (N,N'-tetramethyl-ethylenediamine) as metalating agent (see Scheme 1). Deprotonation occurs initially at the relatively acidic primary amide protons, thereby consuming two equivalents of the metalating agent, before C-H deprotonation takes place. The reaction is applicable, however, only for the tPr and tBu derivatives. The lower N,N'-di-alkylisophthalamides (R = Me, Et) could not be metalated, presumably due to insufficient solubility in tetrahydrofuran. This could easily be monitored by the color changes that occurred during the metalations. Addition of the metalating agent to THF solutions of 1a,b produced brick-red solutions, whereas no such effect was observed for the lower isophthalamides. Since the resulting reaction mixtures are very air and moisture sensitive, they were used directly in the next steps without isolation of the trilithium salts, Li₃ (1a,b).

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CONHR CONLiR
1a,b
a: R = 'Pr
b: R = 'Bu

1a,b
Li3[1a,b]

2a,b (X = D)
3a,b (X = SH)
4a (X = SeH)
5a (X = TeH)

Scheme 1. Preparation of o-lithio isophthalamides and 2-chalcogenol-isophthalamides. i) 3.3 equiv. n-BuLi/TMEDA, -70 °C → +25 °C; ii) D2O, HCl; iii) S, Se, or Te, HCl.

o-Lithiation in the present N,N'-di-alkylisophthalamides can in principle take place at the arene carbon atoms C4 or C2. C-H deprotonation at C2 should be preferred over deprotonation at C4 since the former is activated by both CONHR substituents. This was unambiguously confirmed by a CH/CD exchange experiment. Thus, treatment of the trilithium compounds with deuterium oxide gave exclusively 2-deuterio-N,N'-di-alkyl-isophthalamides (2a,b), proving that C-H deprotonation had occurred regioselectively at C2. Contrary to our findings, metalation of N,N'-d-n-butylisophthalamide has been reported to occur at the C4 position [6, 7].

As expected for organo-lithium compounds, trilithium salts Li3 (1a,b) readily reacted with elemental sulfur, selenium, or tellurium to give the corresponding C2-X compounds (X = SH, SeH, TeH) after hydrolysis. All chalcogenols were found to be very air-sensitive. They were only isolated and characterized in the case of X = SH (3a,b). The corresponding selenol (4a) and telluro compounds (5a) were allowed to oxidize in the presence of air (see below).

In accordance with the C2v symmetric structures of thiols 3a,b only four resonances for the six arene carbon atoms are observed in the 13C NMR spectra. Six signals were to be expected for the C4-SH compounds. The SH proton in 3a,b appears as a rather broad 1H NMR resonance at δ ~ 5.7 to 5.8 – even in [D]6-DMSO solution – presumably due to intramolecular hydrogen bonding interactions with the carbonyl groups. It is readily deprotonated and the corresponding thiolate anion can be alkylated. Treatment of 3b with allyl bromide in the presence of K2CO3, for example, gives the air-stable thioether 6.

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\text{Scheme 2. Preparation of disulfide 7 and benzothiazoles 8a,b.}
\]

Oxidation of chalcogenols

Compounds 3a,b are readily oxidized with a variety of oxidants. The oxidation of 3a has been examined in more detail. Addition of Fe[III]Cl3·6H2O (1 equiv.) in methanol produces the disulfide 7, but only at pH values below 6. In the presence of a base the disulfide 7 readily disproportionates to give equimolar quantities of the starting material 3a and the benzothiazole derivative 8a. Triethylamine as a base is sufficient to bring about the disproportionation and the whole process requires one equivalent. Addition of further oxidant to the reaction mixture results in complete formation of 8a. The disproportionation of 7 may be explained by a mechanism similar to one proposed by Reissert and Manns [10, 11], and by McClelland [12]. Compounds 8a,b could also be obtained by direct oxidation with iodine in the presence of NEt3.

