Supplementary Material for Organic & Biomolecular Chemistry

Supplementary data

Efficient solid phase synthesis of benzo[1,2,3]thiadiazoles and related structures

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Merrifield resin (1-2% cross-linked, 75-150 mesh) was obtained from Polymer Laboratories with loading = 0.97 mmol/g. In order to get the molecular mass of the resin and to calculate the elemental analysis the following calculation had to be performed:

$$\text{molar mass}_{new} = \frac{1000}{\text{Loading}_{old}} - (\text{molar mass}_{Sub} - \text{molar mass}_{Add})$$

Formula 1: Calculation of the molar mass of a derivatised resin

Solvents for reactions of organometallic and other sensitive materials (toluene, ether, tetrahydrofuran, dichloromethane) were distilled from sodium within an argon atmosphere. All resins were washed sequentially by using a vacuum reservoir connected to a sintered glass frit. Cleavage was conducted using Teflon tubes with a frit connected to a vacuum line or with a glass pipette filled with glass wool or just paper-filtered. Evaporation of the solvent was achieved using a rotavapor and high vacuum subsequently (ca. 0.1 mbar).

General washing procedure

(methanol, THF, pentane, dichloromethane) three times

(methanol, DMF, pentane, THF) once

(pentane, dichloromethane, pentane) two times

General procedure 1 Cleavage Protocol to the [1,2,3]Thiadiazoles

The triazene resin was swollen in 10 ml of dichloromethane and mixed with 0.15 ml of trifluoroacetic acid. The mixture was shaken for 30 min. Then the residue was filtered off and the solvent of the filtrate was removed under reduced pressure.

General procedure 2 Synthesis of piperazine resin

Piperazine (17.2 g, 200 mmol) was dissolved in 100 ml DMF at 60 °C. Subsequently triethylamine (4 ml) and Merrifield-resin (20.0 g, loading 1.00 mmol/g, 20.0 mmol) were added and the suspension was stirred for 48 h with a overhead-stirrer at 60 °C. The resin was washed with DMF, diethylether, THF and MeOH and dried under high vacuum (ca. 0.1 mmbar).

General procedure 3 Synthesis of *ortho* halide triazene resin

The *ortho*-halide aniline derivative (10.0 mmol) was dissolved in 50 ml of THF and cooled down to -20 °C. BF_3·etherate (2 ml, 15 mmol) was added and the solution was stirred for 5 min. *tert*-Butylnitrite (1.90 ml, 14.0 mmol) was added slowly. After 30-90 min the diazonium salt precipitated. The solvent was filtered off with a glass filter. The residue was washed twice with 10 ml THF and was subsequently dissolved in acetonitrile (10 ml). Piperazine resin (2.0 g) was swollen in 40 ml THF, cooled to -20 °C and pyridine (4 ml) was added. While stirring, the solution of the diazonium salt was added. This mixture was shaken for 12 h at room temperature. The resin was washed with THF (until the effluent became colourless), diethylether (3 x) and methanol (3 x) and was afterwards dried under high vacuum (ca. 0.1 mbar).

General procedure 4 Palladium-catalysed synthesis of thiol resin

A sealable tube was charged with $Pd(OAc)_2$ (34 mg, 0.15 mmol), PPh_3 (264 mg, 1.00 mmol) Cs_2CO_3 (1.30 g, 4.00 mmol) and 1.00 g resin and was sealed afterwards. The sealed tube was evacuated and refilled with argon. This procedure was repeated three times. Dry toluene (8 ml) and triisopropyl-silanethiol (476 mg, 2.50 mmol) were added subsequently *via* a syringe. The solution turned deep red. It was then warmed to 85 °C and shaken for 16 h. After cooling, the resin was washed according to the general washing procedure and was dried under high vacuum (ca. 0.1 mbar). The resin was swollen in abs. THF and 2.00 ml of a 1 M solution of TBAF in THF (2.00 mmol) was added. The mixture was shaken for 2 h at room temperature and the resin was washed according to the general washing

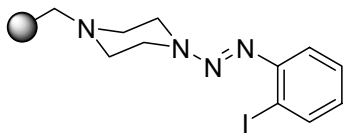
procedure. The resin was subsequently dried under high vacuum (ca. 0.1 mbar). No analyses were recorded, because the analytical data were not significant due to palladium residues on the resin.

