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SYNTHESIS OF 4-METHOXYBENZYLAMINO DERIVATIVES OF DIBENZOTHIADIAZEPINEDIOXIDE

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Abstract- This article reports the synthesis of new dibenzothiadiazepinedioxides bearing a 4-methoxybenzylamino group at 8- or 9-C position of the tricyclic heterocycle. Construction of the 8- or 9-aminodibenzothiadiazepinedioxide is achieved *via* Weber's method and the 4-methoxybenzyl analogues are realized by reductive amination using 4-anisaldehyde.

INTRODUCTION

Substituted thiadiazepinedioxides are known to possess a wide range of pharmaceutical activities. Several derivatives of dibenzothiadiazepinedioxides are found to be active as antidepressant[1-3] or psychotropic agents as well as muscle relaxants.[4,5] A number of triazolothiadiazepines are also found to have antimicrobial,[6] antibacterial,[7] antifungal[8] and analgesic[9] activities. Some benzo- or naphthothiadiazepine derivatives have been reported to possess anti-inflammatory[10] properties. In previous works, we have synthesized pyridobenzoxazepinedioxides with methoxyphenylalkyl moiety at N-11 position of the tricyclic core (1) which displayed potent cytotoxic activity[11] (Figure 1). Herein and in continuation of our work, we synthesized dibenzothiadiazepinedioxyde derivatives bearing 4-methoxybenzylamino chain (8a-b) hoping they may have biological interest as cytotoxic compounds.

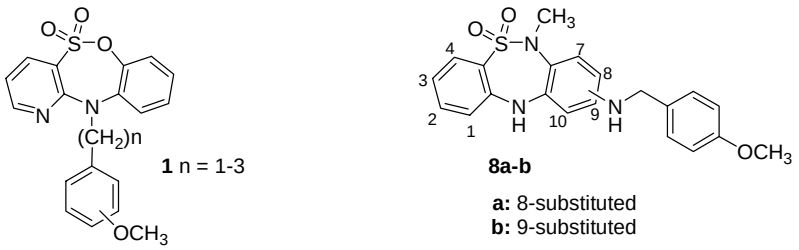
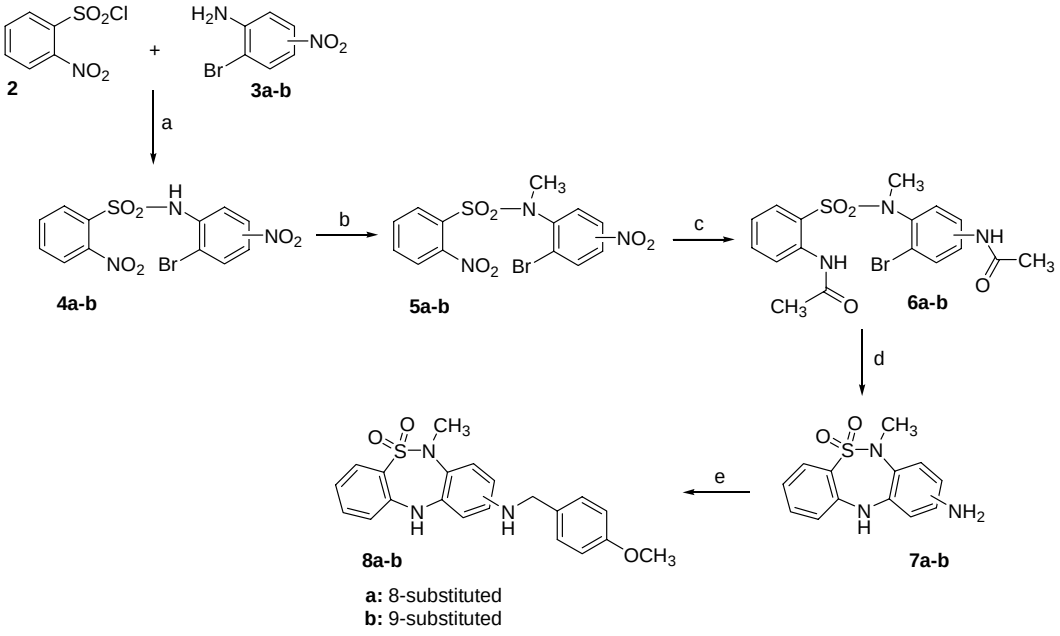


Figure 1

RESULTS AND DISCUSSION

Synthesis of substituted dibenzothiadiazepine heterocycles is well known,[12-14] but no 8- or 9-amino derivatives were described in the litterature. We used Weber's method for synthesis of amino derivatives (**7**) and (**8**) which involves intramolecular S_NAr reaction[1,15] for the construction of the 1,2,5-dibenzothiadiazepine 1,1-dioxide framework (Scheme 1).