Similar to thiols 3a,b the compounds 4a and 5a are oxidized in the presence of base to give the benzisoselenazoles and -tellurazoles 9a and 10a, respectively. It is assumed that these oxidations also involve the formation of diselenide and ditelluride intermediates, and that they disproportionate under the basic reaction conditions.

\[
\text{Fig. 2. Benzisochallogenazoles 8a, b, 9a, and 10a.}
\]
Compounds 8a, b and 9a are colorless air-stable solids, the benzisotellurazole (10a) is pale-yellow. Similar to other benzisothiazoles [13] compounds 8a, b exhibit two strong IR absorptions at 1619 and 1546 cm\(^{-1}\), attributable to the carbonyl stretching vibrations of the ring-CO (secondary amide, lactame) and substituent-CO groups (primary amide). In agreement with this assignment, the ring-CO absorption slightly shifts to lower frequencies with increasing weight of the chalcogen atom, whereas the other absorptions remain nearly unchanged (\(\tilde{\nu}\) (ring-CO): 1619 (S), 1605 (Se), 1593 cm\(^{-1}\) (Te); \(\tilde{\nu}\) (substituent-CO): 1543 (S), 1546 (Se), 1554 (Te)).

The oxidation of benzisothiazole 8a to cyclic sulfinamide 11a and sulfonamide 12a: i) \(\text{H}_2\text{O}_2/\text{HAc}, 25 ^\circ\text{C}\); ii) \(\text{H}_2\text{O}_2/\text{HAc}, \text{reflux, 60 min.}\)

In contrast to 8a and 12a, the cyclic sulfinamide 11a contains an asymmetric sulfur atom. Therefore, the methyl proton resonances of the prochiral isopropyl residues are expected to become inequivalent and together with the methine protons should form two A\(_3\)B\(_3\)X systems. This is confirmed by \(^1\text{H}\) NMR spectroscopy. The four inequivalent methyl groups are also distinguished by four different \(^{13}\text{C}\) NMR resonances in the \(^{13}\text{C}\) NMR spectrum of 11a.

In summary, the metalation of isophthalamides by \(n\)-butyllithium was carried out exclusively at the \(\text{C}^2\) position. Subsequent reactions with the elemental chalcogens followed by oxidation results in the formation of the air-stable benzisochalcogenols. This method thus provides a convenient alternative to the traditional synthesis of such compounds.

**Experimental**

All manipulations with \(n\)-butyllithium were carried out in an atmosphere of dry nitrogen by employing standard Schlenk techniques. Starting chemicals were purchased from Aldrich Chemicals and were used without further purification. Solvents were dried using appropriate drying agents and stored under nitrogen. Silica gel 60 (Merck, 230 - 400 mesh) was used for column chromatography. The \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra were recorded on a Bruker AC-200 instrument (\(^1\text{H}: 200,13\text{ MHz}; \(^{13}\text{C}: 50,32\text{ MHz}\)). CHN-Analyses: Perkin Elmer Elemental Analyzer 240. IR: Bruker IFS25 spectrophotometer (KBr pellets).

