AN ORIGINAL WAY FOR SYNTHESIS OF NEW NITRO-BENZOTHIADIAZOLE DERIVATIVES

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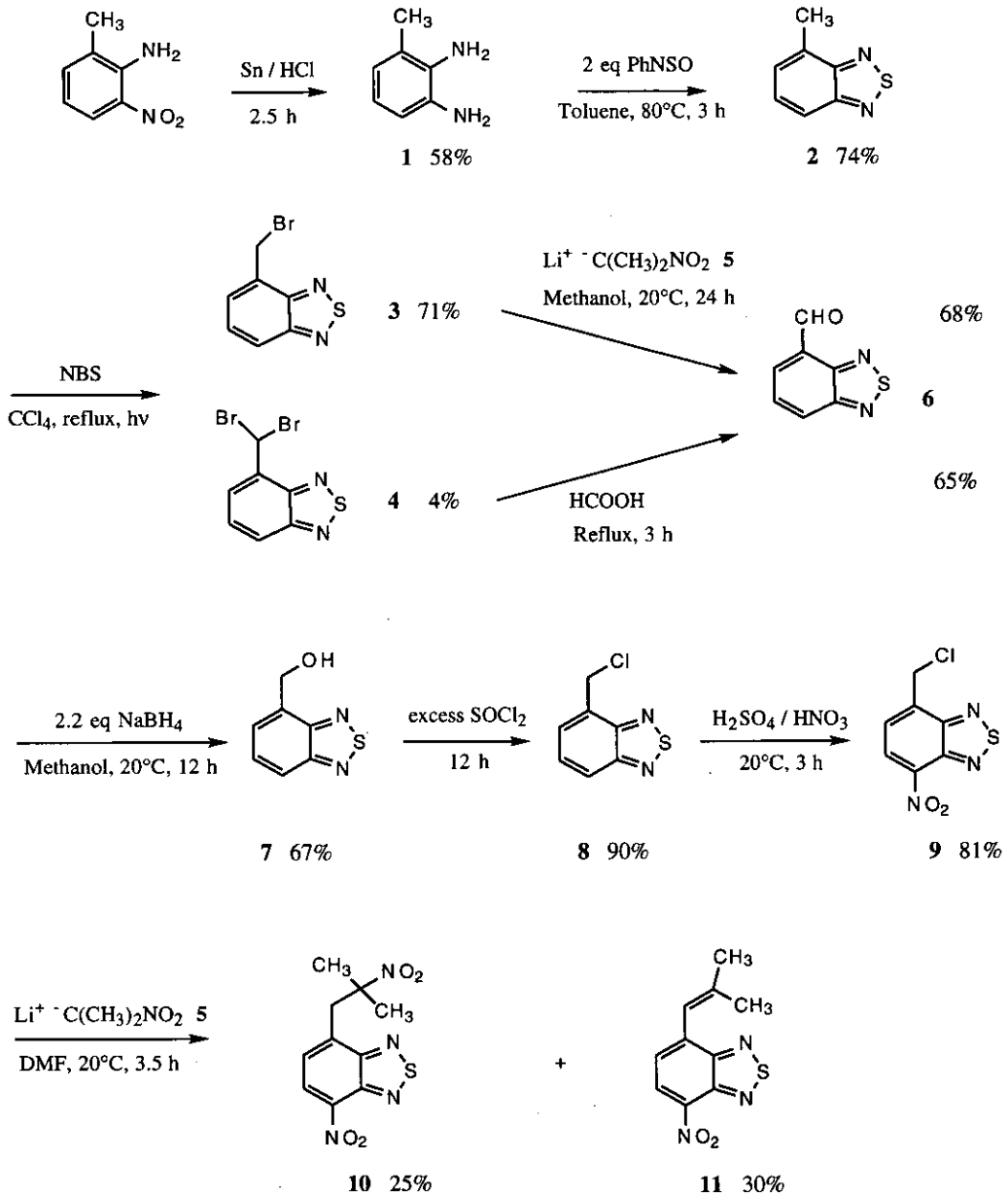
Abstract- The C-alkylation reaction of 4-chloromethyl-7-nitro-2,1,3-benzothiadiazole with 2-nitropropane anion which is shown to proceed by an $S_{RN}1$ mechanism is an original way for the synthesis of new 2,1,3-benzothiadiazoles.

