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Synthesis of 6-nitro-4-sulfanyl-1*H*-indole derivatives from 2,4,6-trinitrotoluene

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ABSTRACT

The synthesis of 6-nitro-4-sulfanyl-1*H*-indoles from 2,4,6-trinitrotoluene (TNT) is described. The first step is the nucleophilic substitution of an *ortho*-nitro group with a thiol to give the corresponding sulfide. The latter were transformed into the corresponding enamines upon treatment with dimethylformamide dimethyl acetal (DMF DMA). The enamines were converted into the indoles applying the Batcho–Leimgruber synthetic protocol.

1. Introduction

The synthesis and reactivity of indole derivatives has been a topic research since indole was first synthesized. The main reason of such interest is the wide range of biological activity found among indoles. The indole ring is present in the amino acid tryptophan; indole-3-acetic acid is a plant growth hormone,[1] while 3-(2-aminoethyl)-5-hydroxyindole (serotonin) is one of the key neurotransmitters in animals.[2] The indole ring is also present in many natural products, such as the indole alkaloids,[3] fungal metabolites,[4] and marine natural products.[5] Indoles having sulfur substituents in position 4 have been shown to exhibit strong antibacterial activity.[6] In connection with this, the development of synthetic methods for preparation of indole derivatives with a programmed substitution pattern is of significance for medicinal chemistry and drug discovery. In this contribution we describe an efficient synthesis of 6-nitroindoles bearing a sulfide substituent at position 4. The motivation for the undertaken research is twofold. First, 4,6-disubstituted indoles are generally difficult to synthesize. Second, to suggest a way of a useful utilization of 2,4,6-trinitrotoluene in the synthesis of the biologically potent heterocycles.

In present paper a facile synthesis of 6-nitro-4-sulfanyl-1*H*-indole derivatives from 2,4,6-trinitrotoluene has been developed. The method consists of 3 steps and involves cheap commercially available reagents.

2. Results and discussion

The first step of the synthesis is the nucleophilic substitution of an *ortho*-nitro group in 2,4,6-trinitrotoluene with thiols in the presence of K_2CO_3. This type of the nucleophilic substitution has been studied in detail by Dutov and co-workers.[7] It has been shown that TNT reacts with thiols[8,9] containing various substituents and thiophenols.[8,10] The reaction occurred with primary thiols, secondary thiols (propane-2-thiol, ethyl 2-mercaptopropanoate,[11] cyclohexanethiol), and with 2-aminothiophenol.

Consequently, for the reaction we selected both simple thiols (thiophenol) and thiols containing functional groups such as hydroxy group, protected amino group, and carbomethoxy group. Also we have examined a possibility to substitute the *ortho*-nitro group with dithiols. For this purpose, ethane-1,2-dithiol was used. The reaction of TNT with thiols proceeded smoothly at 20–25 °C in an aprotic polar solvent, e.g. DMF, NMP, HMPTA (Scheme 1).

The NMR analysis of the crude product showed the presence of the *para*-isomer (3–5%) but its re-crystallization from ^{i}PrOH or MeCN allowed isolation of the desired *ortho*-product in 70–85% isolated yields.

The compounds **1a**–**i** readily reacted with dimethylformamide dimethyl acetal in toluene at 80 °C to furnish enamines **2a**–**f** and **2i** with 80–90% isolated yields (Scheme 2). The synthesized enamines are dark red solids readily soluble in toluene, DCM, and alcohol. The high purity (>92%) of the isolated products allowed compounds **2a**–**f** and **2i** to be used in the next step without further purification.

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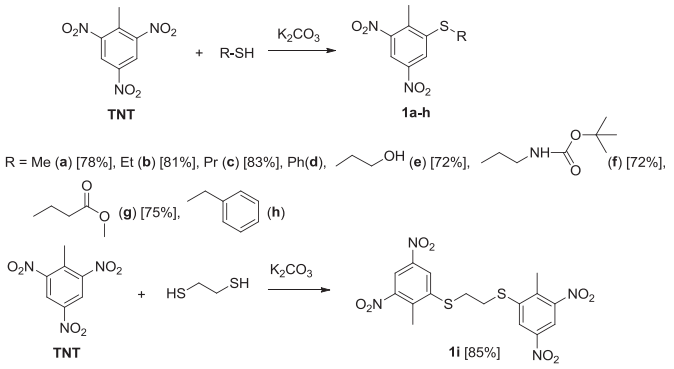
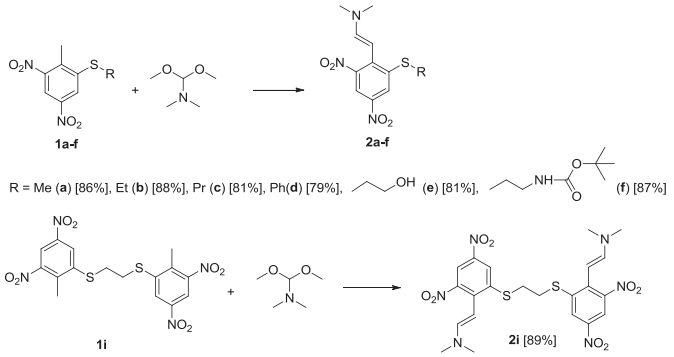


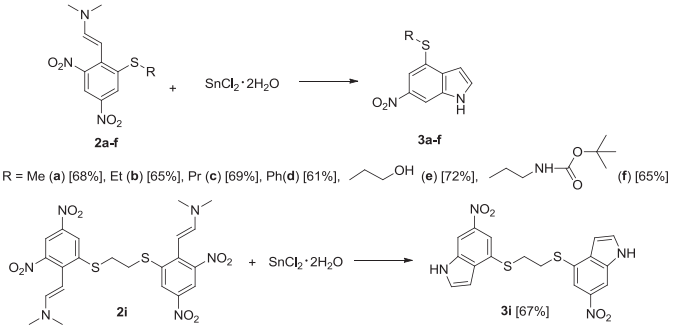
Scheme 1. The preparation of 4,6-dinitro-2-sulfanyltoluene derivatives. Yields (%) given in brackets.



Scheme 2. The preparation of enamine **2**. Yields (%) given in brackets.