**N,N’-Di-isopropyl-isophthalamidine (1a)**

A solution of isopropylamine (24.8 g, 0.42 mol) in dichloromethane (50 ml) was slowly added to a solution of isophthaloyl chloride (20.3 g, 0.10 mmol) in 200 ml of dichloromethane at 0 \(^\circ\text{C}\) and the resulting suspension stirred for another 2 h. Water (200 ml) was then added and the organic solvent removed under reduced pressure resulting in the precipitation of the product as fine white crystals. The crystalline mass was collected by filtration and was washed several times with water. The pure product was dried in an oven at 70 \(^\circ\text{C}\) for 3 d. M. p. 182 - 184 \(^\circ\text{C}\). Yield 23.1 g (93%). IR (KBr, cm\(^{-1}\)): \(\tilde{\nu} = 3251, 3075 \nu(\text{NH}), 1628, 1562 \nu(\text{CO}). \) \(^1\text{H}\) NMR (DMSO-\(d_6\)): \(\delta = 8.34 (d, \text{J} = 7.7 \text{ Hz}, 2 \text{ H, NH}), 8.26 (t, \text{J} = 2.0 \text{ Hz, 1 H, ArH}), 7.94 (dd, \text{J} = 7.6 \text{ Hz, } 4\text{J} = 2.0 \text{ Hz, 2 H, ArH}), 7.50 (t, \text{J} = 7.6 \text{ Hz, 1 H, ArH}), 4.09 (d, 4\text{J} = 7 \text{ Hz, 2 H, CH}_{3}), 1.16 (d, 3\text{J} = 7 \text{ Hz, 12 H, CH}_{3}). \) \(^{13}\text{C}\) \(^1\text{H}\) NMR (DMSO-\(d_6\)): \(\delta = 165.1, 135.0, 129.5, 127.9, 126.3, 126.3, 126.3, 126.3, 22.2.\)

**N,N’-Di-tert-butyl-isophthalamidine (1b)**

This compound was prepared from tert-butylamine (30.7 g, 420 mmol) and isophthaloyl chloride (20.3 g, 100 mmol) by the procedure detailed above for 1a. Transparent needles. M. p. 208 - 210 \(^\circ\text{C}\). Yield: 26.5 g (96%). IR (KBr, cm\(^{-1}\)): \(\tilde{\nu} = 3273, 3066 \nu(\text{NH}), 1640, 1548 \nu(\text{CO}). \) \(^1\text{H}\) NMR (DMSO-\(d_6\)): \(\delta = 8.11 (t, \text{J} = 2 \text{ Hz, 1 H, ArH}), 7.85 (s, 2 \text{ H, NH}), 7.86 (dd, \text{J} = 7.6 \text{ Hz, } 4\text{J} = 2 \text{ Hz, 2 H, ArH}), 7.45 (t, \text{J} = 7.6 \text{ Hz, 1 H, ArH}), 1.37 (s, 18 \text{ H, CH}_{3}). \) \(^{13}\text{C}\) \(^1\text{H}\) NMR (CDCl\(_3\)): \(\delta = 166.0, 135.9, 129.3, 128.6, 124.9, 51.8, 28.8.\)

Calcd C 67.72 H 8.12 N 11.28%, Found C 67.68 H 8.10 N 11.16%.

**C\(_{14}\)H\(_{20}\)N\(_2\)O\(_2\) (248.33)**

Calcd C 67.72 H 8.12 N 11.28%,
Found C 67.68 H 8.10 N 11.16%.

**C\(_{16}\)H\(_{22}\)N\(_2\)O\(_2\) (276.38)**

Calcd C 69.53 H 8.75 N 10.14%,
Found C 69.45 H 8.62 N 9.86%.
2-Sulfanyl-N,N′-di-isopropyl-isophthalamide (3a)

A flask containing a mixture of 1a (4.97 g, 20.0 mmol), TMEDA (7.67 g, 66.0 mmol), and 50 ml of THF was placed in a dry-ice/2-propanol bath. To this suspension was added via syringe n- BuLi (26.4 ml of a 2.5 M solution in hexanes, 66.0 mmol) to give a bright-red solution. The reaction mixture was allowed to warm to 25 °C at which temperature it was stirred for a further 12 h. The suspension was cooled to −60 °C and freshly sublimed sulfur (641 mg, 20.0 mmol) was added in small portions. The resulting suspension was stirred for 1 h at −60 °C and then for 2 d at ambient temperature. The volatiles were removed under reduced pressure and the resulting solid hydrolyzed with 100 ml of water. After filtration, the pH of the filtrate was adjusted to 1 by addition of 12 M HCl and the resulting brown solid isolated by filtration. The crude product was redissolved in 1 M NaOH, filtered, and the filtrate acidified to obtain 3a as an off-white solid. The solid was collected by filtration, and dried over P4O10. Yield: 4.48 g (80%). An analytical sample was obtained by column chromatography (Rf = 0.35, 10% MeOH/CH2Cl2). IR (KBr, cm−1): ν = 3275, 3071 (NH), 1632, 1545 (CO). 1H NMR (DMSO-d6): δ = 8.39 (d, 3J = 7.7 Hz, 2 H, NH), 7.36 (m, 2 H, ArH), 7.18 (m, 1 H, ArH), 6.10 (s br, 1 H, SH), 4.02 (dspt, 3J = 7.7 Hz, 2 H, CH3). 13C{1H} NMR (DMSO-d6): δ = 167.3, 136.3, 130.5, 128.8, 124.2, 41.1, 22.2.

