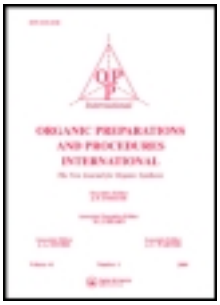

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SYNTHESIS OF 6-CHLOROMETHYL BENZOTHIAZOLIN-2-ONE AND OF 6-CHLOROMETHYL BENZOXAZOLIN-2-ONE

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SYNTHESIS OF 6-CHLOROMETHYL BENZOTHIAZOLIN-2-ONE AND OF 6-CHLOROMETHYL BENZOXAZOLIN-2-ONE

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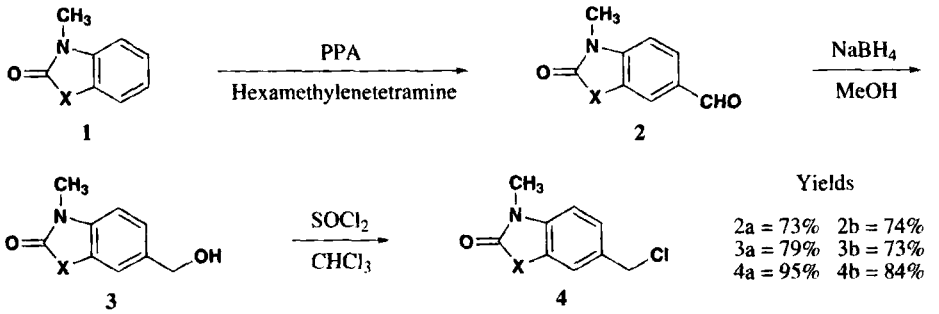
As part of our study of potential atypical antipsychotic agents,[1] the synthesis of 3-methyl-6-chloromethyl benzothiazolin-2-one (**4a**) and benzoxazolin-2-one (**4b**) previously prepared by Carato *et al.*, [1] was reported as shown in *Scheme 1*. The 3-methyl derivatives (**1a** and **1b**) were formylated using hexamethylenetetramine in polyphosphoric acid (PPA),[2,3] to give compounds **2a** and **2b** which were then reduced to the corresponding alcohols **3a** and **3b**. Transformation of the hydroxy group to the corresponding chloro analogues **4a** and **4b** was performed in dry chloroform using $SOCl_2$. This paper describes the synthesis of 6-chloromethylbenzothiazolin-2-one (**13a**) and benzoxazolin-2-one (**13b**), needed for the preparation of potential antipsychotic agents.



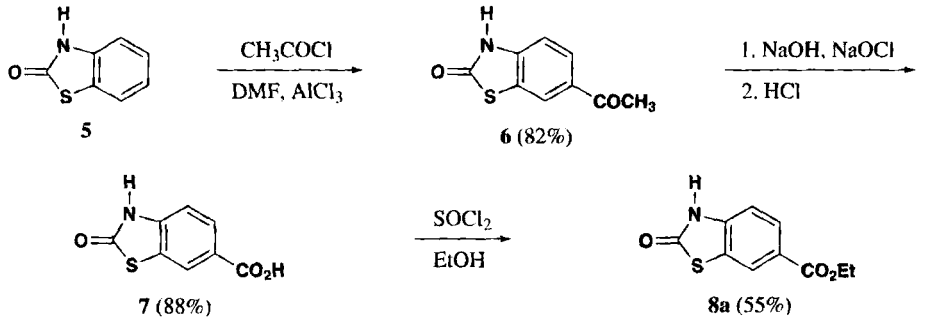
1 2 3 4

a) X = S b) X = O

Scheme 1

Application of the synthetic route employed to access structures **4a** and **4b** to compounds **13a, b** (*Schemes 2,3,4*) was unsuccessful. Indeed, formylation of the N-unsubstituted derivatives, respectively led to the degradation of the starting materials with benzothiazolin-2-one (**5**) and low yield (20%) with benzoxazolin-2-one.[3] Alternative procedures were investigated without success. Thus, neither benzothiazolin-2-one nor benzoxazolin-2-one reacted with hexamethylenetetramine in acetic acid or trifluoroacetic acid.[4] Attempted formylation with dichloromethylmethyl ether[5] in the presence of $AlCl_3$ or reaction of DMF[6] or N-methylformanilide[7] in the presence of $POCl_3$ were equally unsuccessful. It was therefore necessary to develop new approaches.

