Pergamon

Tetrahedron 56 (2000) 3933–3940

TETRAHEDRON

Nucleophilic Intramolecular Cyclization Reactions of Alkynechalcogenolates

M. A. Abramov,[a,b] W. Dehaen,[a,*] B. D'hooge,[a] M. L. Petrov,[b,*] S. Smeets,[a] S. Toppet[a] and M. Voets[a]

[a]*Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven (Heverlee), Belgium*
[b]*St. Petersburg State Institute of Technology, Moskovskii pr. 26, 198013 St. Petersburg, Russian Federation*

Received 15 February 2000; accepted 25 April 2000

Abstract—2-(*ortho*-Hydroxyphenyl)-alkynethiolates and -selenolates, obtained through base catalyzed ring cleavage of 4-(*ortho*-hydroxyphenyl)-1,2,3-thiadiazoles and -1,2,3-selenadiazoles, smoothly transform into 2-benzofuranthiolates and -selenolates. These reactive intermediates can be alkylated in high yield. This reaction sequence could be applied to the synthesis of electron rich thiacrown ethers. The 2-(*ortho*-aminophenyl)-alkynethiolate analogously forms 2-methylsulfanylindole. © 2000 Elsevier Science Ltd. All rights reserved.

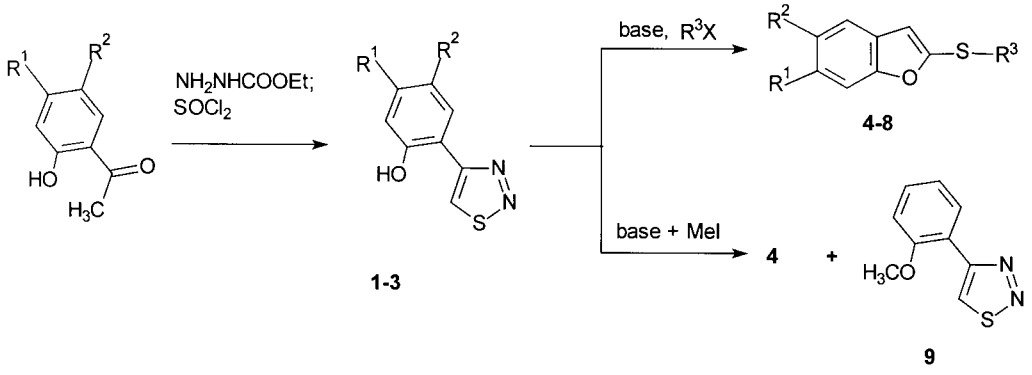
Introduction

1,2,3-Thiadiazoles and 1,2,3-selenadiazoles, that are unsubstituted at the 5 position are usually easily cleaved with liberation of nitrogen and formation of alkynethiolates[1] and alkyneselenolates[2] under the action of strong bases, such as organolithium reagents or potassium ethoxide. The acetylenic thiolates and selenolates have been widely used in organic synthesis for the synthesis of acetylenic sulfides and selenides, in cycloaddition reactions leading to new heterocycles or, after protonation, as a source of reactive thioketenes and selenoketenes.[3]

Results

Some of the results described below have been communicated earlier.[4,5]

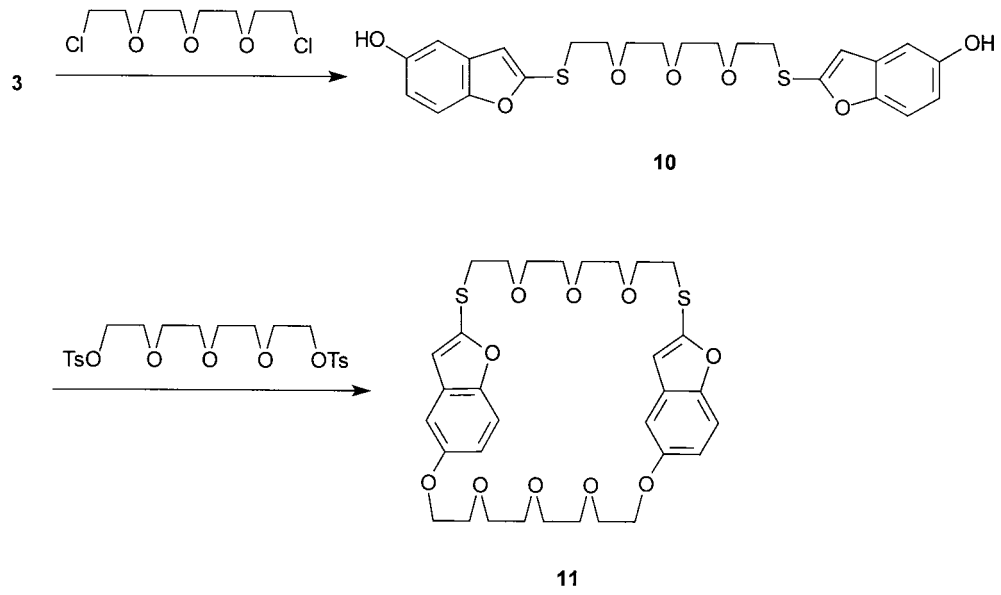
The Hurd–Mori reaction gives access to 4-substituted 1,2,3-thiadiazoles starting from methyl ketones via the reaction of the corresponding ethylcarbazones or tosyl hydrazones with thionyl chloride.[6,7] In order to have an entry to 1,2,3-thiadiazoles, and hence alkynethiolates, having a second functional group, this procedure was used to obtain 4-(*ortho*-hydroxyaryl)-1,2,3-thiadiazoles **1–3** from the



Scheme 1. **1**: R^1=R^2=H; **2**: R^1=OH, R^2=H; **3**: R^1=H, R^2=OH; **4**: R^1=R^2=H, R^3=Me; **5**: R^1=R^2=H, R^3=*n*-hexadecyl; **6**: R^1=R^2=H, R^3=$PhCH_2$; **7**: R^1=OH, R^2=H, R^3=*n*-hexadecyl; **8**: R^1=H, R^2=OH, R^3=*n*-hexadecyl.

Keywords: heterocycles; thiadiazoles; ring opening; cyclization; benzofurans; indoles.
* Corresponding authors. Tel.: +32-16-32-7439; fax: +32-16-32-7990; e-mail: wim.dehaen@chem.kuleuven.ac.be

0040–4020/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(00)00315-X



Scheme 2.