C14H16N2O2S (308.39)
Calcd C 62.13 H 7.70 N 8.76%.
Found C 62.31 H 7.84 N 9.08%.

2-Sulfanyl-N,N′-di-tert-butyl-isophthalamide (3b)

This compound was prepared from 1b (5.52 g, 20.0 mmol) by the procedure detailed above for 3a. 1H NMR (DMSO-d6): δ = 7.92 (s, 2 H, NH), 7.87 (m, 2 H, ArH), 7.47 (m, 1 H, ArH), 1.37 (s, 18 H, CH3).

Allyl-[2,6-di(N-tert-butyl-carbamoyl)phenyl] sulfide (6)

A suspension of 3b (308 mg, 1.00 mmol), allyl bromide (133 mg, 1.10 mmol), and potassium carbonate (152 mg, 1.10 mmol) in acetone (10 ml) was stirred at r.t. for 12 h. To the solution was then added water to precipitate crude 6. The solid was filtered, dried in air, and recrystallized from ethyl acetate. Yield: 296 mg (85%). IR (KBr, cm−1): ν = 3299 (NH), 1646, 1528 (CO). 1H NMR (CDCl3): δ = 7.47 (m, 2 H, ArH), 7.30 (m, 1 H, ArH), 5.70 (s br, 1 H, SH), 4.86 (m, 2 H, =CH2), 3.42 (m, 2 H, S=CH2), 1.41 (s, 18 H, CH3). 13C{1H} NMR (CDCl3): δ = 167.4, 143.8, 133.2 (=CH), 129.2, 128.8, 118.0 (=CH2), 51.9, 40.4 (CH2), 28.6.

C19H28N2O2S (348.50)
Calcd C 65.48 H 8.10 N 8.04%.
Found C 65.32 H 8.02 N 7.76%.

Disproportionation of 7

To a solution of 7 (0.28 g, 0.50 mmol) in methanol (10 ml) was added a solution of NEt3 (50 mg, 0.50 mmol) in methanol (1 ml). The resulting solution contained an...
equimolar mixture of 3a and 8a (vide infra) as evidenced by thin layer chromatography (3a: $R_f = 0.35$, 8a: $R_f = 0.54$). Addition of iodine to the mixture resulted in complete oxidation of 3a to give 8a as the sole product. The product was precipitated by addition of H$_2$O, filtered, and dried in air. Yield: 251 mg (95%). The analytical data for this material are identical to those of 8a (see below).

2-Isopropyl-7-(N-isopropyl-carbamoyl)benzothiazole-3-one (8a)

