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Synthesis of Novel Dioxinobenzothiazole Derivatives

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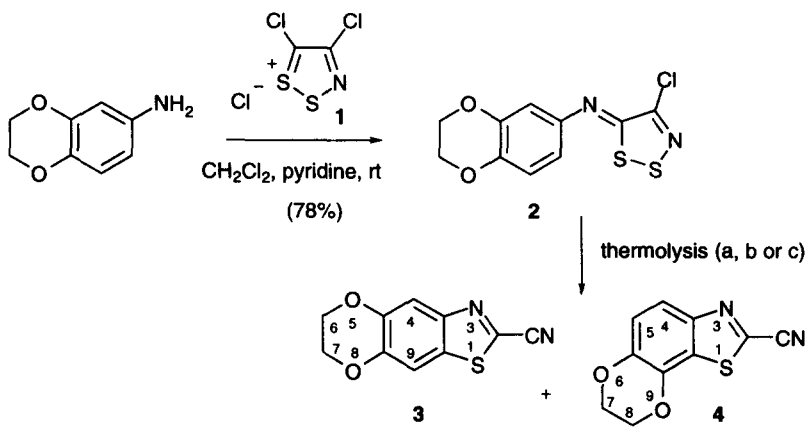
Abstract: The synthesis of new dioxinobenzothiazoles is described. Introduction of the thiazole moiety of these new polyheterocyclic systems was realised by the use of imino-1,2,3-dithiazoles. Several steps in these multistep synthesis were transposed to a focused microwave oven.

Present in many natural and synthetic products, the 2,3-dihydro-1,4-benzodioxin ring has generated much interest in chemistry on account of its excellent biological activity.[1] Because we are interested in new polyheterocyclic systems with potential pharmacological value we decided to prepare new tricyclic thiazolobenzodioxin derivatives. The resulting structures are related to thiazoles which have shown antitumor activity.[2] Fusion of the thiazole ring onto the benzodioxin skeleton suggested the use of imino-1,2,3-dithiazoles which have proved to be highly versatile intermediates in heterocyclic synthesis. [3] In this paper we describe the synthetic route to these new polyheterocyclic compounds. In the course of our work on the application of microwaves in organic chemistry,[4-6] we have transposed many of the reactions to a focused microwave oven (open oven, monomode system) especially designed for organic synthesis with the aim of achieving striking reductions in reaction times, better yields and cleaner reactions than for the purely thermal processes.

Using a standard method applied for the preparation of *N*-arylimino-1,2,3-dithiazoles,[3] the starting 6-aminobenzodioxan was condensed with 4,5-dichloro-1,2,3-dithiazolium chloride **1** in dichloromethane at room temperature, followed by addition of pyridine, to give the desired imine **2** in a good yield (Scheme 1).



Scheme 1. *Thermolysis conditions (for time and yield see Table)* : a) neat, sealed tube, argon, 200°C; b) neat, sealed tube, argon, microwaves, 300W; c) $PyHBr_3$ (1 eq.), DMF/pyridine, reflux.