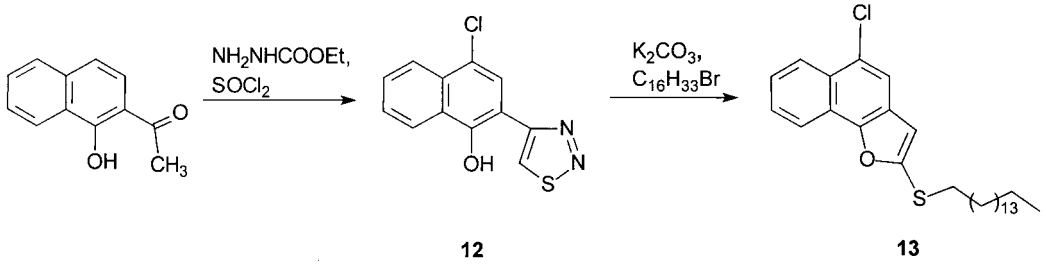
corresponding acetophenones in 37–74% overall yield.[8] When we carried out the base-catalyzed (K_2CO_3) alkylation of **1**–**3**, the unexpected 2-benzofuransulfanyl derivatives **4**–**8** were isolated. To obtain a good yield (90%) of the methylsulfanyl derivative **4** it is necessary to carry out the decomposition reaction of **1** previous to the addition of methyl iodide. In all other cases the alkylating agent (benzyl bromide, 1-bromohexadecane) was present in situ. Reaction of **1** with the much more reactive methyl iodide under the latter conditions gave significant amounts of the *O*-alkylated thiadiazole **9** (40%), next to the benzofuran **4** (56%). Interestingly, the hydroxy functions of **7** and **8** are not alkylated with 1-bromohexadecane under the reaction conditions (see Scheme 1).

An interesting application of this selective alkylation reaction is shown in Scheme 2. 4-(2,5-Dihydroxyphenyl)-1,2,3-thiadiazole **3** was decomposed and alkylated with 0.5 equiv. of 1,11-dichloro-3,6,9-trioxaundecane to give 1,11-bis(5-hydroxybenzofuran-2-sulfanyl)-3,6,9-trioxaundecane **10** in 72% yield. The latter could be transformed by macrocyclization with tetraethylene glycol ditosylate into thiacrown ether **11** in 38% yield. Normally, the synthesis of this type of thia(crown) ethers requires protection/deprotection of the phenolate functions.[9]

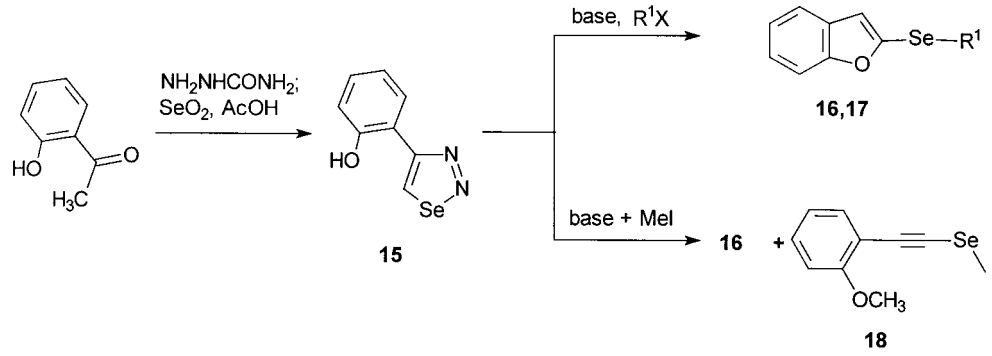
When 2-acetyl-1-naphthol was treated with thionyl chloride, 4-(4-chloro-1-hydroxy-2-naphthyl)-1,2,3-thiadiazole **12** formed unexpectedly. Apparently, the electron rich naphthalene ring is chlorinated under the conditions of the Hurd–Mori reaction. The treatment of the thiadiazole **12** with potassium carbonate in the presence of 1-bromohexadecane lead to 2-*n*-hexadecylsulfanyl-5-chloronaphtho[2,3-a]furan **13** in good yield. A small amount of 4-(4-chloro-1-(hexadecyloxy)-2-naphthyl)-1,2,3-thiadiazole **14** was isolated at the same time. Probably the alkylation reaction of the electron rich naphtholate anion is faster than that of the corresponding phenolate, and will compete with the decomposition reaction (Scheme 3).

We wanted now to study the scope of this reaction by varying both the chalcogen and the nucleophile. Thus, 4-(*ortho*-hydroxyaryl)-1,2,3-selenadiazole **15** was prepared similarly from the semicarbazone of 2-hydroxyacetophenone and selenium dioxide according to the Lalezari procedure[10] in 55% yield. Similarly, the selenides **16**, **17** were obtained in good yield by our tandem decomposition/cyclization/alkylation strategy. When two equivalents of K_2CO_3 base were used in the presence of excess methyl iodide, mainly the acetyleneselenide **18** formed (59% yield), next to small amounts of the benzofuranselenide **16** (see Scheme 4).

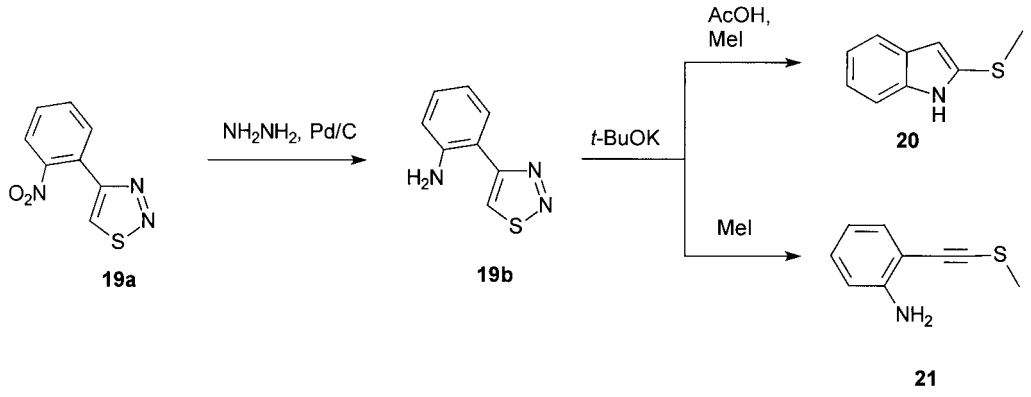
In addition, 4-(2-aminophenyl)-1,2,3-thiadiazole **19b**, prepared by the Hurd–Mori reaction of the semicarbazone