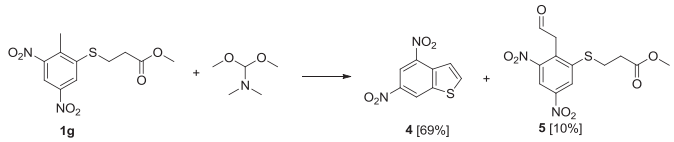
The analytically pure samples of **2** were obtained by recrystallization from $CHCl_3$/hexane.

To transform the enamines into the corresponding indoles the Batcho–Liemgruber synthetic protocol was applied (Scheme 3).[12] The reaction was carried out in a mixture of CH_2Cl_2/MeOH (1:1) with tin(II) chloride as a reducing agent. Tin(II) chloride was used for two reasons. First, the tin salt did not affect the *para*-nitro group of the enamine. Second, the reaction proceeded at room temperature. Upon treatment with $SnCl_2 \cdot 2H_2O$ enamines **2a**–**f** and **2i** were transformed into the corresponding indoles with yields over 50%.



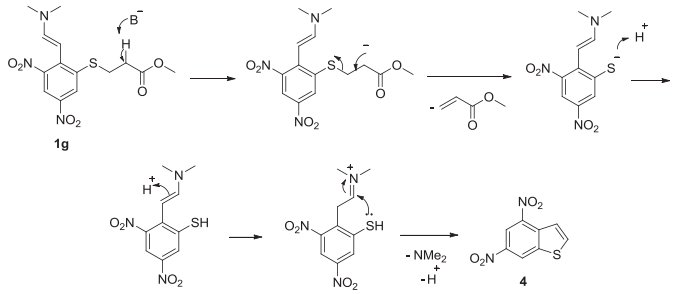
Scheme 3. The Liemgruber–Batcho synthesis of indoles **3**. Yields (%) given in brackets.

Compounds **1g**, **h** did not react properly with dimethylformamide dimethyl acetal. Heating of sulfide **1g** with DMF DMA in toluene gave formerly unknown 4,6-dinitrobenzothiophene **4** and aldehyde **5** (Scheme 4). Compounds **4** and **5** were easily separated by chromatography and product **4** was obtained in a good yield. Aldehyde **5** slowly decomposed upon standing at room temperature. Therefore, it was characterized only by NMR spectroscopy. Most likely, product **5** is a result of a silica gel mediated hydrolysis of the corresponding enamine.



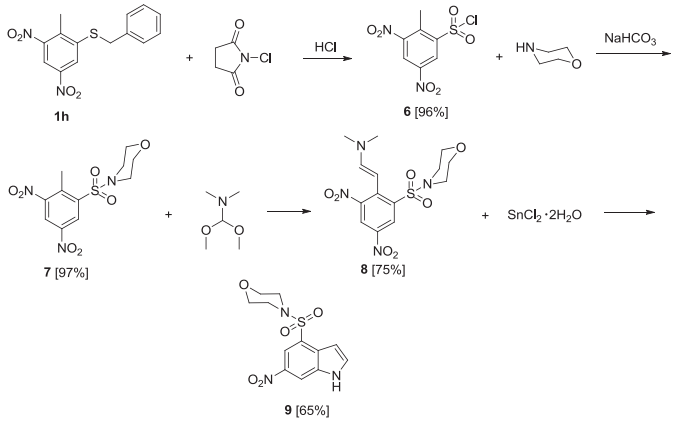
Scheme 4. The reaction of compound **1g** with DMF DMA. Yields (%) given in brackets.

On the basis of the above experimental evidence the *retro*-Michael mechanism was proposed for the formation of 4,6-dinitrobenzothiophene **4** (Scheme 5). The presence of methyl acrylate detected by ^1H NMR analysis of the reaction mixture is another evidence of the suggested mechanism.



Scheme 5. The plausible mechanism of the formation of 4,6-dinitrobenzothiophene **4**.

A reaction of sulfide **1h** with DMF DMA gave no individual product but a complex mixture. However, product **1h** was utilized as a precursor for the synthesis of sulfonyl chloride **6**. It readily reacted with *N*-chlorosuccinimide in the presence of HCl to furnish the corresponding sulfonyl chloride (Scheme 6). Unlike formerly reported multistep preparation[13–15] of compound **6** our method gave the product in two steps from easily available TNT in 85% isolated yield.



Scheme 6. Synthesis of sulfonamide **7** and its transformation into indole **9**. Yields (%) given in brackets.

Sulfonyl chloride **6** was examined in the synthesis of sulfonamides. For this, morpholine was used as an example. The reaction proceeded in water/THF at room temperature in the presence of $NaHCO_3$ yielding sulfonamide **7** in 97% yield. It also was converted into corresponding indole **9** using the Batcho–Liemgruber synthetic protocol in a good yield.

3. Conclusions

The reaction of TNT with thiols(thiophenol) provides 2 substituted 4,6-dinitrotoluenes, which can be transformed into 6-

nitro-4-sulfanyl-1*H*-indoles by Batcho–Liemgruber indole synthesis. Benzyl(2-methyl-3,5-dinitrophenyl)sulfane **1h** has been converted into 4-((2-methyl-3,5-dinitrophenyl)sulfonyl)morpholine **7**, which also has been turned into the corresponding indole. The method shows a versatility of TNT for the synthesis of the biologically potent compounds. The obtained indoles can be useful scaffolds for medicinal chemistry.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR were recorded on a Bruker Avance DRX500 spectrometer (500 MHz and 125 MHz, respectively). Chemical shifts are reported in δ values from TMS as internal standard (s, singlet; d, doublet; m, multiplet; q, quartet; t, triplet; br, broad signal). Coupling constants (*J*) are given in hertz. Melting points measured with a Buchi melting point apparatus. IR spectra were recorded on a Vertex 70 spectrometer. *tert*-Butyl(2-sulfanylehtyl) carbamate, compounds **1d** and **h** were synthesized according to Refs. 16,9,10, respectively.