Scheme 1: Synthesis of 8- and 9-(4-methoxybenzylamino)dibenzothiadiazepines (**8a-b**)



Reagents : (a) DMF, pyridine, 75°C, 68-91%; (b) DMF, NaH, CH_3I, rt, 86-88%; (c) i: Fe, AcOH, reflux; ii: Ac_2O, 60°C, 76-89%; (d) i: DMF, Cu, K_2CO_3, reflux; ii: 12N HCl, EtOH, reflux, 45-72%; (e) THF, AcOH, 4-anisaldehyde, 55°C; ii: THF, $NaBH_3CN$, 50°C, 64-70%.

Compounds (**4a-b**) were prepared from condensation between 2-nitrobenzenesulfonyl chloride (**2**) and commercial available (**3a**) or synthesized bromonitroaniline (**3b**) in DMF in the presence of pyridine as hydrochloric acid trap. 2-Bromo-4-nitroaniline[16] (**3b**) was prepared in 89% yield from reaction of pyridinium tribromide and 4-nitroaniline in a solution of THF and 10% aqueous hydrochloric acid. Methylation of the sulfonamide nitrogen occured with sodium hydride and methyl iodide in DMF. Reduction of the nitro group of derivatives (**5a-b**) with boiling Fe/AcOH followed by acetylation with

Ac_2O led to compounds (**6a-b**). Intramolecular S_NAr reaction is realized according to the Goldberg's method[17] using K_2CO_3 and Cu powder in DMF at reflux. The resulting acetamidothiadiazepines intermediates were refluxed in 12N aqueous hydrochloric acid and ethanol in order to release the primary amino derivatives (**7a-b**). *N*-Alkylation at N-8 or N-9 nitrogen using 4-methoxybenzyl chloride or methanesulfonate in basic conditions (K_2CO_3 or Et_3N) did not provide compounds (**8**) but formation of some N-11 alkylated products. 4-Methoxybenzylamino derivatives (**8a-b**) were synthesized by reductive amination of compounds (**7a-b**) with 4-anisaldehyde, in the presence of $NaBH_3CN$ which allowed reduction of the imino function, in 64-70% yield.

Compounds (**8a-b**) were tested for their antiproliferative activity against the L1210 leukemia cell line. Both compounds (**8a**) and **(8b**) displayed low cytotoxicity, with IC_{50} values of respectively 12.7 μM and 29.9 μM compared to IC_{50} in the submicromolar range for analogues (**1**) bearing the methoxyphenylalkyl moiety at N-11 position. Further studies are in progress to improve the potential cytotoxic activity of these compounds.

EXPERIMENTAL

Melting points were determined on a BÜCHI B-540 apparatus and were uncorrected. IR spectra were recorded as thin films on potassium bromide disks on a BECKMAN ACCULAB IV spectrophotometer. MS spectra were performed on a APPLIED BIOSYSTEMS API 3000 LC/MS/MS (electrospray-ionspray method, Laboratoire d'Application de Spectrométrie de Masse, Faculté de Medecine Henri Warembourg de Lille). ^1H NMR spectra were recorded on a BRUKER AC 300 P and 2D NMR spectra on a BRUKER DPX 300 (LARMN, Universite de Lille 2), using tetramethylsilane as internal standard. Elemental analyses were performed by C.N.R.S. – Vernaison.