To a solution of 3a (280 mg, 1.00 mmol) in methanol (10 ml) was added a solution of I$_2$ (254 mg, 1.00 mmol) in methanol (1 ml), followed by a solution of triethylamine (202 mg, 2.00 mmol) in methanol (2 ml). The reaction mixture was stirred for 30 min, water (10 ml) was added, and the solution was acidified to pH = 1 by addition of 6M HCl. The resulting white precipitate was collected by filtration. An analytical sample was obtained by column chromatography (SiO$_2$, eluent 10% MeOH/CH$_2$Cl$_2$, $R_f =$ 0.54). Yield: 3.0 g (46%). IR (KBr, cm$^{-1}$): 3276, 3076 $\nu$(NH), 1622, 1542 $\nu$(CO). $^1$H NMR (CDCl$_3$): $\delta =$ 8.13 (d, $J = 7.7$ Hz, 1H, ArH), 7.98 (d, $J = 7.7$ Hz, 1H, ArH), 7.40 (t, $J = 7.7$ Hz, 1H, ArH), 7.02 (d, $J = 7$ Hz, 1H, NHCH$_2$), 4.91 (spt, $J = 6.9$ Hz, 1H, NHCH$_2$), 4.35 (d, $J = 6.6$ Hz, 6H, CH$_3$), 1.31 (d, $J = 6.6$ Hz, 6H, CH$_3$). $^{13}$C($^1$H) NMR (CDCl$_3$): $\delta =$ 164.9, 164.0, 141.8, 129.2, 127.7, 127.2, 125.0, 124.4, 45.8, 42.5, 22.6, 22.2.

C$_{12}$H$_{19}$N$_2$O$_2$Se (278.37)
Calcd C 60.41 H 6.52 N 10.06%, Found C 60.30 H 6.31 N 9.83%.

2-tert-Butyl-7-(N-tert-butyl-carbamoyl)-benzothiazole-3-one (8b)

This compound was prepared as described above for 8a from 1a and tellurium (2.00 g, 20.0 mmol). Yield: 1.96 g (26%). IR (KBr, cm$^{-1}$): 3236, 3064 $\nu$(NH), 1595, 1554 $\nu$(CO). $^1$H NMR (CDCl$_3$): $\delta =$ 8.86 (d, $J = 7.0$ Hz, 1H, NH), 8.50 (d, $J = 7.7$ Hz, 1H, ArH), 8.14 (d, $J = 7.7$ Hz, 1H, ArH), 7.39 (d, $J = 7$ Hz, 1H, NHCH$_2$), 4.44 (spt, $J = 6.9$ Hz, 1H, NHCH$_2$), 4.38 (d, $J = 7.0$ Hz, 1H, NHCH$_2$), 1.31 (d, $J = 7.0$ Hz, 6H, CH$_3$), 1.30 (d, $J = 7.0$ Hz, 6H, CH$_3$). $^{13}$C($^1$H) NMR (CDCl$_3$): $\delta =$ 168.0, 166.9, 135.9, 132.8, 131.7 (CH), 129.0, 128.1 (CH), 127.4 (CH), 46.0, 43.3, 24.6, 22.5.

C$_{14}$H$_{18}$N$_2$O$_2$SeTe (373.91)
Calcd C 44.97 H 4.85 N 7.49%, Found C 45.13 H 4.83 N 7.31%.

2-isopropyl-7-(N-isopropyl-carbamoyl)benzotriazole-1,3-dione (11a)

To a solution of 8a (278 mg, 1.00 mmol) in acetic acid (3 ml) was added 30% aqueous hydrogen peroxide (1 ml). After stirring for 12 h at r.t., water (25 ml) was added, and the product extracted three times with CH$_2$Cl$_2$ (35 ml). The combined organic phases were washed with 1 M NaHCO$_3$, dried over MgSO$_4$, filtered and evaporated to dryness. The pale yellow solid was recrystal-
lized from CHCl₃. Yield 261 mg (89%). Rf = 0.41 (MeOH/CH₂Cl₂). IR (KBr, cm⁻¹): 3332, 3077 ν(NH), 1701, 1639, 1550 ν(CO), 1080 ν(SO). ¹H NMR (CDCl₃): δ = 8.03 (dd, 2J = 7.5 Hz, 2J = 2.7 Hz, 1H, ArH), 7.92 (dd, 2J = 7.5 Hz, 2J = 2.7 Hz, 1H, ArH), 7.72 (t, 3J = 7.5 Hz, 1H, ArH), 6.69 (d, 3J = 5.5 Hz, 1H, CONH), 4.67 (spt, 3J = 6.9 Hz, 1H, CH₂), 4.33 (d spt, 3J = 7.5 Hz, 1H, CH₂), 1.59 (d, 3J = 6.5 Hz, 3H, CH₃), 1.57 (d, 3J = 6.5 Hz, 3H, CH₃), 1.33 (d, 3J = 6.5 Hz, 3H, CH₃), 1.29 (d, 3J = 6.5 Hz, 3H, CH₃). ¹³C [¹H] NMR (CD₂OD): δ = 165.9, 164.7, 146.1, 145.9, 135.6, 134.7, 134.5, 133.9, 129.1, 129.1, 123.4, 123.1, 142.5, 142.3, 22.6, 22.5, 22.4, 21.8.