4.2. General procedure for the synthesis of 4,6-dinitro-2-sulfanyltoluenes 1

To a solution of 2,4,6-trinitrotoluene (5 g, 0.022 mol) and a corresponding thiol (0.022 mol) in 50 mL of DMF K_2CO_3 (3.1 g, 0.022 mol) was added. The mixture was stirred at room temperature for 2 h (TLC monitoring) and poured into 500 mL of 5% HCl. The precipitate was collected by filtration and re-crystallized from ^{i}PrOH (in case of **1i** from MeCN) to give an analytically pure products **1**.

*4.2.1. Methyl(2-methyl-3,5-dinitrophenyl)sulfane (**1a**).* Yield: 3.9 g, 78%; mp=95–97 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.37 (1H, d, *J* 2.0 Hz, H_{arom}), 8.15 (1H, d, *J* 2.0 Hz, H_{arom}), 2.66 (3H, s, SMe), 2.54 (3H, s, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 150.4, 146.1, 145.4, 135.6, 120.5, 114.7, 16.1, 15.7. ν_{max} (KBr) 3070 (CH), 2980 (CH), 1530 (NO_2), 1340 (NO_2) cm^{-1}. Anal. found %: C 42.18; H 3.61; N 12.23; S 14.11; Anal. Calcd for $C_8H_8N_2O_4S$ %: C, 42.10; H, 3.53; N, 12.27; S, 14.05.

*4.2.2. Ethyl(2-methyl-3,5-dinitrophenyl)sulfane (**1b**).* Yield: 4.3 g, 81%; mp=72–74 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.35 (1H, d, *J* 2.1 Hz, H_{arom}), 8.20 (1H, d, *J* 2.1 Hz, H_{arom}), 3.14 (2H, q, *J* 7.3 Hz, SCH_2CH_3), 2.54 (3H, s, Me), 1.47 (3H, t, *J* 7.3 Hz, SCH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 150.6, 145.9, 144.2, 136.4, 121.9, 114.9, 27.0, 16.4, 13.2. ν_{max} (KBr): 3090 (CH), 2990 (CH), 1580 (NO_2), 1530 (NO_2), 1340 (NO_2) cm^{-1}. Anal. found %: C 44.69; H 4.22; N 11.51; S 13.29; Anal. Calcd for $C_9H_{10}N_2O_4S$ %: C, 44.62; H, 4.16; N, 11.56; S, 13.24.

*4.2.3. (2-Methyl-3,5-dinitrophenyl)(propyl)sulfane (**1c**).* Yield: 4.7 g, 83%; mp=89–91 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.34 (1H, d, *J* 2.1 Hz, H_{arom}), 8.19 (1H, d, *J* 2.1 Hz, H_{arom}), 3.06 (2H, t, *J* 7.1 Hz, $SCH_2CH_2CH_3$), 2.53 (3H, s, Me), 1.81 (2H, m, $SCH_2CH_2CH_3$), 1.13 (3H, t, *J* 7.3 Hz, $SCH_2CH_2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 150.7, 145.9, 144.4, 136.4, 122.1, 114.9, 34.9, 21.6, 16.4, 13.5. ν_{max} (KBr) 3080 (CH), 2990 (CH), 1540 (NO_2), 1340(NO_2) cm^{-1}. Anal. found %: C 46.89; H 4.81; N 11.61; S 12.59; Anal. Calcd for $C_{10}H_{12}N_2O_4S$ %: C, 46.87; H, 4.72; N, 11.56; S, 12.51.

*4.2.4. 2-((2-Methyl-3,5-dinitrophenyl)thio)ethanol (**1e**).* Yield: 4.1 g, 72%; mp=70–72 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.38 (1H, d, *J* 2.2 Hz, H_{arom}), 8.34 (1H, d, *J* 2.2 Hz, H_{arom}), 3.99 (2H, t, *J* 6.3 Hz, SCH_2CH_2OH), 3.33 (2H, t, *J* 6.3 Hz, SCH_2CH_2OH), 2.58 (3H, s, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 150.7, 145.8, 143.3, 137.1, 123.0, 115.6, 60.5, 35.8, 16.58. ν_{max} (KBr): 3350 (OH), 3100 (CH), 2950 (CH), 2890 (CH), 1580 (NO_2), 1520 (NO_2), 1390 (NO_2) cm^{-1}. Anal. found %: C 41.89; H 3.91; N 10.91; S 12.51; Anal. Calcd for $C_9H_{10}N_2O_5S$ %: C, 41.86; H, 3.90; N, 10.85; S, 12.42.

*4.2.5. tert-Butyl (2-((2-methyl-3,5-dinitrophenyl)thio)ethyl)carbamate (**1f**).* Yield: 5.7 g, 72%; mp=120–122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.37 (1H, d, *J* 2.1 Hz, H_{arom}), 8.32 (1H, d, *J* 2.1 Hz, H_{arom}), 4.96 (1H, br, NH), 3.47 (2H, m, SCH_2CH_2NHBoc), 3.25(2H, t, *J* 6.2 Hz, SCH_2CH_2NHBoc), 2.56 (3H, s, Me), 1.45 (9H, s, ^{t}Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 155.7, 150.8, 146.0, 143.0, 137.0, 122.9, 115.6, 80.1, 39.2, 33.3, 28.4, 16.6. ν_{max} (KBr): 3290 (NH), 3070 (CH), 2980 (CH), 1680 (C=O), 1530 (NO_2), 1370(NO_2) cm^{-1}. Anal. found %: C 47.09; H 5.41; N 11.81; S 9.05; Anal. Calcd for $C_{14}H_{19}N_3O_6S$ %: C, 47.05; H, 5.36; N, 11.76; S, 8.97.

*4.2.6. Methyl 3-((2-methyl-3,5-dinitrophenyl)thio)propanoate (**1g**).* Yield: 5.0 g, 75%; mp=89–93 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.40 (1H, d, *J* 2.1 Hz, H_{arom}), 8.27 (1H, d, *J* 2.1 Hz, H_{arom}), 3.76 (3H, s, OMe), 3.37 (2H, t, *J* 7.1 Hz, $SCH_2CH_2CO_2Me$), 2.78(2H, t, *J* 7.1 Hz, $SCH_2CH_2CO_2Me$), 2.56 (3H, s, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 171.2, 150.8, 145.9, 142.9, 137.2, 123.1, 115.8, 55.2, 33.0, 28.1, 16.6. ν_{max} (KBr): 3090 (CH), 1740 (C=O), 1530 (NO_2), 1350 (NO_2) cm^{-1}. Anal. found %: C 43.96; H 4.10; N 9.41; S 10.73; Anal. Calcd for $C_{11}H_{12}N_2O_6S$ %: C, 44.00; H, 4.03; N, 9.33; S, 10.68.