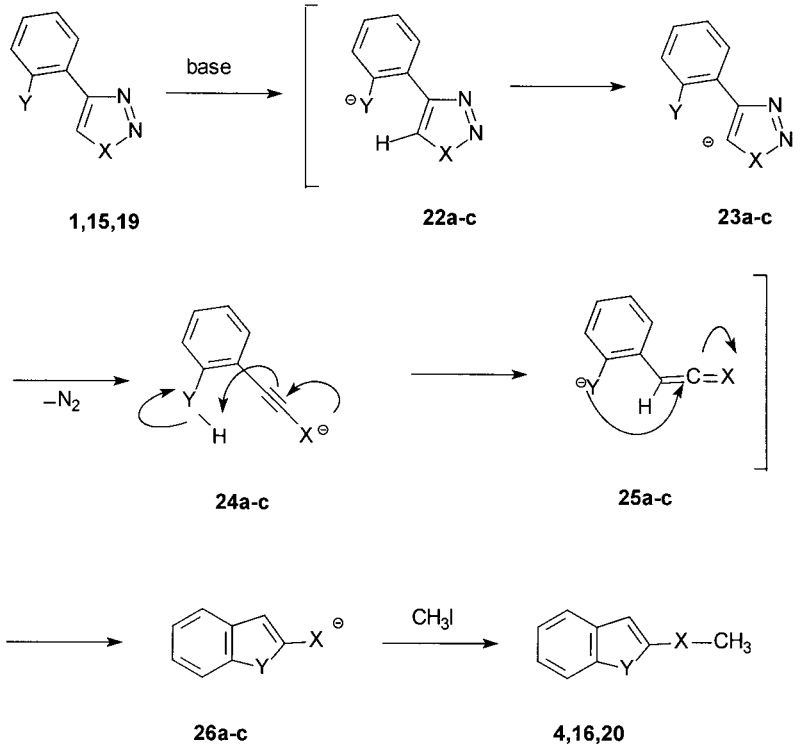
Scheme 3.



Scheme 4. 16: R^1=Me; **17**: R^1=$PhCH_2$.



Scheme 5.



Scheme 6. a: X=S, Y=O; **b**: X=Se, Y=O; **c**: X=S, Y=NH.

of *o*-nitroacetophenone, followed by reduction of the nitro function, formed 2-methylsulfanylindole **20** in 85% yield. In this case we had to use potassium *t*-butoxide as the base. It is very important to add an equivalent amount of acetic acid after the thiadiazole ring cleavage to obtain the indole derivative **20**. When we carried out the methylation without working up of the reaction mixture with acid, only acetylene derivative **21** was isolated in 85% yield (Scheme 5).

Mechanism

We followed the progress of the cyclization reaction of 1,2,3-thiadiazole 1 by ^{1}H NMR spectroscopy in DMSO-d_6 with 1 equiv. of tetrabutylammonium hydroxide and the intermediates **22a**, **24a**, and **26a** were detected as described earlier.[4] On the other hand, in the case of 1,2,3-selenadiazole **15**, the formation of **26b** was observed clearly, without the accumulation of intermediates **22b**–**25b** (see Scheme 6).[5]

The thiolate **26a** apparently results from a multistep process involving the phenolate **22a** which deprotonates the thiadiazole ring with formation of the unstable heteroanion **23a**, which is not detected but immediately decomposes to the alkynethiolate **24a**. Intramolecular proton shift gives the reactive thioketene **25a**, which undergoes intramolecular nucleophilic cyclization to give the thiolate **26a**. Both the cleavage of the 1,2,3-selenadiazole and the ring closure of the resulting alkyneselenolate are too fast to be detected, reflecting the higher reactivity of selenium compounds. The mechanism of the decomposition of aniline goes in a different way. The amine function of **19b** is not acidic enough to form **22c**, therefore **23c** and **24c** are formed directly. This will only occur when the stronger *t*-butoxide base is used, and not in the presence of potassium carbonate. Alkynethiolate **24c** remains stable to intramolecular hydrogen transfer from its amine function and can in fact be alkylated to the acetylene **21**.

Only after the addition of an external source of protons, the thioketene **25c** can be formed and the cyclization to the indole-2-thiolate **26c** takes place.

Experimental

Mp's were determined using a Reichert Thermovar apparatus. NMR spectra were recorded on a Bruker AMX-400 spectrometer. Mass spectra were obtained on a Hewlett–Packard MS Engine no. 5989A in EI (250°C). The solvents DMF, acetone, acetonitrile were dried on molecular sieves 4 Å, and THF was freshly distilled from sodium metal in a nitrogen atmosphere.

4-(*o*-Hydroxyphenyl)-1,2,3-thiadiazole 1.[8] To the ethyl carbazone of *o*-hydroxyacetophenone (1.0 g, 4.50 mmol) thionyl chloride (10 ml) was added while cooling to −78°C with an acetone/CO_2 bath. After the liberation of gas was completed, the reaction mixture was heated gently and then refluxed for 1 h. The excess of thionyl chloride was removed under reduced pressure and the product was purified by silica gel column chromatography with dichloromethane as the eluent. Yield 0.74 g (92%), orange solid, mp 106°C (dichloromethane/*n*-hexane). ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 7.00 (t×d, 1H), 7.15 (d×d, 1H,), 7.36 (t×d, 1H), 7.67 (d×d, 1H), 8.82 (s, 1H, H^5_{het}), 10.54 (s, 1H, OH). ^{13}C NMR spectra ($CDCl_3$, ppm): 114.5, 118.3, 120.1, 127.4, 130.0, 131.4, 156.0, 162.3 (C^4_{het}). Mass spectrum, *m*/*z*, (EI, %): M^+ 458 (21), 176 (11), 150 (18), 149 (100.0), 121 (18), 89 (13), 45 (34), 43 (11).

4-(2,4-Dihydroxyphenyl)-1,2,3-thiadiazole 2. (a) To a solution of 2,4-dihydroxyacetophenone (10.00 g, 32.9 mmol) in a mixture of ethanol (75 ml) and water (75 ml) was added ethyl carbazate (6.84 g, 32.89 mmol). The reaction mixture was refluxed for 22 h and allowed to stay overnight in the refrigerator. The precipitate was filtered off, washed with diethyl ether (2×50 ml) and dried under vacuum. Yield of the carbethoxyhydrazone of 2,4-dihydroxyacetophenone 9.50 g (61%); mp 209°C (ethanol). ^{1}H NMR spectra (DMSO-d_6, δ, ppm): 1.27 (t, 3H, CH_2CH_3), 2.24 (s, 3H, CH_3C═N), 4.19 (q, CH_2CH_3), 6.24 (d, 1H), 6.30 (d×d, 1H), 9.22 (s, 1H, H^5_{het}), 9.75 (br s, 1H), 10.50 (br s, 1H), 13.05 (br s, 1H). ^{13}C NMR spectra (DMSO-d_6, δ, ppm): 13.3, 14.5, 61.0, 103.1, 106.6, 111.7, 129.3, 154.1, 159.8, 160.1. Mass spectrum, *m*/*z*, (EI, %): M^+ 238 (100.0), 237 (26), 221 (44), 192 (33), 165 (23), 150 (20), 149 (25), 136 (59), 135 (39), and 107 (21).