C₁₄H₁₈N₂O₃S (294.37)
Calcd C 57.12 H 6.16 N 9.52%.
Found C 57.03 H 6.14 N 9.40%.

2-tert-Butyl-7-(N-tert-butyl-carbamoyl)benzothio­azole-1,3-dione (11b)

This compound was prepared from 8b (308 mg, 1.00 mmol) by the procedure detailed above for 8a. Yield: 245 mg (76%). ¹H NMR (CDCl₃): δ = 8.03 (dd, 2J = 7.5 Hz, 3J = 2.7 Hz, 1H, ArH), 7.89 (dd, 2J = 7.5 Hz, 2J = 2.7 Hz, 1H, ArH), 7.73 (t, 3J = 7.5 Hz, 1H, ArH), 6.50 (br s, 1H, CONH), 1.75 (s, 9H, CH₃), 1.51 (s, 9H, CH₃). ¹³C [¹H] NMR (CD₂OD): δ = 168.0, 166.5, 145.9, 135.6, 134.5, 133.8, 132.9, 129.7, 60.5, 55.3, 30.2, 29.8.

C₁₆H₂₂N₂O₃S (322.42)
Calcd C 59.60 H 6.88 N 8.69%.
Found C 59.43 H 6.64 N 8.44%.

2-isopropyl-7-(N-isopropyl-carbamoyl)benzothio­azole-1,1,3-trione (12a)

To a solution of 8a (278 mg, 1.00 mmol) in acetic acid (3 ml) was added 30% aqueous hydrogen peroxide (5 ml). After the reaction mixture was refluxed for 1 h, water (25 ml) was added, and the product extracted three times with CH₂Cl₂ (35 ml). The combined organic phases were washed with 1 M NaHCO₃, dried over MgSO₄, filtered, and evaporated to dryness. The pale yellow solid was recrystallized from CHCl₃. Yield: 284 mg (92%). IR (KBr, cm⁻¹): 3305, 3081 ν(NH), 1725, 1636, 1552 ν(CO), 1346, 1182 ν(SO). ¹H NMR (CDCl₃): δ = 8.13 (d, 2J = 7.5 Hz, 1H, ArH), 8.01 (d, 2J = 7.5 Hz, 1H, ArH), 7.76 (t, 3J = 7.5 Hz, 1H, ArH), 6.93 (s br, 1H, CONH), 4.45 (spt, 3J = 6.8 Hz, 1H, CH₂), 4.21 (d spt, 3J = 6.7 Hz, 1H, CH₂), 1.54 (d, 3J = 6.8 Hz, 6H, CH₃), 1.21 (d, 3J = 6.8 Hz, 6H, CH₃). ¹³C [¹H] NMR (CDCl₃): δ = 161.6, 157.8, 134.7, 134.5, 134.1, 130.9, 127.7, 126.6, 47.2, 42.6, 22.0, 20.1.

C₁₆H₁₈N₂O₃S (310.37)
Calcd C 54.18 H 5.85 N 9.03%.
Found C 54.31 H 6.01 N 8.78%.

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