*4.2.7. 1,2-Bis((2-methyl-3,5-dinitrophenyl)thio)ethane (**1i**).* Yield: 8.5 g, 85%; mp=195–197 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.49 (2H, d, *J* 2.2 Hz, H_{arom}), 8.31 (2H, d, *J* 2.2 Hz, H_{arom}), 3.57 (4H, s, SCH_2CH_2S), 2.45 (6H, s, Me). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 150.8, 146.2, 141.6, 137.1, 124.7, 116.4, 31.9,16.7. ν_{max} (KBr): 3090 (CH), 1580 (NO_2), 1340 (NO_2) cm^{-1}. Anal. found %: C 42.25; H 3.15; N 12.39; S 14.16; Anal. Calcd for $C_{16}H_{14}N_4O_8S_2$ %: C, 42.29; H, 3.11; N, 12.33; S, 14.11.

4.3. General procedure for the synthesis of enamines 2

To a solution of 4,6-dinitro-2-sulfanyltoluenes **1** (0.01 mol) in 30 mL of toluene 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (3.6 g, 0.03 mol) (in case of **1i** 7.2 g (0.06 mol) of 1,1-dimethoxy-*N*,*N*-dimethylmethanamine was used) was added. The mixture was stirred at 80 °C for 72 h and the solvent was evaporated in vacuo. The product was recrystallized from hexane/$CHCl_3$ (1:1) (in case of **2i** from $CHCl_3$). All enamines showed in IR spectra a broad band from 3600 to 2200 cm^{-1}.

*4.3.1. (E)-N,N-Dimethyl-2-(2-(methylthio)-4,6-dinitrophenyl)ethenamine (**2a**).* Yield: 2.4 g, 86%; mp=93–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.19 (1H, d, *J* 2.1 Hz, H_{arom}), 8.01 (1H, d, *J* 2.1 Hz, H_{arom}), 6.95 (1H, d, *J* 13 Hz, HC=CH), 5.19 (1H, d, *J* 13 Hz, HC=CH), 2.97 (6H, s, NMe_2), 2.58 (3H, s, SMe). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.1, 146.2, 141.6, 139.9, 137.5, 120.9, 116.2, 87.2, 40.8, 16.6. ν_{max} (KBr) 1560 (NO_2), 1510 (NO_2), 1330 (NO_2) cm^{-1}. Anal. found %: C 46.69; H 4.71; N 14.79; S 11.29; Anal. Calcd for $C_{11}H_{13}N_3O_4S$ %: C, 46.63; H, 4.63; N, 14.83; S, 11.32.

*4.3.2. (E)-2-[2-(Ethylsulfanyl)-4,6-dinitrophenyl]-N,N-dimethylethenamine (**2b**).* Yield: 2.6 g, 88%; mp=95–97 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.18 (1H, d, *J* 2.0 Hz, H_{arom}), 8.07 (1H, d, *J* 2.0 Hz, H_{arom}), 6.94 (1H, d, *J* 13.4 Hz, HC=CH), 5.23 (1H, d, *J* 13.4 Hz, HC=CH), 3.05 (2H, q, *J* 7.3 Hz, SCH_2CH_3), 2.97 (6H, s, NMe_2), 1.41 (3H, t, *J* 7.3 Hz, SCH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.2, 146.3, 141.2, 138.2, 138.2, 122.8, 116.6, 87.6, 40.8, 27.7, 13.3. ν_{max} (KBr) 1550 (NO_2), 1510 (NO_2), 1330 (NO_2), 1310 (NO_2) cm^{-1}. Anal.

found %: C 48.43; H 5.13; N 14.19; S 10.69; Anal. Calcd for $C_{12}H_{15}N_3O_4S$ %: C, 48.47; H, 5.08; N, 14.13; S, 10.78.

*4.3.3. (E)-2-(2,4-Dinitro-6-(propylthio)phenyl)-N,N-dimethylethenamine (**2c**).* Yield: 2.5 g, 81%; mp=85–89 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.16 (1H, d, *J* 1.9 Hz, H_{arom}), 8.07 (1H, d, *J* 1.9 Hz, H_{arom}), 6.95 (1H, d, *J* 13.5 Hz, HC=CH), 5.25 (1H, d, *J* 13.5 Hz, HC=CH), 2.99 (2H, q, *J* 7.2 Hz, S*CH*$_2$CH$_2$CH$_3$), 2.97 (6H, s, NMe_2), 1.77 (2H, m, SCH$_2$*CH*$_2$CH$_3$), 1.11 (3H, t, *J* 7.1 Hz, SCH$_2$CH$_2$*CH*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.2, 146.2, 141.1, 138.4, 139.3, 123.0, 116.6, 87.6, 40.8, 35.7, 21.7, 13.6. ν_{max} (KBr) 1560 (NO_2), 1520 (NO_2), 1320 (NO_2) cm^{-1}. Anal. found %: C 50.13; H 5.59; N 13.59; S 10.39; Anal. Calcd for $C_{13}H_{17}N_3O_4S$ %: C, 50.15; H, 5.50; N, 13.50; S, 10.30.

*4.3.4. (E)-2-[2,4-Dinitro-6-(phenylsulfanyl)phenyl]-N,N-dimethylethenamine (**2d**).* Yield: 2.7 g, 79%; mp=100–104 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.21 (1H, d, *J* 1.8 Hz, H_{arom}), 7.87 (1H, d, *J* 1.8 Hz, H_{arom}), 7.44 (5H, m, Ph), 6.99 (1H, d, *J* 13.2 Hz, HC=CH), 5.33 (1H, d, *J* 13.2 Hz, HC=CH), 2.96 (6H, s, NMe_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.6, 146.3, 141.0, 138.6, 137.5, 133.0, 132.1, 130.1, 129.1, 126.6, 117.9, 87.9, 40.8. IR (KBr): 1640 (NO_2), 1580 (NO_2), 1330 (NO_2). Anal. found %: C 55.59; H 4.45; N 12.21; S 9.33; Anal. Calcd for $C_{16}H_{15}N_3O_4S$ %: C, 55.64; H, 4.38; N, 12.17; S, 9.28.