General procedure 5 Synthesis of thiol resin via a lithiation protocol

In a dry flask containing an argon atmosphere, 1.00 g triazene resin was suspended in 50 ml THF. After cooling to -40 °C, 0.81 ml (5.40 mmol) TMEDA as well as 3.40 ml *n*-Butyllithium (1.6 M, 5.40 mmol) were added. The mixture was slowly warmed to room temperature and 0.17 g (5.40 mmol) of sulfur were added. After shaking the mixture at room temperature for 12 h, the reaction was hydrolyzed with 10 ml of water and the resin was washed according to the general washing procedure. The resin was subsequently dried under high vacuum (ca. 0.1 mbar).

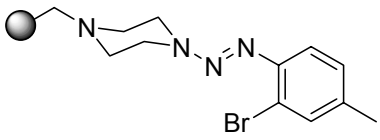
General procedure 6 Synthesis of thioproparyglether resin

In a dry flask with an argon atmosphere, 2.00 g thiol resin, which was synthesised according to the lithiation protocol (General procedure 5), were suspended in 50 ml DMF. After the addition of 1.38 g (10.0 mmol) K_2CO_3 as well as 1.49 g (10.0 mmol) of propargylbromide (80% in THF), the mixture was stirred at 60 °C for 12 h. After cooling to room temperature, 20 ml of water were added and the resin was washed according to the standard protocol.



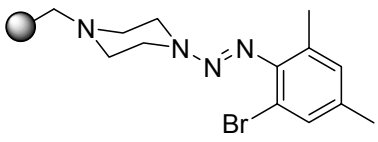
_N_-(2-Iodophenyldiazenyl)piperazinyl-_N'_-methylpolystyrene

The resin was synthesised according to General procedure 3, yielding 2.00 g of a brown solid. EA $C_{86}H_{87}N_4I$: calc. C 79.29, H 6.74, N 4.28 found C 77.11, H 6.81, N 3.70; Loading: 0.49 mmol/g (59%); FTIR (neat, differential towards the Merrifield-resin) ν = 3633, 3536, 3365, 2801, 2768, 2570, 2459, 1683, 1653, 1563, 1470, 1408, 1340, 1301, 1298, 1336, 1319, 1133, 1042, 856, 808, 705 cm^{-1}.



_N_-(2-Bromo-4-methylphenyldiazenyl)piperazinyl-_N'_-methylpolystyrene

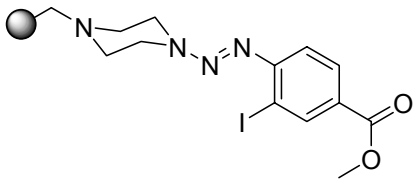
The resin was synthesised according to General procedure 3, yielding 2.00 g of a red solid. EA $C_{87}H_{89}N_4Br$: calc. C 82.27, H 7.08, N 4.39 found C 80.43, H 7.25, N 3.76 Loading: 0.44 mmol/g (52%); FTIR (neat, differential towards the Merrifield-resin) ν = 3649, 3143, 3079, 2800, 2767, 2463, 2365, 1733, 1699, 1684, 1652, 1636, 1507, 1473, 1132, 953, 815, 754, 656 cm^{-1}.



_N_-(2-Bromo-4,6-dimethylphenyldiazenyl)piperazinyl-_N'_-methylpolystyrene

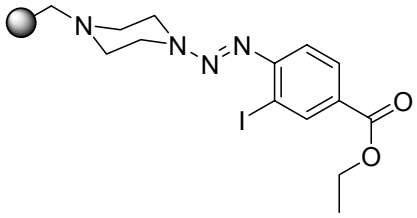
The resin was synthesised according to General procedure 3, yielding 2.00 g of a red solid. EA $C_{88}H_{92}N_4Br$: calc. C 82.27, H 7.08, N 4.63 found C 83.41, H 7.24, N 3.41 Loading: 0.59 mmol/g (75%);

FTIR (neat, differential towards the Merrifield-resin) ν = 3433, 2336, 2310, 1680, 1543, 1351, 1075 cm^{-1}.