The biological importance of benzothiadiazole ring has been established. Several nitrobenzothiadiazoles are effective antifungal,[1] herbicide,[2] acaricide[3] or insecticide[3] agents. Recently, other activities have been reported: there are anthelmintics,[4] hypoglycemic,[5] antiallergic,[6] antiinflammatory,[6] antiasthmatic[6] compounds, antibacterial[7] or antiviral[8] drugs. In our program on scope and limitations of $S_{RN}1$ reaction in search of new potentially bioactive agents,[9] we have synthesized an analogous heterocyclic derivative of *p*-nitrobenzyl chloride. Kornblum[10] and Russell[11] have described the first example of the radical chain mechanism designated $S_{RN}1$ by Bunnett[12] to explain the C-alkylation of nitronate anion by *p*-nitrobenzyl chloride. As a most attractive feature of $S_{RN}1$ reactions is that they proceed under very mild conditions and produce excellent yields of products, the reactivity of 4-chloromethyl-7-nitro-2,1,3-benzothiadiazole could be an original way for synthesis of new 2,1,3-benzothiadiazole derivatives bearing a tertiary nitroalkyl

group or a trisubstituted double bond.

Commercially available 2-methyl-6-nitroaniline was reduced with Sn / HCl to form 2,3-diaminotoluene (**1**) as illustrated by Scheme 1.

Scheme 1



Cyclization of **1** was performed by heating with thionyl chloride[13] or *N*-thionylaniline[14] but the last procedure gave the 2,1,3-benzothiadiazole ring in a higher yield (74% instead of 42.5%). As the free radical chlorination using *N*-chlorosuccinimide (NCS) led to resinous products under different experimental

conditions by varying the concentration of NCS, benzoyl peroxide and the time of reaction, an alternative approach was selected. Thus, the free radical bromination of **2** by *N*-bromosuccinimide (NBS) in carbon tetrachloride allowed formation of two products: 4-bromomethyl-2,1,3-benzothiadiazole (**3**) as major product (71% yield) and the benzal bromide (**4**) as minor product (4% yield). These two compounds were easily converted into 4-formyl-2,1,3-benzothiadiazole (**6**): treatment of **3** with the lithium salt of 2-nitropropane (**5**) in methanol at room temperature during 20 h produced by a classical S_N2 mechanism the desired aldehyde (**6**) in 68% yield while the dibromomethyl derivative reacted in boiling aqueous formic acid during 3 h to give 65% yield of **6**.[15] The aldehyde (**6**) was reduced by $NaBH_4$ into the corresponding alcohol (**7**) which was transformed into the chloride (**8**) after chlorination with thionyl chloride. 4-Chloromethyl-7-nitro-2,1,3-benzothiadiazole (**9**) was obtained by nitration of **8** with a mixture of concentrated sulfuric and nitric acids in 81% yield. This chloride (**9**) was treated under conditions conducive to $S_{RN}1$ reactions (inert atmosphere, photostimulation) with lithium salt of 2-nitropropane (**5**). By using 3 equivalents of 2-nitropropane anion in DMF under Kornblum conditions,[1] the C-alkylation product, 4-(2-methyl-2-nitropropyl)-7-nitro-2,1,3-benzothiadiazole (**10**) and the ethylenic derivative, 4-(2-methyl-1-propenyl)-7-nitro-2,1,3-benzothiadiazole (**11**) formed from the C-alkylation product by base-promoted nitrous acid elimination were isolated in 25 and 30% yields respectively. The phase-transfer conditions[16] (40% tetrabutylammonium hydroxide in water and dichloromethane) with 4 equivalents of 2-nitropropane led only to **11** in 65% yield. $S_{RN}1$ mechanism was assessed when comparing the yield of the reaction under phase transfer conditions in the presence or the absence of two different classical inhibitors (2,2,6,6-tetramethyl-1-piperidinyloxy or TEMPO and *p*-dinitrobenzene).[17] Complete inhibition was observed by addition of stoichiometric quantity of TEMPO and when using equimolecular amount of *p*-dinitrobenzene, **10** and **11** were isolated in 5 and 8% yields respectively.

In conclusion, we have developed an access to new 2,1,3-benzothiadiazole derivatives and described the first example of $S_{RN}1$ reaction involving the benzothiadiazole system.

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EXPERIMENTAL

Melting points were taken on a Büchi apparatus using glass capillary tubes and are uncorrected. The ^1H NMR spectra were recorded on a Bruker 200 MHz instrument and chemical shifts are reported in δ units

(ppm) relative to internal TMS. Microanalyses were performed by the Microanalytical Section of St-Jérôme Faculty, Aix-Marseille 3 University, France.