*4.3.5. (E)-2-((2-(2-(Dimethylamino)vinyl)-3,5-dinitrophenyl)thio)ethanol (**2e**).* Yield: 2.5 g, 81%; mp=76–79 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.16 (1H, d, *J* 2.1 Hz, H_{arom}), 8.07 (1H, d, *J* 2.1 Hz, H_{arom}), 6.91 (1H, d, *J* 13.5 Hz, HC=CH), 5.25 (1H, d, *J* 13.5 Hz, HC=CH), 3.92 (2H, t, *J* 6.8 Hz, SCH$_2$*CH*$_2$OH), 3.22 (2H, t, *J* 6.8 Hz, S*CH*$_2$CH$_2$OH), 2.97 (6H, s, NMe_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.7, 144.8, 142.3, 141.2, 132.1, 130.6, 119.0, 106.6, 61.5, 42.8, 35.6. ν_{max} (KBr) 3070 (OH), 1560 (NO_2), 1510 (NO_2), 1340 (NO_2) cm^{-1}. Anal. found %: C 46.03; H 4.73; N 13.49; S 10.39; Anal. Calcd for $C_{12}H_{15}N_3O_5S$ %: C, 46.00; H, 4.83; N, 13.41; S, 10.23.

*4.3.6. (E)-tert-Butyl (2-((2-(2-(dimethylamino)vinyl)-3,5-dinitrophenyl)thio)ethyl)carbamate (**2f**).* Yield: 3.6 g, 87%; mp=130–133 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.20 (1H, d, *J* 2.0 Hz, H_{arom}), 8.17 (1H, d, *J* 2.0 Hz, H_{arom}), 6.95 (1H, d, *J* 13.5 Hz, HC=CH), 5.30 (1H, d, *J* 13.5 Hz, HC=CH), 4.90 (1H, br, NH), 3.41 (2H, br, SCH$_2$*CH*$_2$NHBoc), 3.14 (2H, t, J 7.0 Hz, S*CH*$_2$CH$_2$NHBoc), 2.99 (6H, s, NMe_2), 1.25 (9H, s, ^{t}Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 155.64, 148.6, 146.1, 140.9, 139.2, 136.3, 124.8, 117.5, 87.6, 79.7, 40.8, 39.2, 34.2, 28.4. ν_{max} (KBr) 1690 (C=O),1560 (NO_2), 1520 (NO_2), 1330 (NO_2), 1310 (NO_2) cm^{-1}. Anal. found %: C 49.54; H 5.93; N 13.59; S 7.72; Anal. Calcd for $C_{17}H_{24}N_4O_6S$ %: C, 49.50; H, 5.86; N, 13.58; S, 7.77.

*4.3.7. (1E,1′E)-2,2′-((Ethane-1,2-diylbis(sulfanediyl))bis(2,4-dinitro-6,1-phenylene))bis(N,N-dimethylethenamine)(**2i**).* Yield: 4.9 g, 89%; mp=165–168 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.21 (2H, d, *J* 2.1 Hz, H_{arom}), 8.14 (2H, d, *J* 2.1 Hz, H_{arom}), 6.94 (2H, d, *J* 14.2 Hz, HC=CH), 5.30 (2H, d, *J* 14.2 Hz, HC=CH), 3.24 (4H, s, SCH$_2$CH$_2$S), 2.98 (12H, s, NMe_2). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 149.5, 145.5, 140.3, 139.0, 135.1, 125.3, 118.1, 87.1, 79.7, 40.3 (inside of DMSO multiplet), 32.2. ν_{max} (KBr) 1570 (NO_2), 1520 (NO_2), 1330 (NO_2) cm^{-1}. Anal. found %: C 46.83; H 4.33; N 12.19; S 11.43; Anal. Calcd for $C_{22}H_{24}N_6O_8S_2$ %: C, 46.80; H, 4.28; N, 12.17; S, 11.36.

4.4. General procedure for the synthesis of indoles 3

To a solution of enamine **2** (0.01 mol) in a mixture of MeOH/CH_2Cl_2 (50 mL, 1:1 ratio) $SnCl_2\cdot 2H_2O$ (6.8 g, 0.04 mol) was added in one portion. The mixture was stirred at room temperature overnight and poured into 500 mL of H_2O. The organic layer was separated, the water layer extracted with EtOAc (3×25 mL), the organic layers were combined, and dried over Na_2SO_4. Sodium sulfate was filtered off, the solvent was evaporated, and the crude product was purified on silica gel using hexane/EtOAc as an eluent to furnish pure indole **3**.

*4.4.1. 4-(Methylthio)-6-nitro-1H-indole (**3a**).* Yield: 1.4 g, 68%; mp=155–158 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 12.03 (1H, br, NH), 8.12 (1H, d, *J* 1.6 Hz, H_{arom}), 7.92 (1H, d, *J* 3.0 Hz, H_{ind}), 7.65 (1H, d, *J* 1.6 Hz, H_{arom}), 6.48 (1H, d, *J* 3.0 Hz, H_{ind}), 2.65 (3H, s, SMe). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 143.4, 132.4, 131.6, 130.6, 125.8, 109.2, 103.2, 96.3, 14.4. ν_{max} (KBr) 3350 (NH_{ind}), 2970 (CH), 1540 (NO_2), 1310 (NO_2) cm^{-1}. Anal. found %: C 51.95; H 3.93; N 13.49; S 15.58; Anal. Calcd for $C_9H_8N_2O_2S$ %: C, 51.91; H, 3.87; N, 13.45; S, 15.40.