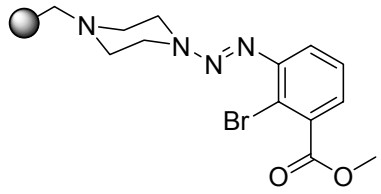
***N*-(2-Iodo-4-methoxycarbonylphenyldiazenyl)piperazinyl-*N'*-methylpolystyrene**

The resin was synthesised according to General procedure 3, yielding 2 g of a light brown solid. EA $C_{88}H_{89}N_4O_2I$: calc. C 77.68, H 6.61, N 4.10 found C 78.22 H 6.98, N 3.54 Loading: 0.60 mmol/g (78%); FTIR (neat, differential towards the Merrifield-resin) ν = 3635, 3540, 3175, 3145, 2986, 2767, 1733, 1693, 1645, 1559, 1472, 1408, 1226, 1134, 855 cm^{-1}.



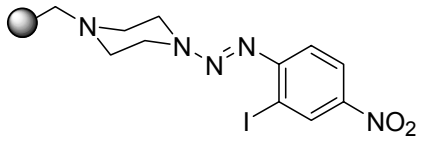
***N*-(2-Iodo-4-ethoxycarbonylphenyldiazenyl)piperazinyl-*N'*-methylpolystyrene**

The resin was synthesised according to General procedure 3, yielding 2 g of a light brown solid. EA $C_{89}H_{91}N_4O_2I$: calc. C 77.76, H 6.69, N 4.06 found C 79.76, H 7.09, N 3.46 Loading: 0.47 mmol/g (60%); FTIR (neat, differential towards the Merrifield-resin) ν = 3544, 3175, 3143, 2987, 2801, 2767, 1690, 1651, 1589, 1556, 1470, 1407, 1340, 1290, 1225, 1167, 1132, 1044, 995, 703 cm^{-1}.



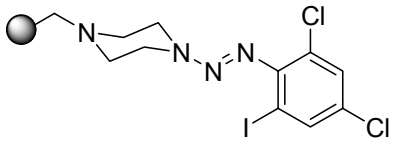
_N_-(2-Bromo-3-methoxycarbonylphenyldiazenyl)piperazinyl-_N'_-methylpolystyrene

The resin was synthesised according to General procedure 3, yielding 2 g of a light brown solid. EA $C_{88}H_{89}N_4O_2Br$: calc. C 80.44, H 6.84, N 4.24 found C 79.51, H 7.13, N 3.77 Loading: 0.54 mmol/g (67%); FTIR (neat, differential towards the Merrifield-resin) ν = 3637, 3545, 3134, 2800, 2766, 2567, 2432, 1735, 1689, 1652, 1565, 1471, 1407, 1133, 1044, 955, 856, 809 cm^{-1}.



_N_-(2-Iodo-4-nitrophenyldiazenyl)piperazinyl-_N'_-methylpolystyrene

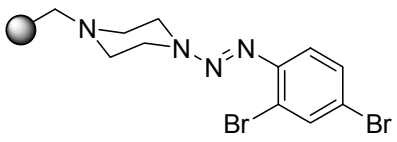
The resin was synthesised according to General procedure 3, yielding 2 g of a brown solid. EA $C_{84.75}H_{84.75}O_{1.66}Cl_{0.17}I_{0.83}N_{4.15}$: calc. C 78.35, H 6.56, N 4.47 found C 77.74, H 6.98, N 4.54 Loading: 0,64 mmol/g (100%); FTIR (neat, differential towards the Merrifield-resin) ν = 3535, 3128, 2983, 2800, 2769, 2612, 1683, 1571, 1523, 1468, 1405, 1227, 1043, 994, 863, 655 cm^{-1}.