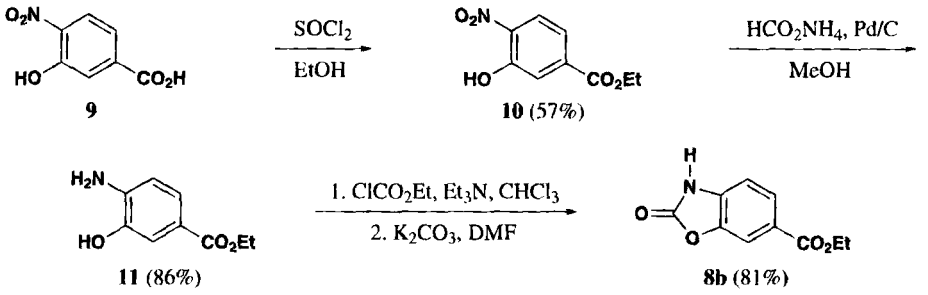
Acetylation of benzothiazolin-2-one (**5**) in $AlCl_3$-DMF led to the known compound **6**.[8] Compound **7**, previously prepared in 81% yield by Ogawa *et al.*[9] by treatment of 6-chloroacetylbenzothiazolin-2-one with pyridine and sodium hydroxide, was obtained in 88% by reaction with sodium hydroxide and sodium hypochlorite in our laboratory.[3] Esterification of **7** (which could not be reduced with sodium borohydride or LAH in a mixture of *t*-butanol and methanol[10]) with ethanol and thionyl chloride gave **8a** (*Scheme 2*).



5 **6** (82%) **7** (88%) **8a** (55%)

Scheme 2

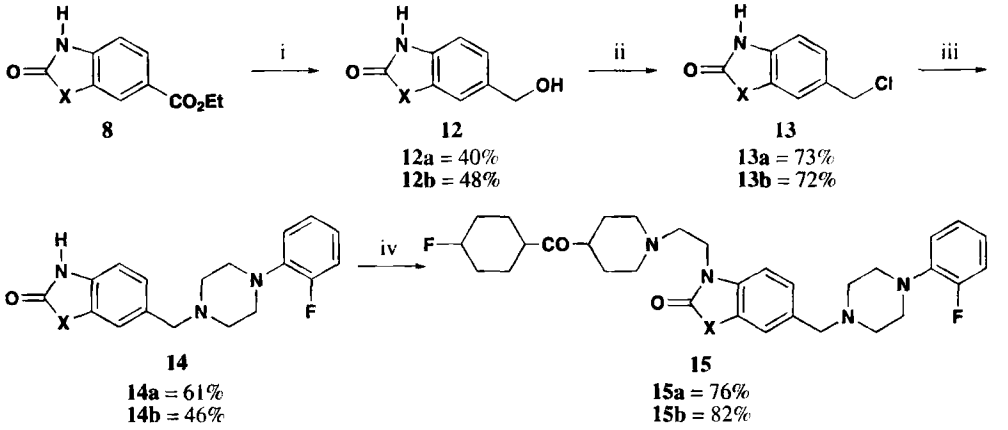
Since 6-acetylbenzoxazolin-2-one underwent concurrent hydrolysis under the conditions[3] of the haloform reaction to give the 2-aminophenol derivative as a by-product with low yield, the synthesis of **8b** was approached from 4-nitro-3-hydroxybenzoic acid (**9**). Esterification of **9** with ethanol and thionyl chloride followed by reduction of the resulting ester (**10**) in methanol with ammonium formate and 10% Pd/C[11] gave **11**. Treatment of **11** with ethyl chloroformate and triethylamine in chloroform, followed by heating in DMF with potassium carbonate regenerated the oxazoline ring to give **8b** (*Scheme 3*).