*4.4.2. 4-(Ethylthio)-6-nitro-1H-indole (**3b**).* Yield: 1.4 g, 65%, mp=160–163 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 12.41 (1H, br, NH), 8.09 (1H, d, *J* 1.7 Hz, H_{arom}), 7.89 (1H, d, *J* 2.7 Hz, H_{ind}), 7.72 (1H, d, *J* 1.7 Hz, H_{arom}), 6.46 (1H, d, *J* 2.7 Hz, H_{ind}), 3.16 (2H, q, *J* 7.6 Hz, S*CH*$_2$CH$_3$), 1.31 (3H, t, *J* 7.6 Hz, SCH$_2$*CH*$_3$). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 143.0, 131.7, 130.9, 130.1, 127.0, 111.5, 103.9, 96.4, 26.1, 14.4. ν_{max} (KBr) 3380 (NH_{ind}), 3010 (CH), 1530 (NO_2), 1340 (NO_2), 1300 (NO_2) cm^{-1}. Anal. found %: C 54.09; H 4.59; N 12.64; S 14.51; Anal. Calcd for $C_{10}H_{10}N_2O_2S$ %: C, 54.04; H, 4.53; N, 12.60; S, 14.43.

*4.4.3. 6-Nitro-4-(propylthio)-1H-indole (**3c**).* Yield: 1.6 g, 69%; mp=84–87 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 12.39 (1H, br, NH), 8.11 (1H, d, *J* 1.8 Hz, H_{arom}), 7.73 (1H, d, *J* 2.9 Hz, H_{ind}), 7.49 (1H, d, *J* 1.8 Hz, H_{arom}), 6.49 (1H, d, *J* 2.9 Hz, H_{ind}), 3.05 (2H, t, *J* 7.8 Hz, S*CH*$_2$CH$_2$CH$_3$), 1.75 (2H, m, SCH$_2$*CH*$_2$CH$_3$), 1.09 (3H, t, *J* 6.9 Hz, SCH$_2$CH$_2$*CH*$_3$). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 143.2, 140.0, 131.1, 130.7, 127.6, 112.5, 103.6, 97.4, 34.6, 22.3, 14.5. ν_{max} (KBr) 3250 (NH_{ind}), 2980 (CH), 1530 (NO_2), 1340 (NO_2) cm^{-1}. Anal. found %: C 55.96; H 5.17; N 11.91; S 15.61; Anal. Calcd for $C_{11}H_{12}N_2O_2S$ %: C, 55.91; H, 5.12; N, 11.86; S, 13.57.

*4.4.4. 6-Nitro-4-(phenylthio)-1H-indole (**3d**).* Yield: 1.6 g, 61%; mp=120–124 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 12.01 (1H, br, NH), 8.25 (1H, d *J* 1.2 Hz, H_{arom}), 7.97 (1H, d, *J* 3.1 Hz, H_{pyrr}), 7.67 (1H, d *J* 1.2 Hz, H_{arom}), 7.42–7.39 (5H, m, Ph), 6.40 (1H, d, *J* 3.1 Hz, H_{pyrr}). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 142.9, 133.1, 132.5, 131.9, 131.4, 130.2, 128.6, 128.3, 127.9, 115.7, 105.4, 97.0. ν_{max} (KBr) 3340 (NH_{ind}), 1520 (NO_2), 1330 (NO_2), 1300 (NO_2). Anal. found %: C 62.25; H 3.76; N 10.40; S 11.92; Anal. Calcd for $C_{14}H_{10}N_2O_2S$ %: C, 62.21; H, 3.73; N, 10.36; S, 11.86.

*4.4.5. 2-((6-Nitro-1H-indol-4-yl)thio)ethanol (**3e**).* Yield: 1.7 g, 72%; mp=135–139 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 12.04 (1H, br, NH), 8.14 (1H, d, *J* 1.3 Hz, H_{arom}), 7.93 (1H, d, *J* 2.9 Hz, H_{pyrr}), 7.82 (1H, d, *J* 1.3 Hz, H_{arom}), 6.52 (1H, d, *J* 2.9 Hz, H_{pyrr}), 5.07 (1H, t, *J* 5.2 Hz, OH), 3.66 (2H, dd, SCH$_2$*CH*$_2$OH), 3.23 (2H, t, *J* 4.5 Hz, S*CH*$_2$CH$_2$OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 143.1, 131.7, 130.8, 130.4, 127.1, 111.8, 103.8, 96.6, 60.2, 34.9. ν_{max} (KBr) 3390 (NH_{ind}), 3190 (OH), 1530 (NO_2), 1350 (NO_2), 1310 (NO_2) cm^{-1}. Anal. found %: C 50.46; H 4.29; N 11.81; S 13.51; Anal. Calcd for $C_{10}H_{10}N_2O_3S$ %: C, 50.41; H, 4.23; N, 11.76; S, 13.46.

*4.4.6. tert-Butyl (2-((6-nitro-1H-indol-4-yl)thio)ethyl)carbamate (**3f**).* Yield: 2.2 g, 65%; mp=138–140 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 12.02 (1H, br, NH), 8.17 (1H, d, *J* 1.3 Hz, H_{arom}), 7.94 (1H, d, *J* 3.1 Hz, H_{pyrr}), 7.85 (1H, d, *J* 1.3 Hz, H_{arom}), 7.05 (1H, br, NH), 6.52 (1H, d, *J* 3.1 Hz, H_{pyrr}), 3.19 (4H, br, S*CH*$_2$*CH*$_2$NHBoc), 1.37 (9H, s, ^{t}Bu). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 156.0, 143.1, 131.9, 130.9, 129.6, 127.5, 112.7, 104.1, 96.7, 78.3, 32.1, 28.7. ν_{max} (KBr) 3440 (NH_{ind}), 3195 (NH), 3000 (NH), 1700 (C=O), 1530 (NO_2), 1330 (NO_2)

cm^{-1}. Anal. found %: C 50.46; H 5.74; N 12.51; S 9.54; Anal. Calcd for $C_{15}H_{19}N_3O_4S$ %: C, 50.40; H, 5.68; N, 12.45; S, 9.50.