_N_-(2-Iodo-4,6-dichloro-phenyldiazenyl)piperazinyl-_N'_-methylpolystyrene

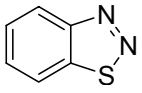
The resin was synthesised according to General procedure 3, yielding 2 g of an orange solid. EA $C_{84.75}H_{83.75}Cl_{1.83}I_{0.83}N_{3.32}$: calc. C 77.17, H 6.40, N 3.53; found C 77.22, H. 6.95, N 3.57 Loading: 0,63

mmol/g (100%); FTIR (neat, differential towards the Merrifield-resin) ν = 3403, 3138, 2984, 2764, 2462, 1685, 1565, 1535, 1469, 1408, 1131, 1043, 994, 860, 808, 707 cm^{-1}.



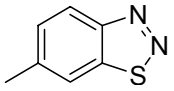
_N_-(2,4-Dibromophenyldiazenyl)piperazinyl-_N'_-methylpolystyrene

The resin was synthesised according to General procedure 3, yielding 2 g of a light brown solid. EA $C_{86}H_{86}N_4Br_2$: calc. C 77.40, H 6.51, N 4.18; found C 74.39, H 6.54, N 3.80; Loading: 0,57 mmol/g (72%); FTIR (neat, differential towards the Merrifield-resin) ν = 3742, 3646, 3522, 3366, 3132, 3080, 3021, 2803, 2768, 2447, 1681, 1569, 1468, 1409, 1341, 1300, 1166, 1131, 1042, 994, 866, 816, cm^{-1}.



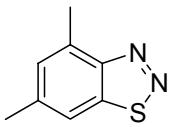
Benzo[1,2,3]thiadiazole

The product was synthesised according to General procedure 4 and General procedure 5. It was purified by column chromatography, yielding 42 mg (0.31 mmol, 62%) by lithiation protocol and 36 mg (0.27 mmol, 53%) by palladium catalysis, respectively, of a light brown solid. R_f = 0.50 (silica gel 60, cyclohexane/ ethyl acetate 5/1); mp: 33-34 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.63 (dd, J = 6.72 Hz, 0.91 Hz, 1 H), 8.10 (dd, J = 7.01 Hz, 0.61 Hz, 1 H), 7.67 (m, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 159.4, 142.0, 130.2, 127.9, 125.0, 120.1; FTIR (neat) ν 3063, 2957, 1778, 1454, 1295, 897 cm^{-1}; EI-MS *m/z* (relative intensity): 136 (66), 108 (100); HR-MS (EI) for $C_6H_4N_2S$ (M^+) calcd 136.0095, found 136.0099.



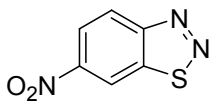
6-Methyl-benzo[1,2,3]thiadiazole

The product was synthesised according to General procedure 4 and General procedure 5. It was purified by column chromatography, yielding 42 mg (0.31 mmol, 62%) by lithiation protokol and 36 mg (0.27 mmol, 53%) by palladium catalysis, of a light brown oil. R_f = 0.45 (silica gel 60, cyclohexane/ ethyl acetate 5/1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.48 (d, J = 8.5 Hz, 1 H), 7.86 (d, J = 1.2 Hz, 1 H), 7.43 (dd, J = 8.5 Hz, 1.2 Hz, 1 H), 2.50 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 157.6, 142.0, 140.7, 129.4, 123.8, 118.9, 22.3; FTIR (neat) ν 2968, 1719, 1550, 1221, 1166, 762 cm^{-1}; EI-MS *m/z* (relative intensity): 150 (51%) [M^+], 121 (100%) [(M^+-N_2]; HRMS (m/z) calculated for $C_7H_6N_2S$ 150.0251, found 150.0249.