(b) To the ethyl carbazone of 2,4-dihydroxyacetophenone (8.00 g, 33.61 mmol), thionyl chloride (70 ml) was added while cooling to −78°C. After the liberation of gas ceased, the reaction mixture was refluxed for a further 3 h. The excess of thionyl chloride was removed under reduced pressure and the product was purified by silica gel column chromatography with dichloromethane/ethyl acetate (10:3) as eluent. Yield of thiadiazole **2** 4.00 g (61%), mp 209°C. ^{1}H NMR spectra (DMSO-d_6, δ, ppm): 6.43 (d×d, 1H), 6.55 (d, 1H), 8.08 (d, 1H), 9.22 (s, 1H, H^5_{het}), 9.7 (v br s, 1H, OH), 10.32 (br s, 1H, OH). ^{13}C NMR spectra (DMSO-d_6, δ, ppm): 102.9, 107.4, 130.2, 131.9 (C^5_{het}), 156.0, 158.8 (C^4_{het}), 159.2. Found, %: C 49.43; H 3.18; N 14.19. $C_8H_6N_2O_2S$. Calcd: C 49.48; H 3.11; N 14.42.

4-(2,5-Dihydroxyphenyl)-1,2,3-thiadiazole 3. (a) To 2,5-dihydroxyacetophenone (2.00 g, 13.1 mmol) in toluene (50 ml) was added *p*-tosyl hydrazide (2.45 g, 13.1 mmol). The reaction mixture was refluxed for 2 h with azeotropic removal of water and allowed to stay overnight in the refrigerator. The precipitate was filtered off and dried under vacuum. Yield of *p*-tosyl hydrazone of 2,5-dihydroxyacetophenone 3.81 g (90%): mp 192°C. ^{1}H NMR spectra (DMSO-d_6, δ, ppm): 2.22 (s, 3H, CH_3), 2.37 (s, 3H, CH_3C═N), 6.66 (d, 1H), 6.71 (d×d, 1H), 6.84 (d, 1H), 7.44 (d, 2H), 7.78 (d, 2H), 8.9 (br s, 1H, NH), 10.93 (s, 1H, OH). ^{13}C NMR spectra (DMSO-d_6, δ, ppm): 14.6, 21.0, 114.0, 117.4, 118.6, 119.6, 127.4, 129.8, 135.4, 143.9, 149.3, 150.2, 158.1. Mass spectrum, *m*/*z*, (EI, %): M^+ 320 (83), 165 (90), 148 (47), 136 (100.0), 120 (23), 107 (47), 91 (80), 79 (44), 65 (65), 53 (27), 51 (22), and 39 (38).

(b) To the *p*-tosyl hydrazone of 2,5-dihydroxyacetophenone (1.10 g, 3.44 mmol) thionyl chloride (10 ml) was added while cooling to −78°C. After the liberation of gas was

completed, the reaction mixture was allowed to reach room temperature and stirred for a further 2 h. The excess of thionyl chloride was removed under reduced pressure and the product was purified by silica gel column chromatography with dichloromethane/ethyl acetate (10:3) as the eluent. Yield of **3** 0.46 g (69%), mp 216°C. ^{1}H NMR spectra (DMSO-d_6, δ, ppm): 6.74 (d, 1H), 6.89 (d×d, 1H), 7.73 (d, 1H), 9.02 (s, 1H, OH), 9.43 (s, 1H, H^5_{het}), 9.77 (s, 1H, OH). ^{13}C NMR spectra (DMSO-d_6, δ, ppm): 114.9, 117.26, 117.33, 134.7 (C^5_{het}), 147.4, 150.0, 158.4 (C^4_{het}). Mass spectrum, *m/z*, (EI, %): M^+ 194 (94), 166 (35), 137 (100.0), 110 (37), 105 (28), 94 (27), 82 (20), 66 (31), 65 (31), 55 (21), 53 (28), 45 (26), 39 (44). Found, %: C 49.52; H 3.15; N 14.32. $C_8H_6N_2O_2S$. Calcd: C 49.48; H 3.11; N 14.42.

2-Methylsulfanylbenzofuran 4 and 4-(*ortho*-methoxyphenyl)-1,2,3-thiadiazole 9. A mixture of thiadiazole **1** (1.0 g, 5.62 mmol), dry acetone (40 ml), K_2CO_3 (0.93 g, 6.74 mmol), and methyl iodide (1.20 g, 8.43 mmol) was stirred overnight under reflux. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The product was purified by silica gel column chromatography with dichloromethane/cyclohexane (1:2) as the eluent. The first fraction contained 0.52 g (56%) of benzofuran **4**, light-yellow oil. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 2.52 (s, 3H, SCH_3), 6.66 (s, 1H,H^3, ^3J=0.9 Hz), 7.18 (t×d, 1H), 7.22 (t×d, 1H), 7.41 (d, 1H), 7.46 (d, 1H). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 17.0 (CH_3S), 107.8 (C^3_{het}), 110.7, 120.1, 122.8, 123.9, 128.5, 152.2 (C^2_{het}), 156.0. Mass spectrum, *m/z*, (EI, %): M^+ 164 (92), 150 (10), $[M-CH_3]^+$ 149 (100.0), 121 (50), 77 (32), 69 (10), 63 (18), 51 (17). HRMS: M 164.0298. C_9H_8OS. Calculated: M 164.0296. The second fraction contained thiadiazole **9** (0.47 g, 40%). ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 3.96 (s, 3H, OCH_3), 7.06 (d, 1H,H^3), 7.14 (t×d, 1H, H^5), 7.41 (t×d, 1H, H^4), 8.50 (d×d, 1H, H^6), 9.06 (s, 1H, H^5_{het}). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 55.5 (CH_3O), 111.2, 119.6, 121.1, 130.0,130.3, 133.3 (C^5_{het}), 156.3, 158.4(C^4_{het}). Mass spectrum, *m/z*, (EI, %): M^+ 193 (30), $M-N_2$ 164 (81), $M-N_2-CH_3$ 149 (100.0), 131 (50), 121 (100.0), 119 (43), 91 (40), 77 (71), 51 (41), 49 (28), 45 (29), 39 (27).

Note: when MeI was added to a refluxing mixture of thiadiazole **1** and K_2CO_3 in dry acetone the benzofuran **4** was isolated in 90% yield.