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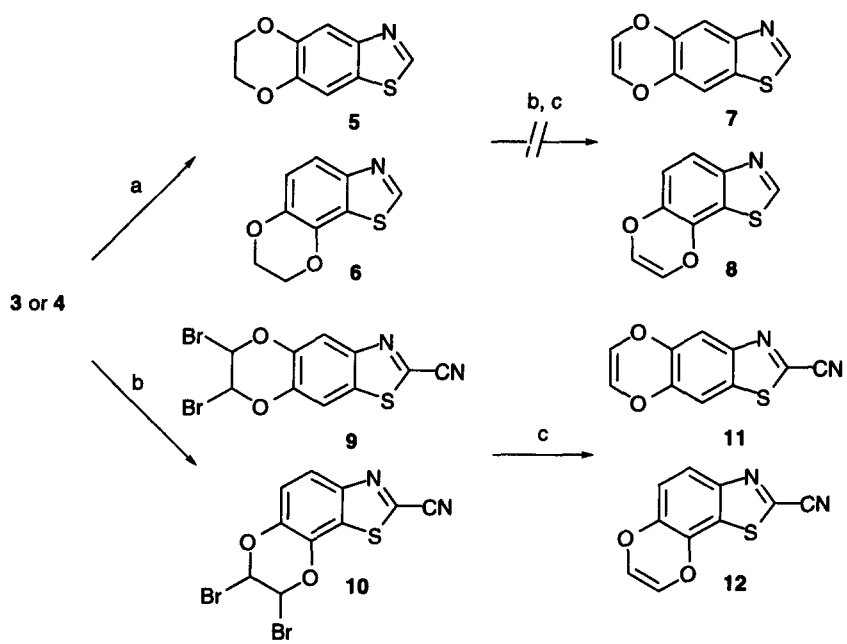
Previous work showed that similar *N*-arylimino compounds cyclised on vigorous heating to give sulfur, hydrogen chloride and 2-cyanobenzothiazoles.[5] The thermolysis procedures consist of heating the neat imine **2** under argon at 200°C (carbon graphite bath) for 3 minutes, or exposing this iminodithiazole to microwave irradiation (neat in a glass vial with a screw-cap lid).[5] A third method consists of heating (oil bath or microwave irradiation) the starting compound **2** in a mixture of pyridine/dimethylformamide at reflux in the presence of pyridinium tribromide. Whatever conditions were used, the two 2-cyanothiazoles **3** and **4** were obtained in very similar yields (see Table). Elimination (hydrolysis and decarboxylation) of the cyano group in the thiazole ring was performed by vigorous heating of compounds **3** and **4** in concentrated hydrochloric acid. The decyanated thiazolobenzodioxins **5** and **6** were isolated in good yields.

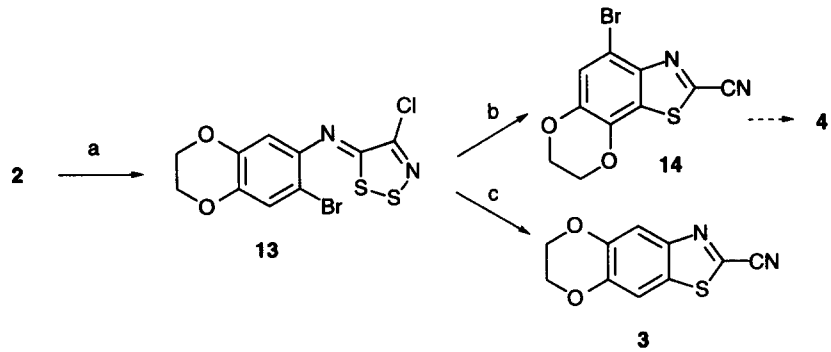
The next step was to introduce unsaturation into the dihydrobenzodioxin ring. The bromination[7] (NBS, CCl_4, AIBN)-debromination (NaI, acetone) sequence previously described in several syntheses of benzodioxins did not lead to the expected compounds **7** and **8**. In fact, the bromination step gave a complex mixture of brominated products. Applying the preceding method to the starting thiazoles **3** and **4** allowed the synthesis of the desired compounds **11** and **12** in good yields *via* the brominated intermediates **9** and **10**. The debromination reaction of this process (**9** → **11** and **10** → **12**) was also transposed to a open microwave oven (Table). Synthesis of the decyanated derivatives **7** and **8** from **11** and **12** was not possible whatever conditions were used. An alternative procedure to reach **7** and **8** from the 1,4-benzodioxin-6-amine was also studied; unfortunately direct introduction of the unsaturation into the starting 2,3-dihydro-1,4-benzodioxin-6-amine failed and afforded complex mixtures (Scheme 2).



Scheme 2. *Reagents and conditions* : a) HCl, reflux; b) NBS / AIBN, CCl_4, reflux, 10h, 71% (**9**) and 30% (**10**); c) NaI, acetone, reflux (for time and yield see Table).