2-Bromo-4-nitroaniline (3b). A solution of pyridinium tribromide (6.95 g, 22 mmol) in THF (50 mL) is added dropwise to a solution of 4-nitroaniline (3 g, 22 mmol) in THF (25 mL) with 10% HCl (10 mL) and stirred at rt for 12 h. The reaction mixture is filtered and the filtrate concentrated *in vacuo*. The residue is dissolved in CH_2Cl_2, washed with 10% sodium bisulfite, dried over sodium sulfate, filtered and evaporated under reduce pressure. The resulting yellow oil is purified by chromatography (petroleum ether/ ethyl acetate 85/15) to afford a yellow powder in 89% yield, mp 105-106°C (isopropyl ether), lit.,[16] 106-107°C

General method for synthesis of sulfonamides (4a-b). 2-Nitrobenzenesulfonyl chloride (4.05 g, 18 mmol) is added portionwise to a solution of bromonitroaniline (**3a-b**) (15 mmol) in DMF (5 mL) and pyridine (1.5 mL, 18 mmol). The reaction mixture is heated at 75°C for 5 h and evaporated under reduce pressure. The oily product precipitated by addition of water (10 mL) and collected by filtration. Recrystallization from ethanol 95% furnished the desired sulfonamides (**4a-b**).

***N*-(2-Bromo-5-nitrophenyl)-2-nitrobenzenesulfonamide (4a).** White powder; yield 91%; mp 192-193°C; IR: 3300, 1570, 1540, 1350, 1180; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 1H, *J*= 8.80 Hz), 7.75 (td, 1H, *J*= 1.40, 7.85 Hz), 7.82 (td, 1H, *J*= 1.40, 7.85 Hz),7.91 (dd, 1H, *J*= 2.30, 8.80 Hz), 7.98 (dd, 1H, *J*= 1.40, 7.40 Hz), 8.08 (dd, 1H, *J*= 1.40, 7.40), 8.35 (s, 1H), 8.64 (d, 1H, *J*= 2.30 Hz). Anal. Calcd for $C_{12}H_8N_3O_6BrS$: C, 35.84; H, 2.00; N, 10.45. Found: C, 35.78; H, 2.03; N, 10.37

***N*-(2-Bromo-4-nitrophenyl)-2-nitrobenzenesulfonamide (4b).** Beige powder; yield 68%; mp 177-178°C; IR: 3280, 1570, 1340, 1180; ^{1}H NMR ($CDCl_3$): δ 7.76 (td, 1H, *J*= 1.30, 7.45 Hz), 7.83 (td, 1H, *J*= 1.30, 7.35 Hz), 7.98 (m, 2H), 8.07 (dd, 1H, *J*= 1.30, 7.35 Hz), 8.22 (dd, 1H, *J*= 2.60, 9.10 Hz), 8.33 (s, 1H), 8.41 (d, 1H, *J*= 2.60 Hz). Anal. Calcd for $C_{12}H_8N_3O_6BrS$: C, 35.84; H, 2.00; N, 10.45. Found: C, 35.72; H, 1.98; N, 10.51

General method for synthesis of *N*-methylsulfonamides (5a-b). Substituted benzenesulfonamide (**4a-b**) (5 mmol) dissolved in DMF (10 mL) is added dropwise to a suspension of 60% sodium hydride (0.4 g, 10 mmol) in DMF (5 mL) and stirred for 3 h at rt. Iodomethane (1 mL, 15 mmol) in DMF (5 mL) is added dropwise to the previous solution and stirred for 12 h at rt. The resulting solution is evaporated under reduced pressure, precipitated from water and filtered. The resulting powder is then recrystallized from 95% ethanol.

***N*-(2-Bromo-5-nitrophenyl)-*N*-methyl-2-nitrobenzenesulfonamide (5a).** Light brown powder; yield 88%; mp 137-138°C; IR: 1580, 1550, 1450, 1350, 1180; ^{1}H NMR ($CDCl_3$): δ 3.47 (s, 3H), 7.63-7.69 (m, 2H), 7.75-7.84 (m, 3H), 8.12 (dd, 1H, *J*= 2.70, 8.55 Hz), 8.20 (d, 1H, *J*= 2.70 Hz). Anal. Calcd for $C_{13}H_{10}N_3O_6BrS$: C, 37.52; H, 2.42; N, 10.10. Found: C, 37.45; H, 2.39; N, 10.02.

***N*-(2-Bromo-4-nitrophenyl)-*N*-methyl-2-nitrobenzenesulfonamide (5b).** Light yellow powder; yield 86%; mp 143-145°C; IR: 1590, 1560, 1450, 1360, 1160; ^{1}H NMR ($CDCl_3$): δ 3.48 (s, 3H), 7.62-7.68 (m, 3H), 7.74-7.79 (m, 2H), 8.23 (dd, 1H, *J*= 2.80, 8.80 Hz), 8.47 (d, 1H, *J*= 2.80 Hz). Anal. Calcd for $C_{13}H_{10}N_3O_6BrS$: C, 37.52; H, 2.42; N, 10.10. Found: C, 37.60; H, 2.36; N, 10.08.