2-*n*-Hexadecylsulfanylbenzofuran 5. A mixture of thiadiazole **1** (0.5 g, 2.81 mmol), dry acetone (40 ml), K_2CO_3 (0.47 g, 3.37 mmol), and 1-bromohexadecane (1.03 g, 3.37 mmol), was stirred overnight under reflux. The reaction mixture was evaporated under reduced pressure and the product was purified by silica gel column chromatography with dichloromethane as eluent. Yield of benzofuran **5** 0.97 g (92%), white solid, mp 30°C. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 0.88 (t, 3H, CH_3), 1.25 (s, 24H, $(CH_2)_{12}$), 1.40 (t×d, 2H, $SCH_2CH_2CH_2$), 1.66 (t×d, 2H, SCH_2CH_2), 2.93 (t, 2H, SCH_2), 6.76 (d, 1H, H^3, ^3J=0.9 Hz), 7.20 (t×d, 1H, H^5), 7.25 (t×d, 1H, H^6), 7.43 (m, 1H, H^7), 7.49 (m, 1H, H^4). ^{13}C NMR spectra ($CDCl_3$, ppm): 14.3, 22.7, 28.5, 29.1, 29.4, 29.5, 29.6, 29.7, 31.9, 34.7 (CH_2S), 110.6, 110.9, 120.3, 122.8, 124.2, 128.7, 150.9 (C^2_{het}), 156.2. Mass spectrum, *m/z*, (EI, %): M^+ 374 (100.0), 151 (13), 150 (97), 149 (19, $M-C_{16}H_{33}$), 121 (15), 71 (11), 69 (11), 57 (31), 55 (27), 43 (65), 41 (44). Found, %: C 76.77; H 10.10. $C_{24}H_{38}OS$. Calcd: C 76.95; H 10.22.

2-Benzylsulfanylbenzofuran 6. A mixture of thiadiazole **1** (1.0 g, 5.62 mmol), dry acetone (40 ml), K_2CO_3 (0.93 g, 6.74 mmol), and benzyl chloride (0.85 g, 6.74 mmol) was stirred overnight under reflux. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The product was purified by silica gel column chromatography with dichloromethane/cyclohexane (1:2) as the eluent. Yield of benzofuran **6** 1.28 g (91%), light-yellow oil. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 4.14 (s, 2H, SCH_2), 6.65 (s, 1H, H^3_{het}), 7.17–7.45 (m, 9H, H_{arom}). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 39.3 (CH_2S), 110.9, 111.8 (C^3_{het}), 120.5, 122.8, 124.8, 127.3, 128.5, 128.8, 137.1, 149.6 (C^2_{het}), 156.3. Mass-spectrum, *m/z*, (EI, %): M^+ 240 (58), $[M-CH_2Ph]^+$ 149 (11), 121 (19), 92 (19), 91 (100.0), 77 (16), 65 (25), 39 (12). HRMS: M 240.0609. $C_{15}H_{12}OS$. Calcd: M 240.0609.

2-*n*-Hexadecylsulfanyl-6-hydroxybenzofuran 7. A mixture of thiadiazole **2** (0.50 g, 2.58 mmol), K_2CO_3 (0.429 g, 3.09 mmol), dry acetone (30 ml) and 1-bromohexadecane (0.79 g, 2.58 mmol) was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and product was purified by silica gel column chromatography with dichloromethane as the eluent. Yield of benzofuran **7**: 0.48 g (46%), white solid, mp 65°C. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 0.88 (t, 3H, CH_3), 1.25 (s, 24H, $(CH_2)_{12}$), 1.39 (t×d, 2H, $SCH_2CH_2CH_2$), 1.63 (t×d, 2H, SCH_2CH_2), 2.87 (t, 2H, SCH_2), 4.95 (br s, 1H), 6.73, (d, 1H, H^3), 6.76 (d×d, 1H, H^5), 6.95 (d, 1H, H^7), 7.32 (d, 1H, H^4). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 14.3, 22.7, 28.4, 29.1, 29.4, 29.5, 29.6, 29.7, 31.9, 35.2 (CH_2S), 98.1, 111.7 (C^3_{het}), 111.9, 120.7, 122.2, 149.2, 153.7, 157.2. Mass spectrum, *m/z*, (EI, %): M^+ 390 (100.0), 167 (12), 166 (83), 165 (21), 137 (12), 69 (11), 57 (24), 55 (23), 43 (44), and 41 (30). Found, %: C 73.64; H 9.81. $C_{24}H_{38}O_2S$. Calcd: C 73.80; H 9.71.

2-(*n*-Hexadecylsulfanyl)-5-hydroxybenzofuran 8. To a solution of thiadiazole **3** (0.16 g, 0.82 mmol) and of *t*-BuOK (0.10 g, 0.90 mmol) in dry acetone (10 ml) was added 1-bromohexadecane (0.25 g, 0.82 mmol) and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the product was purified by silica gel column chromatography with dichloromethane as the eluent. Yield of benzofuran **8** 0.31 g (97%), white solid, mp 72°C. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 0.88 (t, 3H, CH_3), 1.25 (s, 24H, $(CH_2)_{12}$), 1.40 (t×d, 2H, $SCH_2CH_2CH_2$), 1.65 (t×d, 2H, SCH_2CH_2), 2.92 (t, 2H, SCH_2), 4.69 (br s, 1H), 6.65, (d, 1H, H^3), 6.76 (d×d, 1H, H^6), 6.89 (d, 1H, H^4), 7.27 d (1H, H^7). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 14.3, 22.7, 28.5, 29.1, 29.3, 29.5, 29.6, 29.7, 31.9, 34.7 (CH_2S), 105.2, 110.1 (C^3_{het}), 111.3, 112.7, 129.5, 151.3, 151.4, 151.9 (C^2_{het}). Mass spectrum, *m/z*, (EI, %): M^+ 390 (51), 167 (13), 160 (100.0), 137 (15), 71 (12), 57 (31), 55 (28), 43 (62), 41 (46). Found, %: C 73.64; H 9.81. $C_{24}H_{38}O_2S$. Calcd: C 73.80; H 9.71.

1,11-Bis(5-hydroxybenzofuran-2-sulfanyl)-3,6,9-trioxaundecane 10. To a mixture of thiadiazole **3** (1.00 g,

5.16 mmol), K_2CO_3 (0.71 g, 5.16 mmol) in dry acetone (40 ml) 1,11-dichloro-3,6,9-trioxaundecane (0.5 equiv., 0.16 g, 2.58 mmol) was added and the reaction mixture was refluxed for 12 h. The resulting suspension was evaporated under reduced pressure and the product was purified by silica gel column chromatography with dichloromethane/ethyl acetate (10:3) as eluent. Yield of ether **10** 0.90 g (72%): white solid, mp 125°C. ^{1}H NMR spectra (DMSO, δ, ppm): 3.11 (t, 4H, SCH_2), 3.62 (t, 4H), 4.45–4.50 (m, 8H), 6.75 (d×d, 2H, H^6), 6.86 (d, 2H, H^3), 6.87 (d, 2H, H^4), 7.31 (d, 2H, H^7). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 33.3 (CH_2S), 69.1, 69.6, and 69.7 (CH_2O), 104.8, 109.3 (C^3_{het}), 111.0, 113.0, 129.0, 149.8, 150.2 (C^2_{het}), 153.4. Mass spectrum, *m/z*, (EI, %): M^+ 490 (68), 192 (14), 167 (12), 166 (36), 165 (100.0), 137 (22), 87 (10), 73 (15), 45 (24). Found, %: C 58.54; H 5.40. HRMS: M 490.1120. $C_{24}H_{26}O_7S_2$. Calcd: C 58.76; H 5.34. M 490.1120.