2,3-Diaminotoluene (1)

To a suspension of Sn (42 g, 353 mmol) in water (40 mL) were added 2-methyl-6-nitroaniline (20 g, 131 mmol) and dropwise at rt, concentrated hydrochloric acid (53 mL). The reaction mixture was stirred at reflux for 2.5 h. After cooling and filtration, the aqueous layer was washed with chloroform, neutralized with solid K_2CO_3 and filtered. The filtrate was extracted with chloroform. The extract was washed with water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The resulting residue was recrystallized from cyclohexane to give 9.40 g (58%) of **1**. mp 63 °C (Aldrich: 61-63 °C).

4-Methyl-2,1,3-benzothiadiazole (2)

Method A

Thionyl chloride (14.68 g, 123 mmol) was added dropwise at 0 °C to a mixture of 2,3-diaminotoluene (4.93 g, 40.4 mmol) in toluene (80 mL) and triethylamine (25 mL, 179 mmol). The reaction mixture was stirred at reflux for 2 h. After cooling at rt, water (37 mL) and 30% sulfuric acid (5 mL) were added. The resulting mixture was extracted with ethyl acetate. The combined extracts were washed with water, treated with activated charcoal and dried over anhydrous magnesium sulfate. The solvent was removed and the oily residue was purified by distillation to afford pure compound (**2**) (2.58 g, 42.5%). bp 70 °C/1.5 mbar. (lit.,[18] bp 76-78 °C/14 mm Hg).

Method B

To a solution of 2,3-diaminotoluene (7.53 g, 61.6 mmol) in toluene (80 mL), was added *N*-thionylaniline (18.86 g, 136 mmol). The reaction mixture was heated at 80-100 °C for 3 h. The solvent was removed, the residue was dissolved in dichloromethane and the solution was washed with 10% HCl solution and water. Activated charcoal was added to the organic layer and after filtration, the filtrate was evaporated. Purification by chromatography on a silica gel column eluting with chloroform gave 6.81 g (74%) of **2**.

4-Bromomethyl-2,1,3-benzothiadiazole (3)

A solution of 4-methyl-2,1,3-benzothiadiazole (9 g, 60 mmol) in carbon tetrachloride (60 mL) was placed in a round-bottomed flask equipped with a reflux condenser surmonted by a calcium chloride drying tube, and *N*-bromosuccinimide (10.68 g, 60 mmol) was added. The reaction mixture was irradiated with two 150W fluorescent lamps from a distance of 10 cm and refluxed for 3 h. After cooling, the mixture was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on a silica gel column eluting with toluene to afford 9.70 g (71%) of 4-bromomethyl-2,1,3-benzothiadiazole (**3**) mp 84 °C (methanol), lit.,[15] 83 °C as white needles

and 0.73 g (4%) of 4-dibromomethyl-2,1,3-benzothiadiazole (**4**) mp 133 °C (methanol), lit.,[15] 132 °C as brown needles.

4-Formyl-2,1,3-benzothiadiazole (6)

Method A

The lithium salt of 2-nitropropane (2.66 g, 279 mmol) was added to a solution of 4-bromomethyl-2,1,3-benzothiadiazole (5.82 g, 25.4 mmol) in methanol (60 mL). After stirring at room temperature for 24 h, methanol was distilled off on a rotatory evaporator under reduced pressure. The residue was dissolved in dichloromethane and the solvent was washed with water, dried over anhydrous magnesium sulfate and evaporated under vacuum. After purification by recrystallization from cyclohexane, 4-formyl-2,1,3-benzothiadiazole was obtained as a yellow solid (2.82 g, 68%). mp 100 °C, lit.,[19] 101-102 °C.

Method B

Formic acid (8 mL) was added dropwise to a suspension of 4-dibromomethyl-2,1,3-benzothiadiazole (1.16 g, 3.76 mmol) . The reaction mixture was heated at reflux for 3 h. After cooling, the excess of formic acid was evaporated and the residue was dissolved in dichloromethane. The solvent was washed with an aqueous 10% NaOH solution and water. The solution was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude solid was purified by recrystallization from cyclohexane to give 0.4 g (65%) of the product.

4-Hydroxymethyl-2,1,3-benzothiadiazole (7)

To a solution of 4-formyl-2,1,3-benzothiadiazole (2.22 g, 135 mmol) in methanol (50 mL) was added sodium borohydride (1.12 g, 29.7 mmol). The reaction mixture was stirred at rt for 24 h, poured into cold water (100 mL) and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Recrystallization from cyclohexane yielded pure 4-hydroxymethyl-2,1,3-benzothiadiazole (**7**) as yellow crystals (1.5 g, 67%); mp 71 °C, lit.,[15] 70 °C.