9 **10** (57%) **11** (86%) **8b** (81%)

Scheme 3

Reduction of **8a** and **8b** with LAH in THF gave the corresponding hydroxymethyl derivatives **12a** and **12b** which were then converted to the desired chloromethyl compounds **13a** and **13b**, which are useful reagents for the synthesis of medicinally interesting compounds such as **15a** and **15b** (*Scheme 4*). These latter compounds have been successfully exploited in a recent patent[1] which reports the synthesis of high affinity dopaminergic ligands (D_2 and D_4) endowed with potential atypical antipsychotic properties.



8 12 13

12a = 40% 13a = 73%
12b = 48% 13b = 72%

14 15

14a = 61% 15a = 76%
14b = 46% 15b = 82%

a) X = S i) $LiAlH_4$, THF ii) $SOCl_2$, $CHCl_3$ iii) 4-(2-fluorophenylpiperazine), acetone,
b) X = O Et_3N, KI iv) 1-(2-chloroethyl)-4-(4-fluorobenzoyl)piperidine, K_2CO_3, DMF

Scheme 4

EXPERIMENTAL SECTION

Mps (uncorrected) were determined in open capillary tubes using a Büchi SMP 20 melting point apparatus. Infrared spectra were obtained using as KBr disks on a Perkin-Elmer Model 297 spectrometer. ^{1}H NMR spectra were recorded using a AC 300P Brüker spectrometer in DMSO-d_6 at ambient temperature using TMS as an internal reference (δ). Elemental analyses were performed by the Analytical Center of C.N.R.S. of Vernaison (France).

6-Carboxybenzothiazolin-2-one (7).- To a solution of NaOH (20.0g, 0.50 mol) in H_2O (10 mL) at room temperature was added 6-acetylbenzothiazolin-2-one (**6**) (9.65g, 0.05 mol). The resulting solution was treated with 12% NaOCl (400 mL) and heated under reflux for 1 h. The reaction mixture was acidified to pH 1 with conc. HCl. The resulting precipitate was collected, washed with H_2O, and dried. Recrystallization from EtOH-H_2O (8:2, v/v) gave 6.83g (88%) of green crystals, mp > 260°. IR: 3140 (NH), 1670 (CO) cm^{-1}. ^{1}H NMR: δ 7.30 (m, 1H), 7.90 (m, 1H), 8.15 (m, 1H), 12.35 (br s, 1H), 12.95 (br s, 1H).

Anal. Calcd for $C_8H_5NO_3S$: C, 49.22; H, 2.58; N, 7.18. Found: C, 48.94; H, 2.72; N, 7.38

6-Ethoxycarbonylbenzothiazolin-2-one (8a).- To a solution of **7** (1.95g, 0.01 mol) in EtOH (25 mL) (cooled in an ice bath) was added dropwise $SOCl_2$ (3.70 mL, 0.050 mol). The reaction mixture was refluxed for 3 h, evaporated *in vacuo*; the oily residue was dissolved in CH_2Cl_2, and filtered through a bed of silica gel. The filtrate was evaporated *in vacuo* to give a solid. Recrystallization from toluene-cyclohexane (4:7, v/v) gave 1.23g (55%) of white crystals, mp 152-153°. IR: 3120 (NH), 1715 (CO) cm^{-1}. ^{1}H NMR: δ 1.30 (t, 3H, J = 6.80 Hz), 4.30 (q, 2H, J = 6.80 Hz), 7.20 (d, 1H, J = 8.70 Hz), 7.90 (dd, 1H, J = 8.70 Hz, J = 1.20 Hz), 8.20 (d, 1H, J = 1.20 Hz), 12.30 (br s, 1H).

Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27. Found: C, 53.74; H, 4.09; N, 6.28

5-Ethoxycarbonyl-2-nitrophenol (10).- To a solution of **9** (18.31g, 0.1 mol) in EtOH (200 mL)

(cooled in an ice bath) was added dropwise $SOCl_2$ (37.20 mL, 0.5 mol). The reaction mixture was refluxed for 16 h, evaporated *in vacuo* and the oily residue was dissolved in CH_2Cl_2, and filtered over a bed of silica gel. The filtrate was evaporated *in vacuo* to give a solid. Recrystallization from EtOH gave 12.03g (57%) of yellow crystals, mp 89-90°. IR: 3300 (OH), 1720 (CO) cm^{-1}. ^1H NMR: δ 1.35 (t, 3H, J = 7.10 Hz), 4.30 (q, 2H, J = 7.10 Hz), 7.50 (dd, 1H, J = 8.50 Hz, J = 1.40 Hz), 7.70 (d, 1H, J = 1.40 Hz), 8.00 (d, 1H, J = 8.50 Hz), 11.50 (br s, 1H).

Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.30; H, 4.38; N, 6.33

2-Amino-5-ethoxycarbonylphenol Hydrochloride (11).- To a solution of **10** (21.12g, 0.1 mol) in MeOH (200 mL) were added HCO_2NH_4 (31.50g, 0.5 mol) and 10% Pd/C (4.00g). The reaction mixture was refluxed for 30 min, filtered, evaporated *in vacuo*; the oily residue was treated with ether (150 mL). The solution was filtered, and treated with ether (200 mL) saturated with gaseous HCl. The resulting precipitate was collected, washed with diethyl ether and dried. Recrystallization from 2-propanol gave 18.71g (86%) of yellow crystals, mp 219-220°. IR: 3400-3200 (OH, NH), 2980-2540 (NH^+), 1710 (CO) cm^{-1}. ^1H NMR: δ 1.30 (t, 3H, J = 6.95 Hz), 4.30 (q, 2H, J = 6.95 Hz), 7.35 (m, 2H), 7.60 (m, 1H), 9.30 (br s, 4H).

Anal. Calcd for $C_9H_{12}ClNO_3$: C, 49.67; H, 5.56; N, 6.44. Found: C, 49.42; H, 5.57; N, 6.40

6-Ethoxycarbonylbenzoxazolin-2-one (8b).- To chloroform (200 mL) was added **11** (21.65g, 0.10 mol), Et_3N (43.30 mL, 0.30 mol) and ethyl chloroformate (14.80 mL, 0.15 mol) portionwise. The reaction mixture was stirred at room temperature for 2.5 h, washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The oily residue was dissolved in DMF (70 mL), treated with K_2CO_3 (27.60g, 0.2 mol), stirred and heated at 70° for 3 h. Acidification with 3N HCl (400 mL) gave the precipitate which was collected and dried. Recrystallization from EtOH gave 16.78g (81%) of white crystals, mp 174-175°. IR: 3250 (NH), 1760 (CO-N), 1700 (CO-O) cm^{-1}. ^1H NMR: δ 1.30 (t, 3H, J = 6.00 Hz), 4.40 (q, 2H, J = 6.00 Hz), 7.10 (d, 1H, J = 8.00 Hz), 7.95 (m, 2H), 9.80 (br s, 1H).

Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.67; H, 4.33; N, 6.69

6-Hydroxymethylbenzothiazolin-2-one (12a).- To an ice-cooled solution of **8a** (2.23g, 0.01 mol) in dry THF (50 mL) was added portionwise $LiAlH_4$ (1.14g, 0.03 mol). The suspension was stirred for 30 min at room temperature and was hydrolyzed by adding H_2O (100 mL), acidified to pH 1 with conc. HCl, extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated *in vacuo* to give a solid residue, which upon recrystallization from acetonitrile gave 0.72g (40%) of beige crystals, mp 168-170°. IR: 3300 (NH, OH), 1650 (CO) cm^{-1}. ^1H NMR: δ 4.50 (m, 2H), 5.20 (brs, 1H), 7.10 (d, 1H, J = 8.00 Hz), 7.25 (d, 1H, J = 8.00 Hz), 7.50 (m, 1H), 11.85 (br s, 1H).

Anal. Calcd for $C_8H_7NO_2S$: C, 53.03; H, 3.89; N, 7.73. Found: C, 53.22; H, 3.85; N, 7.86

6-Hydroxymethylbenzoxazolin-2-one (12b).- Starting from **8b** (2.07g, 0.01 mol), compound **12b** was synthesized using the same procedure as that for **12a**. Recrystallization from acetonitrile gave 0.79g (48%) of white crystals, mp 153-154°. IR: 3330 (OH, NH), 1740 (CO) cm^{-1}. ^1H NMR: δ 4.60 (m, 2H), 5.30 (br s, 1H), 7.00 (m, 2H), 7.30 (m, 1H), 11.60 (br s, 1H).

Anal. Calcd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.41; H, 4.36; N, 8.32

6-Chloromethylbenzothiazolin-2-one (13a).- To a solution of **12a** (1.81g, 0.01 mol) in dry $CHCl_3$ (50 mL) (cooled in an ice bath) was added dropwise $SOCl_2$ (1.50 mL, 0.02 mol). The reaction mixture was refluxed for 3 h and evaporated *in vacuo* to give a solid residue. Recrystallization from toluene gave 1.45g (73%) of beige crystals, mp 183-184°. IR: 3140 (NH), 1660 (CO) cm^{-1}. ^1H NMR: δ 4.80 (s, 2H), 7.10 (d, 1H, J = 8.25 Hz), 7.50 (d, 1H, J = 8.25 Hz), 7.65 (s, 1H), 12.00 (br s, 1H).

Anal. Calcd for C_8H_6ClNOS: C, 48.13; H, 3.03; N, 7.02. Found: C, 48.30; H, 3.15; N, 7.19

6-Chloromethylbenzoxazolin-2-one (13b).- Starting from **12b** (1.65g, 0.01 mol), compound **13b** was synthesized using the same procedure as that for **13a**. Recrystallization from 2-propanol gave 1.32g (72%) of brown crystals, mp 186-187°. IR: 3200 (NH), 1760 (CO) cm^{-1}. ^1H NMR: δ 4.80 (s, 2H), 7.20 (m, 3H), 11.75 (br s, 1H).

Anal. Calcd for $C_8H_6ClNO_2$: C, 52.34; H, 3.29; N, 7.63. Found: C, 52.61; H, 3.47; N, 7.67

6-{4-[(2-Fluorophenyl)piperazin-1-yl]methyl}benzothiazolin-2-one Hydrochloride (14a).- A mixture of **13a** (1.64g, 0.01 mol), N-(2-fluorophenyl) piperazine (2.16g, 0.012 mol), Et_3N (2.90 mL, 0.020 mol) and KI (0.17g, 0.001 mol) in acetone (50 mL) was refluxed for 2 days. The solvent was evaporated under reduced pressure. The oily residue was taken up with an aqueous solution of 1 N HCl (30 mL) and with ethyl acetate (20 mL). The mixture was stirred for 1 hour, collected by filtration, washed with ethyl acetate (100 mL), and dried. Recrystallization from 95° EtOH gave 2.31g (61%) of white crystals, mp >260°. IR: 3120 (NH), 2740-2540 (NH^+),1670 (CO) cm^{-1}. ^1H NMR: δ 3.10 (m, 4H), 3.50 (m, 4H), 4.50 (s, 2H), 7.10 (m, 5H), 7.50 (d, 1H, J = 8.20 Hz), 7.80 (s, 1H), 9.70 (br s, 1H), 12.15 (br s, 1H).