1,11-Dithiabis-2,5-benzofuro[36]crown-10 11. A mixture of NaH (0.70 g, 24.5 mmol, 80% suspension in oil) and THF (200 ml) was stirred for 30 min and 1,11-bis(5-hydroxybenzofuran-2-sulfanyl)-3,6,9-trioxaundecane **10** (0.60 g, 1.22 mmol) in THF (200 ml) was added dropwise. The reaction mixture was heated to 65°C, the solution of 1,11-bis(tosyloxy)-3,6,9-trioxaundecane (0.74 g, 1.47 mmol) in THF (200 ml) was added dropwise for 12 h and this solution was stirred at 65°C for 72 h. The reaction mixture was allowed to cool to room temperature, several drops of water were added and the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of toluene (200 ml) and water (100 ml), the organic layer was washed with 0.5 N NaOH (50 ml), 2 N HCl (80 ml) and water (2×100 ml). This organic layer was evaporated under reduced pressure and the product was purified by silica gel column chromatography with ethyl acetate as the eluent. Yield of crown ether **11** 0.30 g (38%): white solid, mp 64°C. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 3.09 (t, 4H, SCH_2), 3.58 (t, 8H), 3.65–3.75 (m, 12H), 3.84 (t, 4H), 4.06 (t, 4H), 6.65 (s, 2H, H^3), 6.83 (d×d, 2H, H^6), 6.87 (d, 2H, H^4), 7.23 (d, 2H, H^7). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 33.9 (CH_2S), 68.4, 69.8, 70.0, 70.5, 70.7, 70.79, and 70.84 (CH_2O), 104.1, 11.1 (C^3_{het}), 111.3, 113.8, 129.0, 150.6 (C^2_{het}), 151.4, 155.2. Mass spectrum, *m/z*, (EI, %): M^+ 648 (100.0), 192 (10), 191 (21), 165 (28), 148 (11), 89 (10), 45 (50), 43 (19). Found, %: C 59.31; H 6.25. $C_{32}H_{40}O_{10}S_2$. Calcd: C 59.24; H 6.21.

4-(4-Chloro-1-hydroxy-2-naphtyl)-1,2,3-thiadiazole 12. (a) To a solution of 2-acetyl-1-naphthol (2.00 g, 10.7 mmol) in a mixture of ethanol (20 ml) and water (20 ml) was added ethyl carbazide (1.12 g, 10.7 mmol). The reaction mixture was refluxed for 3 h and allowed to cool overnight. The yellow crystalline precipitate was filtered off and dried under vacuum. Yield of the carbethoxyhydrazone of 2-acetyl-1-naphthol 2.27 g (78%), mp 170°C. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 1.43 (t, 3H, CH_2CH_3), 2.34 (s, 3H, $CH_3C{=}N$), 4.37 (q, 2H, CH_2CH_3), 7.29 (d, 1H), 7.45–7.52 (m, 3H), 7.73 (d, 1H,), 7.8–8.8 (v. br. s, 1H, NH), 8.45 (d, 1H), 13.64 (s, 1H, OH). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 12.4, 14.5, 62.5, 111.9, 117.9, 123.6, 123.7, 125.3, 125.7, 127.0, 127.7, 134.7, 156.4. Mass spectrum, *m/z*, (EI, %): M^+ 272 (100.0), 255 (28), 226 (37), 211 (13), 184 (12), 183 (47), 170 (30), 140 (13), 128 (14), 115 (35).

(b) To the ethyl carbazone of 2-acetyl-1-naphthol (0.70 g, 2.57 mmol), thionyl chloride (10 ml) was added while cooling to −78°C with an acetone/CO_2 bath. When the liberation of gas ceased, the reaction mixture was allowed to reach room temperature and stirred for a further 1 h. The excess of thionyl chloride was removed under reduced pressure and the product was purified by silica gel column chromatography with dichloromethane as the eluent. Yield of **12** 0.17 g (25%), orange solid, mp 153°C. ^{1}H NMR spectra (DMSO-d_6, δ, ppm): 7.70 (t, 1H), 7.77 (t, 1H), 8.16 (d, 1H), 8.41 (s, 1H, H^3_{naphth}), 8.47 (d, 1H), 9.82 (s, H^5_{het}), 11.17 (s, 1H, OH). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 111.5, 121.7, 123.4, 123.8, 125.5, 126.4, 126.7, 128.7, 130.7, 135.5 (C^5_{het}), 150.3, 158.8 (C^4_{het}). Mass spectrum, *m/z*, (I, %): M^+ 262/264 (68/26), 235 (12), 234/236 (56/21), 205 (40), 199 (89), 173 (19), 171 (100.0), 126 (20), 85 (18). Found, %: C 54.24; H 2.77; N 10.44. $C_{12}H_7N_2ClOS$. Calcd: C 54.86; H 2.69; N 10.66.

2-*n*-Hexadecylsulfanyl-5-chloronaphtho[2,3-a]furan 13. To a mixture of thiadiazole **12** (0.13 g, 0.48 mmol) and dry acetone (15 ml) K_2CO_3 (0.47 g, 3.37 mmol) and 1-bromohexadecane (1.03 g, 3.37 mmol) was added and this was stirred under reflux overnight. The mixture was filtered and evaporated under reduced pressure. The reaction product was purified by silica gel column chromatography with dichloromethane/cyclohexane (1:1) as the eluent. Yield of naphthofuran **13** 0.18 g (82%), mp 30°C. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 0.88 (t, 3H, CH_3), 1.25 (s, 24H, $(CH_2)_{12}$), 1.43 (t×d, 2H, $SCH_2CH_2CH_2$), 1.69 (t×d, 2H, SCH_2CH_2), 2.97 (t, 2H, SCH_2), 6.88 (s, 1H, H^3), 7.59 (t, 1H), 7.64 (t, 1H), 7.69 (s, 1H, H^4), 8.31 (d, 1H, H^9). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 14.1, 22.7, 28.4, 29.1, 29.4, 29.5, 29.55, 29.64, 29.67, 29.8, 31.9, 35.4 (CH_2S), 111.9 (C^3), 119.0, 120.5, 121.6, 124.0, 125.4, 126.2, 126.9, 127.2, 128.1, 150.6, 151.0. Mass spectrum, *m/z*, (EI, %): M^+ 458 (100.0), 263 (10), 234 (42), 233 (13, M–$C_{16}H_{33}$), 69 (12), 55 (32), 49 (18), 43 (93), 41 (66). Found, %: M 458.2413. $C_{28}H_{38}OSCl$. Calcd: M 458.2410.

