New Access to 5-Substituted 1,3-Benzothiazol-2(3*H*)-ones and Their *N*-Methyl Analogues by a Palladium Coupling Reaction

Céline Pirat,[a] Vincent Ultré,[b] Nicolas Lebegue,[a] Pascal Berthelot,[a] Saïd Yous,[a] Pascal Carato*[a]

[a] Faculté de Pharmacie, Laboratoire de Chimie Thérapeutique (EA 4481), Université Lille Nord de France, 3 rue du Professeur Laguesse, BP 83, 59006 Lille Cedex, France
E-mail: pascal.carato@univ-lille2.fr; fax +3(33)20959009

[b] Faculté de Pharmacie, LARMN, Université Lille Nord de France, 3 rue du Professeur Laguesse, BP 83, 59006 Lille Cedex, France

Received 18 October 2010; revised 28 October 2010

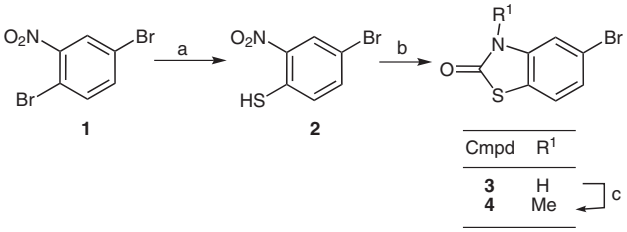
Abstract: 5-Substituted 1,3-benzothiazol-2(3*H*)-ones and their *N*-methyl analogues were readily prepared from the corresponding 5-bromo-1,3-benzothiazol-2(3*H*)-ones by means of Stille and Suzuki reactions. The compounds were substituted at the C-5 position with vinyl, acyl, or aryl groups optionally carrying electron-withdrawing or electron-donating substituents.

Key words: heterocycles, coupling, catalysis, benzothiazolones, Stille reaction

2(*3H*)-Benzazolones (1,3-dihydro-2*H*-indol-2-ones) have received considerable attention from the medicinal chemists because of their ability to mimic a phenol or a catechol moiety. All the structures so far described have been substituted at the nitrogen or at the C-6 position of the heterocycle. N-Substituted 2(*3H*)-benzazolones have been prepared by nucleophilic substitution with an acyl chloride or a halogenated reagent. Products with substituents at the C-6 position were obtained regioselectively under standard condition for electrophilic substitution by using chlorinating, sulfonating, or nitrating agents, or under Friedel–Crafts conditions in the presence of aluminum chloride–*N*,*N*-dimethylformamide or poly(phosphoric acid) and the appropriate acyl chloride.[1] Such substitution reactions provide access to a wide variety of compounds that exhibit therapeutic activities, such as anxiolytic, antipsychotic,[2–5] or antidiabetic[6] activity. Whereas methods for synthesizing 6-substituted 2(*3H*)-benzazolones are well known, fewer methods have been described for preparing their 5-substituted analogues. A patent mentions the synthesis of 5-substituted 2(*3H*)-benzoxazolones by Friedel–Crafts acylation,[7] but research in our laboratory[8] has shown that these acylations actually occurred at the C-6 positions of 1,3-benzoxazol-2(3*H*)-one and 1,3-benzothiazol-2(3*H*)-one. In the benzoxazolone series, compounds substituted at the C-5 position have been obtained in two steps starting from 2-aminophenol. An electrophilic reaction in the presence of aluminum chloride–*N*,*N*-dimethylformamide and the appropriate acyl chloride gave the corresponding 2-amino-4-acylphenol,[9] which was subsequently treated with urea in concentrated hydrochloric acid to give the corresponding 5-acyl-1,3-benzoxazol-2(3*H*)-one. This approach for synthesizing 5-acyl-1,3-benzoxazol-2(3*H*)-one has been explored in the benzothiazolone series, but the electrophilic reaction was unsuccessful in the case of 2-aminobenzenethiol. 5-Acyl-1,3-benzothiazol-2(3*H*)-ones have been prepared in four steps starting from 4-chloro-3-nitrobenzoyl chloride with subsequent formation of the thiazole ring.[10] We have investigate a simpler route starting from 5-bromo-1,3-benzothiazol-2(3*H*)-one that involves one or two steps.