Because we were not satisfied by the relatively low overall yield observed for the formation of the angular isomer **12**, we wished to improve the yield of **4** by a preliminary bromination of the starting imine **2**. Thermal cyclisation of the dithiazole **13** and debromination[8] of the angular bromodioxinobenzothiazole **14** was expected to give **4** in better yield. However, the first step gave the *ortho*-brominated imine **13** in very good yield (98%);

thermolysis of this product proceeded in very low yield (less than 20%) whatever method (metal bath or microwaves) was applied. In contrast we discovered that heating the bromo derivative **13** in the presence of cuprous iodide in pyridine at reflux afforded a very good yield of the linear isomer **3** improving the overall yield of the dioxin analogue **11**.[6] As described before for the other thermal reactions, the reaction time was reduced by exposing the mixture to microwaves (Scheme 3, Table).



Scheme 3. *Reagents and conditions (for time and yield see Table):* a) Br_2 (1 eq.), CH_3COOH, rt, 2h, 98%; b) $PyHBr_3$ (1 eq.), DMF/pyridine, reflux; c) CuI (1 eq.), pyridine, reflux.

Table. Reaction results with conventional heating or under microwave irradiation.

Starting material	Product	Conventional heating[a]		Microwave irradiation[b]	
		reaction time (min)	Yield (%)	reaction time (min)	Yield (%)
2	**3**[c]	3	30	4.5	31
2	**3**[d]	90	29	5.5	42
2	**4**[c]	3	15	4.5	14
2	**4**[d]	90	29	5.5	42
13	**3**[e]	90	55	20	68
3	**5**[f]	150	70	15	80
4	**6**[f]	150	51	15	65
9	**11**[g]	120	98	30	97
10	**12**[g]	120	90	30	90
13	**14**[d]	120	25	25	45

a) oil bath; b) microwaves, 300W; c) 200°C , metal bath; d) $PyHBr_3$ (1 eq.), DMF/pyridine, reflux ; e) CuI, pyridine, reflux. f) HCl, reflux; g) NBS / AIBN, CCl_4, reflux, 10h,

The recent development and use of open focused microwave ovens[9] allow comparison of conventional heating (oil or metal bath) and microwave irradiation. The experimental conditions are now similar except for the heating source. On this point our results confirm that focused microwave irradiation is a very powerful technique for accelerating thermal organic reactions. To our knowledge this is the first time that several steps in a multistep synthesis were performed under microwave irradiation; this result opens the door to many promising applications.

EXPERIMENTAL

Mps were determined using a Kofler block and are uncorrected. IR spectra were recorded on a Perkin-Elmer Paragon 1000PC instrument. ^{1}H and ^{13}C-NMR were recorded on a JEOL JNM LA400 (400 MHz) spectrometer (Laboratoire Commun d'Analyse, Université de La Rochelle); chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) which was used as internal standard. Coupling constants *J* are given in Hz. Mass spectra were recorded on a Varian MAT311 spectrometer in the Centre de Mesures Physiques de L'Ouest (C.R.M.P.O.), Université de Rennes. Chromatography was carried out on silica gel 60 at medium pressure and the reaction mixtures were applied to the column preadsorbed onto silica. Light petroleum refers to the fraction b.p. 40-60°C. Further solvents were used without purification. Thin-layer chromatography was performed on Merck Kieselgel 60 F254 aluminium backed plates.
Focused microwave irradiations were carried out at atmospheric pressure with a Synthewave S402 (capacity of the quartz reactors used: 10 and 70 ml) Prolabo microwave reactor (300W, monomode system) which has a quartz reactor, variable speed rotation, visual control, irradiation (300W) monitored by PC computer, infrared measurement and continuous feedback temperature control (by PC).[9]

The salt **1** is a pale greenish yellow solid, insoluble in organic solvents. It is completely stable in a dry inert atmosphere but reacts slowly with moisture to form 4-chloro-1,2,3-dithiazol-5-one.[10]
Spectral data for compound **2** are consistent with assigned structures as previously described in ref. 11.