General method for synthesis of diacetamides (6a-b). Substituted dinitrobenzenesulfonamide (**5a-b**) (5 mmol) in acetic acid (45 mL) with iron powder (2.95 g, 50 mmol) is refluxed for 1 h. The reaction mixture is filtered, the filtrate is added to acetic anhydride (10 mL) and stirred for 12 h at 60°C. The solution is concentrated *in* vacuo, diluted with water (20 mL) and extracted with dichloromethane. The organic extracts are dried over sodium sulfate, filtered, evaporated under reduced pressure and crystallized from the appropriate solvent.

2-Acetamido-*N*-(5-acetamido-2-bromophenyl)-*N*-methylbenzenesulfonamide (6a). Beige powder; yield 76%; mp 122-126°C (isopropyl ether); IR: 3360, 3320, 1690, 1680, 1590, 1440, 1340, 1180; ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H), 2.16 (s, 3H), 3.16 (s, 3H), 6.87 (d, 1H, *J*= 2.60 Hz), 7.30 (td, 1H, *J*= 0.85, 8.15 Hz), 7.57-7.67 (m, 3H), 7.76 (dd, 1H, *J*= 2.60, 8.60 Hz), 7.93 (dd, 1H, *J*= 1.70, 8.15 Hz), 8.21 (dd,

1H, *J*= 1.90, 8.60 Hz), 9.07 (s, 1H). Anal. Calcd for $C_{17}H_{18}N_3O_4BrS$: C, 46.37; H, 4.12; N, 9.54. Found: C, 46.31; H, 4.02; N, 9.60.

2-Acetamido-*N*-(4-acetamido-2-bromophenyl)-*N*-methylbenzenesulfonamide (6b). Beige powder; yield 89%; mp 190-192°C (95% ethanol); IR: 3340, 3320, 1690, 1670, 1580, 1430, 1340, 1140; ^{1}H NMR ($CDCl_3$): δ 1.87 (s, 3H), 2.18 (s, 3H), 3.21 (s, 3H), 7.10 (d, 1H, *J*= 8.70 Hz), 7.21 (td, 1H, *J*= 0.90, 7.80 Hz), 7.45 (dd, 1H, *J*= 2.30, 8.70 Hz), 7.58 (td, 1H, *J*= 1.40, 8.25 Hz), 7.85 (dd, 1H, *J*= 1.40, 7.80 Hz), 7.90 (d, 1H, *J*= 2.30 Hz), 8.00 (s, 1H), 8.39 (dd, 1H, *J*= 1.75, 8.30 Hz), 9.22 (s, 1H). Anal. Calcd for $C_{17}H_{18}N_3O_4BrS$: C, 46.37; H, 4.12; N, 9.54. Found: C, 46.28; H, 4.05; N, 9.51.

General method for syntesis of aminodibenzothiadiazepines (7a-b). A solution of substituted diacetamidobenzenesulfonamide (**6a-b**) (5 mmol) in DMF (20 mL) is treated with potassium carbonate (1.5 g, 10 mmol), copper powder (0.17 g, 3 mmol), stirred and heated under reflux for 8 h. After this time, the mixture is filtered and the solution evaporated under reduced pressure. The residue is precipitated in water and collected by filtration. The resulting powder is heated under reflux for 2,5 h in a solution of ethanol 95% (20 mL) with 12N HCl (4 mL). The reaction mixture is diluted with water and 10% aqueous ammoniac solution is added untill precipitation. The precipitate is collected by filtration and recrystallized from 95% ethanol.

8-Amino-6,11-dihydro-6-methyldibenzo[*c,f*][1,2,5]thiadiazepine 5,5-dioxide (7a). Light purple powder; yield 45%; mp 235-238°C; IR: 3460, 3360, 1600, 1440, 1300, 1150; ^{1}H NMR ($CDCl_3$): δ 2.86 (s, 3H), 4.99 (s, 2H), 6.17 (d, 1H, *J*= 2.75 Hz), 6.55 (dd, 1H, *J*= 2.75, 8.80 Hz), 6.79 (td, 1H, *J*= 7.15, 8.80 Hz), 6.88 (d, 1H, *J*= 8.80 Hz), 7.17 (dd, 1H, *J*= 1.65, 8.25 Hz), 7.38 (td, 1H, *J*= 1.65, 8.25 Hz), 7.60 (dd, 1H, *J*= 1.65, 8.25 Hz), 8.90 (s, 1H). Anal. Calcd for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.59; H, 4.69; N, 15.20.