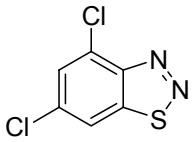
4,6-Dimethyl-benzo[1,2,3]thiadiazole

The product was synthesised according to General procedure 5. It was purified by column chromatography, yielding 50 mg (0.33 mmol, 56%) by lithiation of an red oil. R_f = 0.36 (silica gel 60, cyclohexane/ ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (s, 1 H), 7.16 (s, 1 H,), 2.70 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 141.6, 135.5, 130.8, 129.7, 126.2, 20.6, 18.7; FTIR (neat) 2999 (w, υ Aryl-H) cm^{-1}



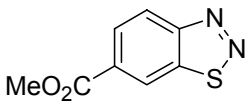
6-Nitro-benzo[1,2,3]thiadiazole

The product was synthesised according to General procedure 4 and was purified by column chromatography, yielding 43 mg (0.24 mmol, 37%) of a light brown solid. R_f = 0.50 (silica gel 60, cyclohexane/ ethyl acetate 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.05 (d, 1 H, *J* = 2.1 Hz, H 7), 8.80 (d, 1 H, *J* = 9.1 Hz, H 4), 8.51 (dd, 1 H, *J* = 9.1 Hz, 2.1 Hz, H 5); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.5, 147.7, 141.1, 124.9, 122.0, 115.7 ppm; FTIR (neat) ν 3098, 1522, 1348, 1289, 1220, 863, 755 cm^{-1}; EI-MS *m/z* (relative intensity): 181 (85), 153 (29), 107 (22), 95 (20), 69 (34), 63 (100); HRMS (m/z) calculated for $C_6H_3O_2N_3S$ 180.9946 found 180.9942.



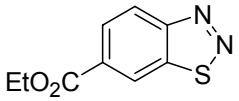
4,6-Dichloro-benzo[1,2,3]thiadiazole

The product was synthesised according to General procedure 4 and was purified by column chromatography, yielding 13 mg (63 μmol, 10%) of a light yellow solid. R_f = 0.90 (silica gel 60, cyclohexane/ethyl acetate 9:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.99 (d, 1 H, *J* = 1.8 Hz), 7.66 (d, 1 H, *J* = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.6, 136.7, 128.4, 127.9, 120.5, 117.2 ppm; FTIR (neat) ν 2927, 1453, 1101, 701 cm^{-1}; EI-MS *m/z* (relative intensity): 208 (5), 206 (35), 204 (51), 180 (9), 178 (46), 176 (86), 141 (25), 97 (21), 43 (100); HRMS (m/z) calculated for $C_6H_2Cl_2N_2S$ 203.9316 found 203.9315.



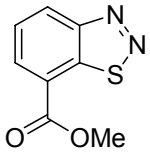
Benzo[1,2,3]thiadiazole-6-carboxylic acid methyl ester

The product was synthesised according to General procedure 4 and was purified by column chromatography, yielding 38 mg (0.20 mmol, 34%) of a white solid. R_f = 0.08 (silica gel 60, cyclohexane/ethyl acetate 9:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.83 (d, 1 H, *J* = 1.4 Hz), 8.69 (d, 1 H, *J* = 8.8 Hz), 8.29 (dd, 1 H, *J* = 8.8 Hz, 1.4 Hz), 4.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.9, 159.7, 140.8, 130.7, 127.7, 123.9, 121.3, 52.9 ppm; FTIR (neat) ν 3109, 2963, 1712, 1433, 1309, 1125, 851, 769 cm^{-1}; EI-MS *m/z* (relative intensity): 194 (41), 166 (22), 135 (100), 107 (15); HRMS (m/z) calculated for $C_8H_6N_2SO_2$ 194.0150 found 194.0146.