Dihydro[1,4]dioxinobenzothiazoles 3 and 4: thermolysis procedures
Method A: conventional heating : *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2,3-dihydro-1,4-benzodioxin-6-amine **2** (0.1 g, 0.35 mmol) was heated under nitrogen at 200° C (carbon graphite bath). The product was purified by column chromatography. Light petroleum-dichloromethane eluted sulfur and then the desired product.
Method B: microwave irradiation. Starting imine **2** was placed in the microwave oven in a 10 ml glass vial with a screw-cap lid. The irradiation was programmed for 15 min with a delay of 5 s to obtain 100% power output (300W). The initial temperature (infrared measurement) was constant over a period of 30 s to 1 min followed by a sharp increase in temperature over a period of 2 to 3 min. Thereafter, the temperature appeared to reach a plateau (105-106°C) and remained constant. The irradiation was stopped one minute later. After cooling, the crude product was purified as above .
Method C: cyclisation with $PyHBr_3$. Pyridinium tribromide (0.383 g, 1.2 mmol) and starting imine (0.286g, 1 mmol) were dissolved in pyridine (20 ml). The reaction mixture was heated at reflux (oil bath or microwave irradiation) for the time shown (Table). After cooling, the solvent was removed and the product was purified as above.
6,7-Dihydro[1,4]dioxino[2,3-f]benzothiazole-2-carbonitrile (3). Colourless needles, mp 177-178°C (from ethanol); ν_{max} (KBr)/cm^{-1} 2919, 2224 (CN), 1548, 1480, 1438, 1327, 1295, 1062, 873, 809; δ_H (400 MHz, $CDCl_3$) 4.32-4.4 (4H, m, O-CH_2-CH_2-O), 7.38 (1H, s, H_{arom}), 7.67 (1H, s, H_{arom}); δ_C (100 MHz, $CDCl_3$) 64.05, 64.50, 108.00, 111.83, 113.21, 128.91, 134.51, 145.14, 146.28, 147.43. (Anal. Calcd. for $C_{10}H_6N_2O_2S$: C, 55.03; N, 12.84; H, 2.77. Found : C, 54.76; N, 12.67; H, 2.60).
7,8-Dihydro[1,4]dioxino[2,3-g]benzothiazole-2-carbonitrile (4). Colourless needles, mp 155-156°C (from ethanol); ν_{max} (KBr)/cm^{-1} 2945, 2228 (CN), 1602, 1570, 1490, 1289, 1243, 1084, 940, 812; δ_H (400 MHz, $CDCl_3$) 4.29-4.46 (4H, m, O-CH_2-CH_2-O), 7.18 (1H, d, *J* 8.9, H_{arom}), 7.69 (1H, d, *J* 8.9, H_{arom}); δ_C (100 MHz, $CDCl_3$) 64.60, 64.90, 113.15, 117.94, 119.52, 124.90, 134.30, 137.00, 142.82, 147.92. (Anal. Calcd. for $C_{10}H_6N_2O_2S$: C, 55.03; N, 12.84; H, 2.77. Found : C, 54.73; N, 12.65; H, 2.52).

Dihydro[1,4]dioxinobenzothiazoles 5 and 6: general procedure.

A suspension of benzodioxinothiazole (**3** or **4**) (0.1 g, 0.46 mmol) in concentrated hydrochloric acid (20 ml) was heated at reflux (oil bath or microwave irradiation) for the time shown (Table). The mixture was allowed to cool to room temperature and neutralised (pH8). The mixture was washed with dichloromethane and the combined extracts were dried. Recrystallisation of the crude product from isopropanol gave the *title compounds*.