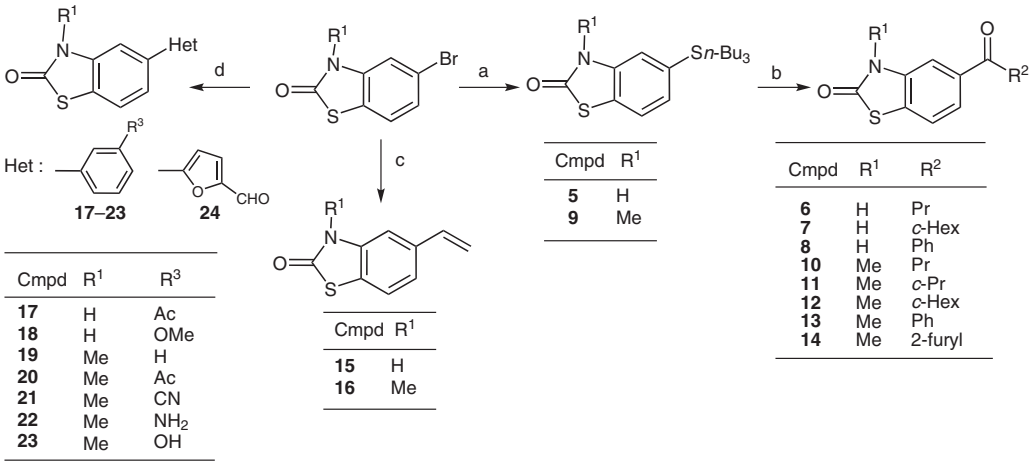
In this context, we have developed a new method for the preparation of 1,3-benzothiazol-2(3*H*)-ones substituted at the C-5 position by vinyl, substituted aryl, or acyl groups by means of palladium chemistry. Such derivatives could open the way to new therapeutic activities. Futhermore, N-unsubstituted benzothiazolones can be readily substituted at the nitrogen to give the corresponding products, which may have potential activities. We also developed a method for preparing 5-substituted 3-methyl-1,3-benzothiazol-2(3*H*)-ones from 5-bromo-3-methyl-1,3-benzothiazol-2(3*H*)-one.

Initially, we examined Stille and the Suzuki reactions of the N-unsubstituted and N-methylated bromo compounds **3** and **4,** respectively. The synthesis of key intermediate **3** that is described in the literature involves the use of high-pressure carbon monoxide,[11,12] so we decided to prepare it by a simpler route. Treatment of commercially available 1,4-dibromo-2-nitrobenzene (**1**) with sodium sulfide in ethanol gave 4-bromo-2-nitrobenzenethiol (**2**).[13] Treatment of thiol **2** with triphosgene [$CO(OCCl_3)_2$][14] under reductive conditions in acetic acid containing zinc[15] gave 5-bromo-1,3-benzothiazol-2(3*H*)-one (**3**; Scheme 1). The *N*-methyl derivative **4** was obtained by methylation of 5-bromo-1,3-benzothiazol-2(3*H*)-one (**3**) with dimethyl sulfate in aqueous sodium hydroxide.



Scheme 1 Synthesis of the starting bromo compounds **3** and **4**. *Reagents and conditions:* (a) Na_2S, EtOH; (b) Zn, AcOH, then $(Cl_3CO)_2CO$ (c) Me_2SO_4, aq NaOH.