Anal. Calcd for $C_{18}H_{19}ClFN_3OS$: C, 56.91; H, 5.04; N, 11.06. Found: C, 56.63; H, 5.22; N, 10.86

6-{4-[(2-Fluorophenyl)piperazin-1-yl]methyl}benzothiazolin-2-one (14b).- Starting from **13b** (1.83g, 0.01 mol), compound **14b** was synthesized using the same procedure as that for **14a**. Recrystallization from toluene gave 1.50g (46%) of white crystals, mp 177-179°. IR: 3240 (NH), 1760 (CO) cm^{-1}. ^1H NMR: δ 2.50 (m, 4H), 3.00 (m, 4H), 3.50 (s, 2H), 7.00 (m, 6H), 7.20 (s, 1H), 11.50 (br s, 1H).

Anal. Calcd for $C_{18}H_{18}FN_3O_2$: C, 66.04; H, 5.54; N, 12.84. Found: C, 66.33; H, 5.62; N, 12.74

3-{2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl}-6-{[(4-(2-fluorophenyl)piperazin-1-yl] methyl}benzothiazolin-2-one Dihydrochloride (15a).- A mixture of **14a** (3.79g, 0.010 mol) and K_2CO_3 (8.28g, 0.060 mol) in DMF (50 mL) was refluxed for 30 min. 1-(2-chloroethyl)-4-(4-fluorobenzoyl)piperidine hydrochloride (3.67g, 0.012 mol) was added dropwise in the reaction. The solution was refluxed for 1 h, filtered, hydrolyzed in cold H_2O (100 mL). The resulting precipitate was collected, washed with H_2O, dried, and dissolved in acetone (10 mL). A solution of ether (100 mL) saturated with gaseous HCl was added dropwise to the acetone solution. The precipitate was collected, washed with ether, and dried. Recrystallization from EtOH gave 4.93g (76%) of yellow crystals, mp 251-253°. IR: 2740-2280 (NH^+), 1670 (CO) cm^{-1}. ^1H NMR: δ 2.00 (m, 4H), 3.20 (m, 4H), 3.45 (m, 11H), 4.45 (m, 4H), 7.10 (m, 4H), 7.40 (m, 2H), 7.80 (m, 2H), 8.00 (s, 1H), 8.10 (m, 2H), 11.25 (br s, 1H), 11.70 (br s, 1H).

Anal. Calcd for $C_{32}H_{36}Cl_2F_2N_4O_2S \cdot 2H_2O$: C, 56.05; H, 5.88; N, 8.17; Cl, 10.34

Found: C, 55.93; H, 5.94; N, 7.78; Cl, 9.97

3-{2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl}-6-{[4-(2-fluorophenyl)piperazin-1-yl] methyl}benzothiazolin-2-one (15b).- Starting from **14b** (3.27g, 0.01 mol), compound **15b** was synthesised using the procedure as that for **15a**. Recrystallization from EtOH gave 4.60g (82%) of beige crystals, mp 124-126°. IR: 1775 (CO) cm^{-1}. ^1H NMR: δ 1.55 (m, 4H), 2.50 (m, 4H), 2.65 (t, 2H, J = 5.95 Hz), 3.00 (m, 8H), 3.35 (m, 1H), 3.55 (s, 2H), 3.90 (t, 2H, J = 5.95 Hz), 7.05 (m, 5H), 7.30 (m, 4H), 8.00 (m, 2H).

Anal. Calcd for $C_{32}H_{34}F_2N_4O_3.H_2O$: C, 66.42; H, 6.27; N, 9.68. Found: C, 66.71; H, 5.94; N, 9.47.

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