6,7-Dihydro[1,4]dioxino[2,3-f]benzothiazole (5). Colourless needles, mp 140-142°C (from isopropanol) (Found M^+, 193.0197. $C_9H_7NO_2S$ requires M, 193.0197); ν_{max} (KBr)/cm^{-1} 3081, 2926, 1553, 1477, 1437, 1303, 1261, 1142, 1071, 903, 850; δ_H (400 MHz, $CDCl_3$) 4.25 (4H, m, O-CH_2-CH_2-O), 7.31 (1H, s, H_{arom}), 7.56 (1H, s, H_{arom}) 8.76 (1H, s, N=CH); δ_C (100 MHz, $CDCl_3$) 64.12, 64.29, 108.42, 110.53, 126.53, 143.29, 143.48, 148.22, 152.58; m/z 193 (M^+, 100%), 137 (M^+ - [C_2H_4, CO], 77), 109 (M^+ - [C_2H_4, 2 CO], 29).

7,8-Dihydro[1,4]dioxino[2,3-g]benzothiazole (6). Colourless needles, mp 100-102°C (from isopropanol) (Found M^+, 193.0197. $C_9H_7NO_2S$ requires M, 193.0197); ν_{max} (KBr)/cm^{-1} 3076, 2990, 2931, 2874, 1604, 1576, 1482, 1405, 1273, 1255, 1074, 942; δ_H (400 MHz, $CDCl_3$) 4.25 - 4.38 (2H, m, O-CH_2-), 4.42 - 4.48 (2H, m, O-CH_2-), 7.09 (1H, d, J 8.6, H_{arom}), 7.64 (1H, d, J 8.6, H_{arom}), 8.83 (1H, s, N=CH); δ_C (100 MHz, $CDCl_3$) 64.41, 64.98, 115.99, 117.24, 122.70, 137.51, 140.47, 149.21, 151.92; m/z 193 (M^+, 100%); 165 (M^+ - [C_2H_4], 2), 137 (M^+ - [C_2H_4, CO], 89), 110 (M^+ - [C_2H_4, CO, HCN], 78).

Dioxinobenzothiazoles 11 and 12: bromination-debromination sequence

A mixture of dioxinobenzothiazoles (**3** or **4**) (0.1 g, 0.46 mmol), *N*-bromosuccinimide (NBS, 0.163 g, 0.92 mmol) in carbon tetrachloride (10 ml) was heated at reflux for 10 h in the presence of AIBN (0.005 g) under argon. After cooling, the precipitate of succinimide was eliminated by filtration, the solvent was evaporated and the brominated product (**9** or **10**) was purified by column chromatography (eluent : light petroleum-dichloromethane).

The compound (**9** or **10**) obtained was dissolved in acetone (10 ml) and the mixture was heated (oil bath or microwave irradiation) at reflux for 2h in the presence of sodium iodide (NaI, 0.137 g, 0.92 mmol). Purification by column chromatography gave the *title compounds*.

[1,4]Dioxino[2,3-f]benzothiazole-2-carbonitrile (11). Yellow needles, mp 174-176°C (from isopropanol); ν_{max} (KBr)/cm^{-1} 3113, 3043, 2228 (CN), 1675, 1553, 1480, 1437, 1308, 1122, 913, 868; δ_H (400 MHz, $CDCl_3$) 5.97-5.99 (2H, m, O-CH=CH-O), 7.1 (1H, s, H_{arom}), 7.37 (1H, s, H_{arom}); δ_C (100 MHz, $CDCl_3$) 107.28, 110.86, 112.90, 126.50, 126.80, 131.30, 135.32, 144.17, 145.02, 149.18; m/z 216 (M^+, 100%), 188 (M^+ - [CO], 2), 160 (M^+ - [2 CO], 44), 134 (M^+ - [2 CO, CN], 5). (Anal. Calcd. for $C_{10}H_4N_2O_2S$: C, 55.61; N, 12.97; H, 1.87. Found : C, 55.33; N, 12.78; H, 1.71).