9-Amino-6,11-dihydro-6-methyldibenzo[*c,f*][1,2,5]thiadiazepine 5,5-dioxide (7b). Light purple powder; yield 72%; mp 208-213°C; IR: 3460, 3340, 1600, 1580, 1320, 1150; ^{1}H NMR ($CDCl_3$): δ 2.79 (s, 3H), 5.30 (s, 2H), 6.21 (dd, 1H, *J*= 2.10, 8.50 Hz), 6.30 (d, 1H, *J*= 2.10 Hz), 6.88 (m, 2H), 7.28 (d, 1H, *J*= 8.50 Hz), 7.38 (dd, 1H, *J*= 6.90, 7.45 Hz), 7.64 (d, 1H, *J*= 6.90 Hz), 9.04 (s, 1H). Anal. Calcd for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.62; H, 4.63; N, 15.18 .

General method for syntesis of 4-methoxybenzylaminodibenzothiadiazepines (8a-b). A solution of **7a** or **7b** (2 mmol), 4-anisaldehyde (2.2 mL, 20 mmol) and acetic acid (0.2 mL, 4 mmol) in THF (40 mL) is heated at 55°C untill TLC indicates starting aminodibenzothiadiazepine is consumed. After concentration, ether (30 mL) is added and the precipitate is collected by filtration. The resulting solid is dissolved in THF (30 mL) and $NaBH_3CN$ (0.18 g, 3 mmol) is slowly added. The suspension is stirred at rt for 1 h and at 50°C for 5 days. After cooling, aqueous 1N NaOH is added and the solution is extracted

with ethyl acetate. The combined extracts are dried over sodium sulfate, filtered, evaporated under reduce pressure and purified by chromatography (ethyl acetate/ petroleum ether 7/3).

6,11-Dihydro-9-(4-methoxybenzylamino)-6-methyldibenzo[*c,f*][1,2,5]thiadiazepine 5,5-dioxide (8a). Light brown powder; yield 64%; mp 185-186°C (80% ethanol); IR: 3360, 1590, 1510, 1440, 1320, 1160; ^{1}H-NMR (DMSO-d_6): δ 2.78 (s, 3H), 3.73 (s, 3H), 4.19 (d, 2H, *J*= 6.05 Hz), 6.23-6.29 (m, 2H), 6.44 (t, 1H, *J*= 6.05 Hz), 6.84-6.92 (m, 4H), 7.27-7.31 (m, 3H), 7.42 (td, 1H, *J*= 1.65, 7.65 Hz), 7.64 (dd, 1H, *J*= 1.65, 8.25 Hz), 9.05 (s, 1H). MS (EI) *m/z* 395 (M+). Anal. Calcd for $C_{21}H_{21}N_3O_3S$: C, 63.78; H, 5.35; N, 10.63. Found: C, 63.72; H, 5.39; N, 10.68.

6,11-Dihydro-8-(4-methoxybenzylamino)-6-methyldibenzo[*c,f*][1,2,5]thiadiazepine 5,5-dioxide (8b). Light yellow powder; yield 70%; mp 202-203°C (95% ethanol); IR: 3340, 1580, 1500, 1450, 1310, 1160; ^{1}H-NMR (DMSO-d_6): δ 2.84 (s, 3H), 3.73 (s, 3H), 4.15 (s, 2H), 6.05 (s, 1H), 6.50 (d, 1H, *J*= 2.80 Hz), 6.59 (dd, 1H, *J*= 2.80, 8.80 Hz), 6.79 (td, 1H, J= 1.80, 8.30 Hz); 6.91 (m, 3H), 7.27 (d, 1H, *J*= 8.80 Hz), 7.29-7.41 (m, 3H), 7.61 (dd, 1H, *J*= 1.40, 7.85 Hz), 8.93 (s, 1H). MS (EI) *m/z* 395 (M+). Anal. Calcd for $C_{21}H_{21}N_3O_3S$: C, 63.78; H, 5.35; N, 10.63. Found: C, 63.81; H, 5.29; N, 10.65.

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