*4.4.7. 1,2-Bis((6-nitro-1H-indol-4-yl)thio)ethane (**3i**).* Yield: 2.8 g, 67%; mp=110–114 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 12.04 (2H, br, NH), 8.15 (2H, d, *J* 1.5 Hz, H_{arom}), 7.92 (2H, d, *J* 2.9 Hz, H_{pyrr}), 7.85 (2H, d, *J* 1.5 Hz, H_{arom}), 6.49 (2H, d, *J* 2.9 Hz, H_{pyrr}), 3.39 (4H, s, SCH_2CH_2S). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 142.9, 132.0, 131.0, 128.3, 127.8, 113.6, 104.5, 96.7, 32.2. ν_{max} (KBr) 3410 (NH_{ind}), 1550 (NO_2), 1320 (NO_2) cm^{-1}. Anal. found %: C 52.19; H 3.44; N 13.59; S 15.54; Anal. Calcd for $C_{18}H_{14}N_4O_4S_2$ %: C, 52.16; H, 3.40; N, 13.52; S, 15.47.

4.5. 4,6-Dinitrobenzo[*b*]thiophene 4 and methyl 3-((3,5-dinitro-2-(2-oxoethyl)phenyl)thio)propanoate 5

A solution of compound **1g** (2 g, 0.007 mol) and 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (2.5 g, 0.021 mol) was stirred in 30 mL of toluene at 80 °C for 72 h. The solvent was evaporated and the residue was chromatographed on silica gel eluting with hexane/EtOAc (4:1) to give thiophene **4**, and then gradually increasing the eluent ratio to 2:1 to obtain aldehyde **5**.

*4.5.1. 4,6-Dinitrobenzo[b]thiophene (**4**).* Yield: 1.1 g, 69%; mp=159–162 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.61 (1H, d, *J* 0.8 Hz, H_{arom}), 8.95 (1H, d, *J* 0.8 Hz, H_{arom}), 8.65 (1H, d, *J* 5.5 Hz, H_{thiop}), 8.20 (1H, d, *J* 5.5 Hz, H_{thiop}). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 143.2, 143.1, 142.1, 142.8, 136.3, 126.0, 122.9, 117.3, 79.7. ν_{max} (KBr) 3110 (CH), 1520 (NO_2), 1350 (NO_2), 1310 (NO_2), 790 (thiophene). Anal. found %: C 42.86; H 1.83; N 12.58; S 14.39; Anal. Calcd for $C_8H_4N_2O_4S$ %: C, 42.86; H, 1.80; N, 12.50; S, 14.30.

*4.5.2. 3-((3,5-Dinitro-2-(2-oxoethyl)phenyl)thio)propanoate (**5**).* Yield: 0.2 g, 10%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.82 (1H, s, C*H*O), 8.66 (1H, d, *J* 1.82 Hz, H_{arom}), 8.48 (1H, d, *J* 1.82 Hz, H_{arom}), 4.42 (2H, s, C*H*$_2$CHO), 3.74 (3H, s, OCH_3), 3.34 (2H, t, *J* 7.0 Hz, SCH_2), 2.72 (2H, t, *J* 7.0 Hz, $CH_2CO_2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): 194.7, 171.2, 150.5, 146.7, 143.5, 134.4, 126.5, 117.4, 52.1, 45.0, 33.1, 29.7.

4.6. 2-Methyl-3,5-dinitrobenzene-1-sulfonyl chloride 6

To a mixture of benzyl(2-methyl-3,5-dinitrophenyl)sulfane **1h** (5 g, 0.016 mol) in 10 mL of glacial AcOH and 10 mL (0.1 mol) conc. HCl *N*-chlorosuccinimide (3.2 g, 0.024 mol) was added in small portions at 0–5 °C. The mixture was stirred at room temperature for 5 h and triturated with 100 mL of cold water. The water layer was decanted; the residue was washed with cold water (3×50 mL) with hexane (3×50 mL) and collected by filtration. The solid was dried and used without further purification. The analytically pure sample was obtained by re-crystallization from benzene/hexane (1:1). Yield: 4.3 g, 95%; mp=110–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.17 (1H, d *J* 2.0 Hz, H_{arom}), 8.90 (1H, d, *J* 2.0 Hz, H_{arom}), 3.01 (3H, s, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 152.6, 146.0, 145.6, 139.2, 126.7, 124.5, 16.1. ν_{max} (KBr): 3095 (CH), 1538 (NO_2), 1374 (NO_2), 1353 (NO_2), 1150 (SO_2Cl) cm^{-1}. Anal. found %: C 30.01; H 1.75; N 9.95; S 11.43; Anal. Calcd for $C_7H_5ClN_2O_6S$ %: C, 29.96; H, 1.80; N, 9.98; S, 11.43.

4.7. 4-((2-Methyl-3,5-dinitrophenyl)sulfonyl)morpholine 7

To a solution of $NaHCO_3$ (5 g, 0.059 mol) and morpholine (0.61 g, 0.007 mol) in 100 mL of H_2O a solution of sulfonyl chloride **4** (2 g, 0.007 mol) in 5 mL of THF was added at 0–5 °C. The mixture was stirred at 25 °C for 1 h and the obtained precipitate was collected by filtration to furnish pure sulfonamide **7**. Yield: 1.9 g, 97%; mp=185–187 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.01 (1H, d, *J* 1.9 Hz, H_{arom}), 8.74 (1H, d, *J* 1.9 Hz, H_{arom}), 3.64 (4H, br, CH_2OCH_2), 3.22 (4H, br, CH_2NCH_2), 2.72 (3H, s, Me). ^{13}C NMR (125 MHz, DMSO-d_6): 152.7, 146.0, 139.6, 138.3, 128.0, 123.6, 66.1, 45.6, 16.1. ν_{max} (KBr): 3079 (CH), 2863 (CH), 1539 (NO_2), 1350 (NO_2), 1353 (NO_2), 1173 (S=O), 1147 (S=O), 1107 (S=O) cm^{-1}. Anal. found %: C 39.86; H 3.91; N 12.62; S 9.59; Anal. Calcd for $C_{11}H_{13}N_3O_7S$ %: C, 39.88; H, 3.96; N, 12.68; S, 9.68.