SYNTHESIS 2011, No. 3, pp 0480–0484
Advanced online publication: 20.12.2010
DOI: 10.1055/s-0030-1258377; Art ID: Z25510SS



Cmpd	R^1	R^3
17	H	Ac
18	H	OMe
19	Me	H
20	Me	Ac
21	Me	CN
22	Me	NH_2
23	Me	OH

Cmpd	R^1
15	H
16	Me

Cmpd	R^1
5	H
9	Me

Cmpd	R^1	R^2
6	H	Pr
7	H	*c*-Hex
8	H	Ph
10	Me	Pr
11	Me	*c*-Pr
12	Me	*c*-Hex
13	Me	Ph
14	Me	2-furyl

Scheme 2 Synthesis of 5-substituted 1,3-benzothiazol-2(3*H*)-ones **5–24**. *Reagents and conditions* (a) R^1 = Me: $(Bu_3Sn)_2$, $Pd(PPh_3)_4$, anhyd toluene; R^1 = H: Bu_3SnCl, NaH, BuLi, anhyd THF; (b) R^2COCl, $PdCl_2(PPh_3)_2$, anhyd toluene (R^1 = Me) or anhyd THF (R^1 = H); (c) $Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$, dry toluene; (d) substituted boronic acid, $Pd(PPh_3)_4$, K_2CO_3, THF.

The substituted derivatives **5–24** were prepared by Stille or Suzuki coupling reactions of the corresponding 5-bromo-1,3-benzothiazol-2(3*H*)-ones **3** and **4** as key intermediates (Scheme 2).

For the synthesis of compounds **6–8** by the Stille reaction, intermediate **5** was prepared as described for the preparation of 6-(tributylstannyl)-1,3-benzothiazol-2(3*H*)-one.[16] 5-Bromo-1,3-benzothiazol-2(3*H*)-one (**3**) was treated with sodium hydride in dry tetrahydrofuran at 0 °C and then with butyllithium at –78 °C to form a lithiated intermediate that was treated with tributyl(chloro)stannane to give the desired 5-tributylstannylated product **5**. Stille coupling reactions of **5** with acid chlorides in the presence of dichlorobis(triphenylphosphine)palladium in dry toluene gave the corresponding 5-substituted 1,3-benzothiazol-2(3*H*)-ones **6–8**. As described previously,[17] the use of less than 1.3 equivalents of the stannyl compound **5** led to the formation of a mixture of 3,5-disubstituted 1,3-benzothiazol-2(3*H*)-ones.

For the 3-methyl series of compounds, standard Stille conditions were used to prepare various 5-substituted 3-methyl-1,3-benzothiazol-2(3*H*)-ones **10–14**. Treatment of the *N*-methyl derivative **4** with tetrakis(triphenyl)phosphine and hexabutyldistannane in dry toluene under dry argon gave the stannylated intermediate **9** in 65% yield. Stille coupling reactions of this compound with acid chlorides in the presence of dichlorobis(triphenylphosphine)palladium and in dry toluene under dry argon gave the corresponding 5-substituted 3-methyl-1,3-benzothiazol-2(3*H*)-ones **10**–**14** (Scheme 2). This method allowed the introduction of various substituents, such as butanoyl (**10**), cycloalkylcarbonyl (**11**–**12**), benzoyl (**13**) or hetaroyl (**14**) in good yields (65–89%).

Vinyl group were similarly introduced into **3** and **4** through a Stille reaction with tetrakis(triphenylphosphine)palladium and tributyl(vinyl)stannane in dry toluene to give products **15** and **16**, respectively.

We also examined the Suzuki coupling reactions of compounds **3** and **4** (Scheme 2) to give 5-aryl-1,3-benzothiazol-2(3*H*)-ones **17**–**24**. Treatment of **3** or **4** with tetrakis(triphenylphosphine)palladium, potassium carbonate, and the appropriately substituted boronic acid in dry toluene gave the corresponding 5-aryl derivatives **17**–**23**. Groups with electron-withdrawing (R^3 = Ac, CN) or electron-donating (R^3 = OMe, NH_2, OH) substituents on the phenyl ring were introduced with excellent yields (72–89%). A hetaryl ring with an electron-withdrawing substituent (CHO) was also introduced with 54% yield in the case of compound **24**.

We have therefore developed a new route to 1,3-benzothiazol-2(3*H*)-ones and their *N*-methyl derivatives substituted at the 5-position with butanoyl, cycloalkyl, or optionally substituted aryl groups through Stille or Suzuki coupling reactions. The aryl substituents can, in turn, carry electron-withdrawing or electron-donating substituents.