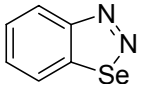
Benzo[1,2,3]thiadiazole-6-carboxylic acid ethyl ester

The product was synthesised according to General procedure 4 and was purified by column chromatography, yielding 39 mg (0.19 mmol, 41%) of a white bluish solid. R_f = 0.31 (silica gel 60, cyclohexane/ethyl acetate 9:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.83 (s, 1 H), 8.69 (d, 1 H, *J* = 8.7 Hz), 8.30 (d, 1 H, *J* = 8.7 Hz), 4.47 (q, 2 H, *J* = 6.8 Hz), 1.45 (t, 3 H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.4, 159.7, 140.8, 131.0, 127.7, 123.8, 121.2, 62.0, 14.3 ppm; FTIR (neat) ν 3109, 2927, 2852, 1717, 1596, 1508, 1426, 1282, 1019, 725 cm^{-1}; EI-MS *m/z* (relative intensity):208 (42), 180 (29), 135 (100), 107 (11), 63 (18); HRMS (m/z) calculated for $C_9H_8N_2SO_2$ 208.0307 found 208.0303.



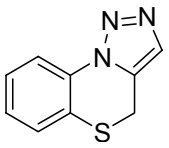
Benzo[1,2,3]thiadiazole-7-carboxylic acid methyl ester

The product was synthesised according to General procedure 4, using only 800 mg resin and was purified by column chromatography, yielding 15 mg (77 μmol, 15%) of a red solid. R_f = 0.20 (silica gel 60, cyclohexane/ethyl acetate 9:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.85 (dd, *J* = 8.3 Hz, 0.9 Hz, 1 H), 8.40 (dd, *J* = 7.3 Hz, 0.9 Hz, 1 H), 7.77 (dd, *J* = 8.3 Hz, 7.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.4, 158.9, 140.6, 130.6, 128.7, 127.2, 123.0, 53.2 ppm; IR (cm^{-1}, KBr): 3091, 2955, 2925, 2853, 1737, 1696, 1561, 1434, 1406, 1285, 1213, 1141, 1025, 845, 761, 608 cm^{-1}; EI-MS *m/z* (relative intensity): 194 (6.), 166 (100), 135 (67), 107 (16); HRMS (m/z) calculated for $C_6H_4N_2S$ 194.0150, found 194.0147.



Benzo[1,2,3]selenadiazole

The product was synthesised according to General procedure 5 using grey selen instead of sulfur and was purified by column chromatography, yielding 11 mg (0.31 mmol, 63%) of a light brown oil. R_f = 0.55 (silica gel 60, cyclohexane/ ethyl acetate 5/1); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* = 8.68 (ddd, *J* = 8.17 Hz, 1.56 Hz, 0.62 Hz, 1 H), 8.12 (ddd, *J* = 7.85 Hz, 1.30 Hz, 0.63 Hz, 1 H), 7.60-7.67 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* = 161.1, 145.0, 129.4, 126.4, 126.4, 123.2 ppm; IR (cm^{-1}, KBr): 2957, 2869, 1677, 11432, 1201 cm^{-1}; EI-MS *m/z* (relative intensity): 184 (50%) [M^+], 156 (100%) [M^+-N_2]; HR-MS (EI) for $C_6H_4N_2S$ (M^+) calcd 183.9539, found 183.9543.



4*H*-[1,2,3]-Triazolo[5,1-c][1,4]benzothiazine

To a stirred solution of 2.00 g thiopropargylether resin (General procedure 6) in 50 ml toluene, 1.14 g (10.0 mmol) trifluoroacetic acid and 1.15 g (10.0 mmol) trimethylsilylazid were added. After refluxing for 1 h, the mixture was filtered and the organic phase washed with saturated sodium bicarbonate solution. After drying over sodium sulfate, the solvent was evaporated and the residue was purified by column chromatography yielding 15 mg of a brown solid (79 µmol, 14% over 4 steps). R_f = 0.10 (silica gel 60, cyclohexane/ethyl acetate 5:1); mp: 65 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.18 (dd, J = 9.5 Hz, 1.5 Hz, 1 H), 7.61 (s, 1 H), 7.29-7.47 (m, 3 H), 4.11 (s, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 139.6, 129.9, 129.2, 128.5, 128.3, 127.8, 124.2, 119.6, 20.0; FTIR (neat): 3296, 2962, 2931, 1693, 1613, 1454; EI-MS *m/z* (relative intensity): 189 (100), 161 (78); HRMS (m/z) calculated for $C_9H_7N_3S$ 189.0360, found 189.0363.