4-(4-Chloro-1-hexadecyloxy-2-naphthyl)-1,2,3-thiadiazole 14 was isolated from the same reaction as a side product with 0.02 g (9%) yield. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 0.88 (t, 3H, CH_3), 1.26 (s, 24H, $(CH_2)_{12}$), 1.85 (q, 2H, $OCH_2CH_2CH_2$), 1.98 (q, 2H, OCH_2CH_2), 3.82 (t, 2H, OCH_2), 7.62–7.69 (m, 2H, H^6_{naphth} and H^7_{naphth}), 8.22 (d), and 8.30 (d, 2H, H^5_{naphth} and H^8_{naphth}), 8.56 (s, 1H, H^3_{naphth}), 9.25 (s, 1H, H^5_{tda}). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 14.1, 22.7, 26.1, 29.3, 29.4, 29.5, 29.6, 29.7, 30.4, 31.9, 74.9 (CH_2O), 120.4, 123.1, 125.1, 126.8, 127.2, 128.0, 128.1, 129.5, 132.2, 134.2 (C^5_{het}), 152.0, 158.8 (C^4_{het}). Mass spectrum, *m/z*, (EI, %): M^+ 486 (23), 413 (25), 262 (54), 234 (61), 234 (26), 202 (67), 43 (100.0), 41 (65).

4-(*o*-Hydroxyphenyl)-1,2,3-selenadiazole 15. To the semicarbazone of *o*-hydroxyacetophenone (3.8 g, 20 mmol) in glacial acetic acid (10 ml) SeO_2 (2.2 g, 20 mmol) was added in one portion. The reaction mixture was heated to 60°C and stirred for 2 h. The dark, cherry red solution was diluted with water (20 ml), the precipitate was filtered off, washed with water and dried. Yield of the crude product **15**: 3.24 g (72%). After recrystallization from a mixture ethanol–water 2.48 g (55%) pure selenadiazole **15** was

isolated as light brown plates, mp 103–105°C. ^{1}H NMR spectra (DMSO-d_6, δ, ppm): 6.99 (q, 1H, H^5_{arom}), 7.08 (d, 1H, H^3_{arom}), 7.28 (q, 1H, H^4_{arom}), 8.26 (d, 1H, H^6_{arom}), 10.09 (s, 1H, H^5_{het}, with satellites $^2J_{HSe}$=42 Hz), 10.35 (br s, 1H, OH). ^{13}C NMR spectra (DMSO-d_6, δ, ppm): 116.4, 119.5, 129.6, 130.1 (C^3, C^4, C^5, C^6_{arom}), 118.8 (C^1_{arom}), 142.1 d (C^5_{het}, $^1J_{CH}$=196 Hz, satellites $^1J_{CSe}$=133 Hz), 155.2 (C^4_{het}). Mass spectrum, *m/z*, (EI, %): M^+ 226(1.5), 198(11.4), 197(11.3), 118(100.0). Found, %: C 42.23; H 2.91. $C_8H_8N_2OSe$. Calcd, %: C 42.69, H 2.69.

2-Methylselenobenzofuran 16. A mixture of selenadiazole **15** (0.4 g, 0.18 mmol), dry acetone (5 ml), and K_2CO_3 (0.3 g, 22 mmol) was stirred under reflux for 2 h and methyl iodide (0.43 g, 30 mmol) was added. After reflux for 1 h the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography with heptane/CCl_4 (1:1) as eluent. Yield of benzofuran **16** 0.29 g (76%), light-yellow oil. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 2.41 (s, 3H, $SeCH_3$), 6.80 (s, 1H, H^3), 7.16 (m, 1H), 7.24 (m, 1H), 7.48 (d, 1H), 7.57 (d, 1H). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 8.0 (CH_3Se), 110.8 (C^3_{het}), 111.5, 120.0, 122.8, 123.9, 128.8, 145.0 (C^2_{het}), 157.0. Mass spectrum, *m/z*, (EI, %): M+ 212 (100.0), 197 (83.8), 169 (33.2), 132 (10.2), 131 (15.3), 89 (44.6).

2-Benzylselenobenzofuran 17. A mixture of selenadiazole **15** (0.5 g, 22 mmol), dry acetone (5 ml), benzyl chloride (0.31 g, 24 mmol), and K_2CO_3 (0.6 g, 43 mmol) was stirred under reflux for 5 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The reaction product was purified by silica gel column chromatography with benzene as the eluent. Yield of benzofuran **17** 0.41 g (65%), light-yellow oil. ^{1}H NMR spectra (CCl_4, δ, ppm): 7.61–6.4 (m, 9H, H_{arom}), 6.52 (s, 1H, H^3_{het}), 3.96 (s, 2H, CH_2Se). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 27.3 (CH_2Se), 110.9 (C^3_{het}), 111.2, 120.5, 122.8, 124.8, 127.3, 128.4, 128.8, 137.1, 145.6 (C^2_{het}), 156.9. Mass spectrum, *m/z*, (EI, %): M^+ 288 (38.7), 197 (19.8), 169 (16.8), 91 (100.0). M287.22.

Methyl (*ortho*-methoxy-phenylethynyl)selenide 18. A mixture of selenadiazole **15** (0.4 g, 18 mmol), dry acetone (5 ml), methyl iodide (0.43 g, 30 mmol), K_2CO_3 (0.3 g, 22 mmol) was refluxed with stirring for 5 h. Then methyl iodide (0.21 g, 15 mmol) was added and stirring was continued for 15 min. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The pure product was obtained by silica gel column chromatography with benzene as the eluent. The first fraction contained a small amount of benzofuran **16**. Yield of **18** 0.13 g (59%), light-yellow oil. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 2.38 (s, 3H, $SeCH_3$), 3.87 (s, 3H, OCH_3), 6.80 (d, 1H, H^3_{arom}), 6.88 (q, 1H, H^5_{arom}), 7.29 (q, 1H, H^4_{arom}), 7.40 (d, 1H, H^6_{arom}). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 9.93 ($SeCH_3$), 55.7 (CH_3O), 75.0 (C≡*C*–Se), 94.3 (*C*≡C–Se), 110.5, 120.3, 123.1, 129.5, 133.3, 157.0. Mass-spectrum, *m/z*, (EI, %): M^+ 226 (63.6), 211 (6.3), 183 (6.3), 168 (14), 131 (100.0), 119 (20.7), 91 (24.7), 77 (9.9).