TLC was performed on silica gel 60 F_{254} plates, and column chromatography was performed on silica gel 60 (230–400 mesh). All the reagents and solvents were of AR grade. Melting points were determined by using a Büchi 510 capillary apparatus and are uncorrected. IR spectra were recorded on a Beckman ACCULAB IV spectrometer as pellets in KBr. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance 300 spectrometer and chemical shifts are given in ppm relative to TMS as the internal standard. Mass spectra were recorded on a Thermo Finnigan Surveyor MSQ single quadrupole mass spectrometer operated in the electrospray positive single-ion mode. The degree of purity (>97%) was determined from the relative peak area in the chromatogram, as detected by UV.

5-Bromo-1,3-benzothiazol-2(3*H*)-one (3)

Zn (9.0 g, 140 mmol) was added to a soln of thiol **2**[13] (3.6 g, 15.4 mmol) in AcOH (200 mL), and the mixture was heated at 65 °C for 15 h. The mixture was cooled at r.t., triphosgene (3.1 g, 10.3 mmol) was added, and the mixture was refluxed for 18 h. The soln was then concentrated under reduced pressure and hydrolyzed with H_2O (300 mL). The precipitate was filtered and washed with H_2O and 5% aq

NaOH (200 mL). The basic soln was then acidified (pH 2) with 6 M aq HCl to give a precipitate that was filtered off, washed with H_2O, and recrystallized (EtOH); yield: 68%; mp 242–243 °C.

IR (KBr): 1682 (CON).

^{1}H NMR (DMSO): δ = 7.22 (d, *J* = 1.9 Hz, 1 H, H_4), 7.31 (dd, *J* = 8.4, 1.9 Hz, 1 H, H_6), 7.55 (d, *J* = 8.4 Hz, 1 H, H_7), 12.05 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 114.4, 119.2, 123.2, 124.8, 125.5, 138.1, 170.6.

MS (APCI$^+$): *m/z* = 231.0 $[M + H]^+$.

5-Bromo-3-methyl-1,3-benzothiazol-2(3*H*)-one (4)

To a soln of bromo derivative **3** (5.0 g, 21.6 mmol) and NaOH (0.90 g, 21.6 mmol) in H_2O (100 mL), Me_2SO_4 (2.4 mL, 25.9 mmol) was added dropwise. The mixture was stirred at 25 °C for 2 h. The precipitate was filtered off, washed with H_2O, and recrystallized (toluene); yield: 76%; mp 121–122 °C.

IR (KBr): 1675 (CON).

^{1}H NMR ($CDCl_3$): δ = 3.45 (s, 3 H, NCH_3), 7.21 (m, 1 H, H_4), 7.31 (m, 2 H, H_6, H_7).

^{13}C NMR ($CDCl_3$): δ = 29.2, 113.7, 119.8, 121.4, 123.7, 126.1, 138.8, 169.8.

MS (APCI$^+$): *m/z* = 245.1 $[M + H]^+$.

5-(Tributylstannyl)-1,3-benzothiazol-2(3*H*)-one (5)

A soln of NaH (700 mg, 17.2 mmol) in anhyd THF (80 mL) was added to a soln of bromo derivative **3** (2 g, 8.6 mmol) in anhyd THF (20 mL) at 0 °C under dry argon. The soln was cooled to –78 °C and a 2.5 M soln of BuLi in hexane (6.9 mL, 17.2 mmol) was added. The soln was stirred for 15 min and then a 3.69 M soln of Bu_3SnCl in THF (7.0 mL, 25.8 mmol) was added dropwise at –78 °C. The mixture was stirred for 1 h at –78 °C and then allowed to warm slowly to r.t. The soln was then poured into 10% aq AcOH (100 mL). The aqueous layer was extracted with Et_2O (2 × 30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel, cyclohexane–EtOAc (95:5)] to give a colorless oil; yield: 60%.

IR (KBr): 1681 (CON).