4.8. (*E*)-*N*,*N*-Dimethyl-2-(2-(morpholinosulfonyl)-4,6-dinitrophenyl)ethenamine 8

To a solution of compound **7** (2 g, 0.006 mol) in 30 mL of toluene 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (2.14 g, 0.018 mol) was added. The mixture was stirred at 80 °C for 72 h and the solvent was evaporated in vacuo. The product **8** was re-crystallized from hexane/$CHCl_3$ (1:1). Yield: 1.5 g, 75%; mp=182–184 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.78 (1H, d *J* 2.0 Hz, H_{arom}), 8.40 (1H, d, *J* 2.0 Hz, H_{arom}), 6.87 (1H, d, *J* 13 Hz, CH=CH), 5.85 (1H, d, *J* 13 Hz, CH=CH), 3.74 (4H, br, CH_2OCH_2), 3.27 (4H, br, CH_2NCH_2), 3.04 (6H, s, NMe_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.6, 146.9, 139.1, 138.9, 133.9, 128.6, 123.5, 87.9, 66.4, 66.0, 45.9. ν_{max} (KBr) 1570 (NO_2), 1320 (NO_2) cm^{-1}. Anal. found %: C 43.55; H 4.75; N 14.55; S 8.23; Anal. Calcd for $C_{14}H_{18}N_4O_7S$ %: C, 43.52; H, 4.70; N, 14.50; S, 8.30.

4.9. 4-((6-Nitro-1*H*-indol-4-yl)sulfonyl)morpholine 9

To a solution of enamine **8** (1 g, 2.59 mmol) in a mixture of MeOH/CH_2Cl_2 (25 mL, 1:1 ratio) $SnCl_2\cdot 2H_2O$ (2.33 g, 10.36 mmol) was added in one portion. The mixture was stirred at room temperature overnight and poured into 300 mL of H_2O. The organic layer was separated, the water layer extracted with EtOAc (3×25 mL), the organic layers were combined, and dried over Na_2SO_4. Sodium sulfate was filtered off, the solvent was evaporated, and the crude product was purified on silica gel using hexane/EtOAc (4:1) as an eluent to furnish pure indole **9**. Yield: 0.5 g, 65%; mp=245–247 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 12.37 (1H, br, NH), 8.58 (1H, d, *J* 2.0 Hz, H_{arom}), 8.20 (2H, H_{arom} and H_{pyrr}), 6.84 (1H, d, *J* 2.9 Hz, H_{pyrr}), 3.60 (4H, br, CH_2OCH_2), 3.01 (4H, br, CH_2NCH_2). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 141.5, 134.5, 132.9, 126.7, 124.4, 116.2, 110.4, 98.6, 65.9, 46.3. ν_{max} (KBr) 3440 (NH_{ind}), 3160 (SO_2N), 2940 (SO_2N), 1520 (NO_2), 1480 (NO_2), 1270 (NO_2) cm^{-1}. Anal. found %: C 46.35; H 4.25; N 13.55; S 10.23; Anal. Calcd for $C_{12}H_{13}N_3O_5S$ %: C, 46.30; H, 4.21; N, 13.50; S, 10.30.

References and notes

1. Schneiderland, E. A.; Wrightman, F. *Phytohorm. Relat. Compds. Compr. Treatise* **1978**, *1*, 29.
2. *Biology of Serotonergic Transmission*; Osborne, N. N., Ed.; Jonh Wiley & Son: Chichester, UK, 1982.
3. Southon, I. W.; Buckingham, J. Dictionary of Alkaloids In*Saxton, J. E., Ed., Chemistry of Heterocyclic Compounds*; Chapman and Hall: London, UK, 1989–1994; Vol. 25.
4. Betina, V. *Dev. Food Sci.* **1984**, *8*, 415.
5. Christophersen, C. *Alkaloids* **1985**, *24*, 25; *Mar. Nat. Prod. Chem. Biol. Perspect.* **1983**, *5*, 391.
6. Liang, H.-T.; Hsu, H.-D.; Chang, C.-P.; Ku, H.-E.; Wang, W.-S. *Hua Hsuesh Hsuesh Pao* **1976**, *34*, 129; *Chem. Abstr.* **1977**, *87*, 1659482; *Sci. Sin. (Engl. Ed.)* **1977**, *20*, 106; *Chem. Abstr.* **1977**, *87*, 98565g; Brown, M. J.; Carter, P. S.; Fenwick, A. E.; Fosberry, A. P.; Hamprecht, D. W.; Hibbs, M. J.; Jarvest, R. L.; Mensah, L.; Milner, P. H.; O'Harlon, P. J.; Pope, A. J.; Richardson, C. M.; West, A.; Witty, D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3171.
7. Shevelev, S. A.; Dutov, M. D.; Serushkina, O. V. *Russ. Chem. Bull.* **1995**, *44*, 2424.
8. Zlotin, S. G.; Kistitsin, P. G.; Samet, A. V.; Serebryakov, E. A.; Konyushkin, L. D.; Semenov, V. V.; Buchanan, A. C.; Gakh, A. A. *J. Org. Chem.* **2000**, *65*, 8430.
9. Serushkina, O. V.; Dutov, M. D.; Shevelev, S. A. *Russ. Chem. Bull.* **2001**, *50*, 261.
10. Serushkina, O. V.; Dutov, M. D.; Solkan, V. N.; Shevelev, S. A. *Russ. Chem. Bull.* **2001**, *50*, 2406.

11. Tartakovskii, V. A.; Shevelev, M. D.; Dutov, M. D.; Serushkina, O. V.; Kachala, V. V. *Russ. J. Org. Chem.* **2003**, *39*, 397.
12. Batcho, A. D.; Leimgruber, W. U.S. Patent 3,976,639, 1976. *Chem. Abstr.* **1977**, *86*, 29624; Batcho, A. D.; Leimgruber. *Org. Synth.* **1985**, *63*, 214.
13. Dutov, M. D.; Serushkina, O. V.; Shevelev, S. A. *Russ. J. Org. Chem.* **2007**, *43*, 1167.
14. Hirwe, N. W.; Jambhekar, M. R. *J. Indian Chem. Soc.* **1934**, *11*, 239.
15. Piskov, V. B.; Oksanova, L. K.; Koblova, I. A. *Zh. Org. Khim.* **1969**, *5*, 1642 (in Russian).
16. Saha, U. K.; Roy, R. *J. Chem. Soc., Chem. Commun.* **1995**, 2571.