2-Methylsulfanylindole 20. (a) To the ethyl carbazone of *o*-nitroacetophenone (2.2 g, 10.6 mmol) thionyl chloride (30 ml) was added dropwise while cooling to −78°C with an acetone/CO_2 bath. After the liberation of gas was completed, the reaction mixture was refluxed for 2 h. The excess of thionyl chloride was removed under reduced pressure and the product was purified by silica gel column chromatography with dichloromethane as the eluent. Yield of 4-(2-nitrophenyl)-1,2,3-thiadiazole **19a** 1.55 g (70%), yellow-brown plates, mp 75–76°C. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 7.64 (t×d, 1H), 7.73 (t×d, 1H,), 7.81 (d×d, 1H), 8.00 (d×d, 1H), 8.64 (s, 1H, H^5_{het}). ^{13}C NMR spectra ($CDCl_3$, ppm): 124.6, 125.3, 130.3, 132.1, 132.8, 134.1, 149.0, 157.5 (C^4_{het}). Mass spectrum, *m/z*, (EI, %): MH^+ 208 (100.0), 135 (2), 134 (2).

(b) To a suspension of 5% Pd/C (2 g) in ethanol (160 ml) 4-(2-nitrophenyl)-1,2,3-thiadiazole **19a** (1.21 g, 5.85 mmol) and of hydrazine hydrate (1.46 g, 29.2 mmol) was added. The reaction mixture was refluxed for 24 h, cooled, filtered over Celite and the filtrate was evaporated under reduced pressure. The product was purified by silica gel column chromatography with dichloromethane as the eluent. Yield of 4-(2-aminophenyl)-1,2,3-thiadiazole **19b** 0.81 g (78%), light-red plates, mp 84–85°C. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 5.53 (br s, 2H, NH_2, 6.78–6.84 (m, 2H, H^3_{arom} and H^5_{arom}), 7.21 (t×d, 1H, H^4_{arom}), 7.49 (d×d, 1H, H^6_{arom}), 8.62 (s, 1H, H^5_{het}). ^{13}C NMR spectra ($CDCl_3$, δ, ppm): 114.4 (*ipso*-TDA), 117.2, 117.9, 129.5, 130.4 (C^5_{het}, $^1J_{CH}$= 190 Hz), 130.8, 145.5 (*ipso*-NH_2), 163.1 (C^4_{het}). Mass spectrum, *m/z*, (EI, %): M^+ 177 (63), 149 (78), 117 (100.0), 89 (33), 77 (26), 49 (32).

(c) To 4-(2-aminophenyl)-1,2,3-thiadiazole **19b** (0.15 g, 0.85 mmol) in THF (20 ml) *t*-BuOK (0.112 g, 1 mmol) was added under argon and mixture was stirred for 15 min, when the liberation of gas ceased. One drop of acetic acid was added, and the reaction mixture was stirred for another 10 min, follow by adding MeI (0.18 g, 1.275 mmol) in one portion. The mixture was stirred for 1 h, the solvent was removed under reduced pressure and the product was purified by silica gel column chromatography with hexane/dichloromethane (1:3) as the eluent. Yield of 2-methylsulfanylindole **20** 0.12 g (85%), light-brown solid, mp 47–48°C (mp 48–49[11]). ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 2.44 (s, 3H, SCH_3), 6.52 (s, 1H,H^3), 7.07–7.20 (m, 3H), 7.50 (d, 1H), 8.00 (br s, 1H, NH).

When the reaction was carried out without the addition of acetic acid only 2-(2-aminophenyl)ethynylsulfanylmethane **21** was isolated in 85% yield as an oil. ^{1}H NMR spectra ($CDCl_3$, δ, ppm): 2.44 (s, 3H, SCH_3), 4.20 (br s, 2H, NH_2), 6.65 (m, 2H), 7.08 (m, 1H), 7.23 (m, 1H). Mass spectrum, *m/z*, (EI, %): M^+ 163 (73), 148 (100.0), 121 (21), 104 (11), 77 (13), 49 (8).

Acknowledgements

We thank the University, the Ministerie voor Wetenschapsbeleid and the FWO Vlaanderen for their continuing support. B. D. and S. S. thanks the I.W.T. for predoctoral fellowship.

References

1. Raap, R.; Micetich, R. G. *Can. J. Chem.* **1968**, *46*, 1057.
2. Laishev, V. Z.; Petrov, M. L.; Petrov, A. A. *Zh. Org. Khim.* **1982**, *18*, 281 (see also p. 514).
3. Zmitrovich, N. I.; Petrov, M. L. *Zh. Obsch. Khim.* **1999**, *35*, 781; Murai, T.; Esaka, T.; Kato, S. *Bull. Chem. Soc. Jpn* **1998**, *71*, 1193; Murai, T.; Kakami, K.; Hayashi, A.; Komuro, T.; Takada, H.; Fujii, M.; Kanda, K.; Kato, S. *J. Am. Chem. Soc.* **1997**, *119*, 8592; L'abbé, G.; Dehaen, W.; Haelterman, B. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2203; Terenteva, N. A.; Petrov, M. L.; Potekhin, K. A.; Galichev, B. A.; Struchov, Yu. T. *Zh. Org. Khim.* **1994**, *30*, 1471; Ishihara, H.; Yoshimi, M.; Kato, S. *Angew. Chem.* **1990**, *102*, 572; Petrov, M. L.; Petrov, A. A. *Usp. Khim.* **1987**, *61*, 267.
4. D'hooge, B.; Smeets, S.; Toppet, S.; Dehaen, W. *J. Chem. Soc., Chem. Commun.* **1997**, 1753.
5. Petrov, M. L.; Abramov, M. A.; Dehaen, W.; Toppet, S. *Tetrahedron Lett.* **1999**, *40*, 3903.
6. Butler, R. N.; O'Donoghue, D. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1223.
7. Hurd, C. D.; Mori, R. I. *J. Am. Chem. Soc.* **1955**, *77*, 5359.
8. The synthesis of thiadiazole **1** has been reported before in a patent without experimental data: Muchowski, J. M.; Fried, J. H. US Pat. 3940407, 1976; *Chem. Abstr.* **1976**, *85*, P63072a.
9. Asakawa, M.; Ashton, P. R.; Dehaen, W.; L'abbe, G.; Menzer, S.; Nouwen, J.; Raymo, F. M.; Stoddart, J. F.; Tolley, M. S.; Toppet, S.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1997**, *3*, 772.
10. Lalezari, I.; Shaffiee, A.; Yalpani, M. *Tetrahedron Lett.* **1969**, *58*, 5105; Caplin, A. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 30; Lalezari, I.; Shaffiee, A.; Yalpani, M. *J. Org. Chem.* **1971**, *36*, 2836.
11. Plate, R.; Ottenheijn, H. C. J. *Tetrahedron* **1986**, 4510.