4-Chloromethyl-2,1,3-benzothiadiazole (8)

4-Hydroxymethyl-2,1,3-benzothiadiazole (1 g, 6.02 mmol) was placed in a round-bottomed flask equipped with a reflux condenser surmonted by a chloride calcium drying tube and thionyl chloride (8.75 mL, 120 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 12 h. The excess of thionyl chloride was evaporated under vacuum and the residue was dissolved in dichloromethane. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by chromatography on a silica gel column eluting with toluene to give 4-chloromethyl-2,1,3-benzothiadiazole (**8**) as a yellow solid (1 g, 90%). mp 73°C (cyclohexane),

lit.,[19] 77-78 °C.

4-Chloromethyl-7-nitro-2,1,3-benzothiadiazole (9)

To a solution of 4-chloromethyl-2,1,3-benzothiadiazole (0.4 g, 2.17 mmol) in 30% sulfuric acid (5 mL), fuming nitric acid (5 mL) was added dropwise. The reaction mixture was stirred at rt for 3 h. The mixture was poured into cold ice and extracted with dichloromethane. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under vacuum and the crude solid was purified by recrystallization from cyclohexane. Yield: 0.4 g (81%). mp 86°C. ^{1}H NMR ($CDCl_3$) δ: 5.12 (s, 2H, CH_2Cl); 7.80 (d, J = 7.7 Hz, 1H, H_5); 8.51 (d, J = 7.7 Hz, 1H, H_6). Anal. Calcd for $C_7H_4N_3O_2ClS$: C, 36.61; H, 1.76; N, 18.30; Cl, 15.44 ; S, 13.96. Found: C, 36.71; H, 1.70; N, 18.37; Cl, 15.50; S, 14.00.

The lithium salt of 2-nitropropane (**5**)[10,20] was prepared as previously described.

Procedure for $S_{RN}1$ reactions

* Kornblum conditions

To a solution of 0.40 g (1.74 mmol) of 4-chloromethyl-7-nitro-2,1,3-benzothiadiazole (**9**) in 20 mL of dry DMF, 0.5 g (5.22 mmol) of lithium salt of 2-nitropropane was added under nitrogen and anhydrous conditions. The reaction mixture was then irradiated with two 60W fluorescent lamps from a distance of 10 cm. After stirring at rt for 3.5 h, the reaction mixture was poured into water (200 mL). The aqueous solution was extracted with benzene (3 x 40 mL) and ether (1 x 40 mL). The organic extracts were washed with water (3 x 100 mL), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Purification by chromatography on a silica gel column eluting with dichloromethane gave:

- 123 mg of 4-(2-methyl-2-nitropropyl)-7-nitro-2,1,3-benzothiadiazole (**10**), yellow solid, mp 152 °C (cyclohexane), ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 6H, CH_3); 3.41 (s, 2H, CH_2); 7.40 (d, J = 7.9 Hz, 1H, H_5); 8.40 (d, J = 7.9 Hz, 1H, H_6). Anal. Calcd for $C_{10}H_{10}N_4O_4S$: C, 42.55; H, 3.57; N, 19.85; S, 11.36. Found: C, 42.60; H, 3.61; N, 19.96; S, 11.40.
- 123 mg of 4-(2-methyl-1-propenyl)-7-nitro-2,1,3-benzothiadiazole (**11**), yellow solid, mp 131 °C (cyclohexane), ^{1}H NMR ($CDCl_3$) δ 1.92 (m, 6H, CH_3); 6.90 (br s, 1H, ethylenic H); 7.50 (d, J = 7.9 Hz, 1H, H_5); 8.50 (d, J = 7.9 Hz, 1H, H_6). Anal. Calcd for $C_{10}H_9N_3O_2S$: C, 51.05; H, 3.86; N, 17.86; S, 13.63. Found: C, 51.13; H, 3.92; N, 17.96; S, 13.60.

* Norris conditions

Under nitrogen atmosphere, an aqueous solution of 40% tetrabutylammonium hydroxide in water (4.6 mL, 7 mmol) was reacted with 2-nitropropane (0.62 g, 7 mmol) for 1 h. A solution of 4-chloromethyl-7-nitro-2,1,3-benzothiadiazole (**9**) (0.40 g, 1.74 mmol) in 20 mL of dichloromethane was added and the mixture

was stirred for 24 h under nitrogen and irradiation with fluorescent lamps. The organic layer was separated and the aqueous layer was extracted with three portions of dichloromethane (20 mL). The combined organic layers were evaporated under reduced pressure. The obtained residue was dissolved in 40 mL of benzene, washed twice with 40 mL of water, dried over anhydrous magnesium sulfate and evaporated. The purification already described gave 266 mg (65%) of **11**.

Inhibition studies with *p*-dinitrobenzene and TEMPO were carried out by adding the required amount of *p*-dinitrobenzene and TEMPO to the reaction mixture immediately prior to the chloride.

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