[1,4]Dioxino[2,3-g]benzothiazole-2-carbonitrile (12). Yellow needles, mp 148-150°C (from isopropanol); ν_{max} (KBr)/cm^{-1} 2924, 2230 (CN), 1677, 1604, 1598, 1488, 1298, 1107, 1039, 945, 816, 727; δ_H (400 MHz, $CDCl_3$) 5.97 (1H, d, *J* 3.8 Hz, O-CH=), 6.02 (1H, d, *J* 3.8 Hz, O-CH=), 6.98(1H, d, *J* 8.5 Hz, H_{arom}), 7.72 (1H, d, *J* 8.5 Hz, H_{arom}); δ_C (100 MHz, $CDCl_3$) 112.74, 118.03, 120.63, 123.51, 126.80, 127.40, 135.61, 136.28, 141.84, 149.82 ; m/z 216 (M^+, 100%), 187 (M^+ - [CHO], 12), 160 (M^+ - [2 CO], 52). (Anal. Calcd. for $C_{10}H_4N_2O_2S$: C, 55.61; N, 12.97; H, 1.87. Found : C, 55.45; N, 12.82; H, 1.80).

7-Bromo-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2,3-dihydrobenzodioxin-6-amine (13).

To a solution of the imine **2** (0.286 g, 1 mmol) in acetic acid (10ml) was added bromine (0.159 g, 1 mmol). The mixture was stirred at room temperature for 4 h then water (10 ml) was added. The yellow precipitate obtained was filtered off, washed with water and dried to provide the *title compound* as yellow needles (0.357 g, 98%), mp 158-160°C (from isopropanol) (Found M^+, 363.8740. $C_{10}H_6{}^{79}BrClN_2O_2S_2$ requires M, 363.8742);

ν_{max} (KBr)/cm^{-1} 2989, 2884, 1595, 1487, 1396, 1304, 1249, 1192, 1170, 1052, 877; δ_H (400 MHz, $CDCl_3$) 4.28 (4H, s, O-CH_2-CH_2-O), 6.78 (1H, s, H_{arom}), 7.21 (1H, s, H_{arom}); δ_C (100 MHz, $CDCl_3$) 64.33, 64.39, 106.43, 107.84, 121.88, 142.36, 142.91, 143.56, 148.63, 159.38; m/z 366 (M^+, 100%); 364 (M^+, 72); 287 (M^+ - [^{81}Br], 37); 285 (M^+ - [^{79}Br], 88), 273 (M^+ - [ClCNS], 33), 271 (M^+ - [ClCNS], 32), 241 (M^+ - [$ClCNS_2$], 97); 239 (M^+ - [$ClCNS_2$], 94), 226 (M^+ - [Cl^{81}BrCN], 23), 224 (M^+ - [Cl^{79}BrCN], 23).

4-Bromo-7,8-dihydro[1,4]dioxino[2,3-g]benzothiazole-2-carbonitrile (14). Pyridinium tribromide (0.383 g, 1.2 mmol) and imine **13** (0.364 g, 1 mmol) were dissolved in pyridine (20 ml). The reaction mixture was heated at reflux (oil bath or microwave irradiation) for the time shown in the Table. After cooling, the solvent was removed and the product was purified by column chromatography (light petroleum-dichloromethane) as orange needles, mp 251°C (from isopropanol); ν_{max} (KBr)/cm^{-1} 3058, 2232 (CN), 1762, 1718, 1684, 1654, 1560, 1508, 1458, 937, 722; δ_H (400 MHz, $CDCl_3$) 4.43 (4H, m, O-CH_2-CH_2-O), 7.44 (1H, s, H_{arom}); δ_C (100 MHz, $CDCl_3$) 64.67, 64.93, 109.13, 112.68, 122.47, 125.26, 134.72, 136.55, 143.20, 145.85; m/z 298 (M^+, 100%), 296 (M^+, 95), 270 (M^+ - [C_2H_4], 2), 268 (M^+ - [C_2H_4], 3), 242 (M^+ - [C_2H_4, CO], 63), 240 (M^+ - [C_2H_4, CO], 59), 161 (M^+ - [C_2H_4, CO, HBr], 76). (Anal. Calcd. for $C_{10}H_5BrN_2O_2S$: C, 40.58; N, 9.46; H, 1.70. Found : C, 40.29; N, 9.22; H, 1.42).

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