^{1}H NMR ($CDCl_3$): δ = 0.90 [t, *J* = 6.7 Hz, 9 H, $(CH_3)_3$], 1.10 [m, 6 H, $(CH_2)_3$], 1.25 [m, 6 H, $(CH_2)_3$], 1.50 [m, 6 H, $(CH_2)_3$], 7.15 (d, *J* = 7.6 Hz, 1 H, H_4), 7.35 (dd, *J* = 7.6, 0.9 Hz, 1 H, H_6), 7.45 (s, 1 H, H_7), 9.55 (br s, 1 H, NH).

MS (APCI$^+$): *m/z* = 441.2 $[M + H]^+$.

5-Substituted 1,3-Benzothiazol-2(3*H*)-ones 6–8; General Procedure

$PdCl_2(PPh_3)_2$ (0.12 g, 0.017 mmol) was added to a soln of the appropriate acid chloride (0.87 mmol) in anhyd toluene (5 mL) under N_2, and the mixture was stirred at r.t. for 10 min. A soln of benzothiazolinone **5** (0.50 g, 1.13 mmol) in toluene (10 mL) was then added dropwise and the mixture was stirred at 110 °C for 15 h. When conversion was complete (TLC), the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography [silica gel, cyclohexane–EtOAc (95:5)].

5-Butyryl-1,3-benzothiazol-2(3*H*)-one (6)

Yield: 64%; mp 197–198 °C.

IR (KBr): 3087 (NH), 1679 (CON), 1671 (CO).

^{1}H NMR ($CDCl_3$): δ = 1.04 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.81 (sext, *J* = 7.3 Hz, 2 H, CH_2), 2.98 (t, *J* = 7.3 Hz, 2 H, CH_2), 7.52 (d, *J* = 8.0 Hz, 1 H, H_7), 7.77 (d, *J* = 1.6 Hz, 1 H, H_4), 7.79 (dd, *J* = 8.0, 1.6 Hz, 1 H, H_6), 9.06 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 13.8, 17.8, 40.5, 110.5, 122.6, 123.2, 129.6, 135.3, 135.7, 171.0, 199.2.

MS (APCI$^+$): *m/z* = 222.1 $[M + H]^+$.

5-(Cyclohexylcarbonyl)-1,3-benzothiazol-2(3*H*)-one (7)

Yield: 58%; mp 190–191 °C.

IR (KBr): 3097 (NH), 1711 (CON), 1673 (CO).

^{1}H NMR ($CDCl_3$): δ = 1.3–2.0 (m, 10 H, CH_2), 3.26 (tt, *J* = 11.0, 3.0 Hz, 1 H, CH), 7.52 (d, *J* = 8.2 Hz, 1 H, H_7), 7.77 (dd, *J* = 8.2, 1.6 Hz, 1 H, H_6), 7.80 (d, *J* = 1.6 Hz, 1 H, H_4), 9.85 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ =25.8, 25.9, 29.5, 45.7, 111.1, 122.5, 123.3, 129.5, 134.8, 135.7, 171.1, 203.0.

MS (APCI$^+$): *m/z* = 262.0 $[M + H]^+$.

5-Benzoyl-1,3-benzothiazol-2(3*H*)-one (8)

Yield: 65%; mp 194–195 °C.

IR (KBr): 2924 (NH), 2854, 1724 (CON), 1650 (CO).

^{1}H NMR (DMSO-d_6): δ =7.44 (d, *J* = 1.4 Hz, 1 H, H_4), 7.51 (dd, *J* = 8.1, 1.4 Hz, 1 H, H_6), 7.57 (m, 2 H, H_{Ar}), 7.67 (d, *J* = 8.1 Hz, 1 H, H_7), 7.76 (m, 3 H, H_{Ar}), 12.09 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ =112.4, 122.3, 125.4, 128.5, 129.2, 130, 132.7, 135.0, 136.0, 137.2, 170.8, 195.6.

MS (APCI$^+$): *m/z* = 256.1 $[M + H]^+$.

3-Methyl-5-(tributylstannyl)-1,3-benzothiazol-2(3*H*)-one (9)

$(Bu_3Sn)_2$ (8.3 mL, 16.4 mmol) was added to a soln of bromo derivative **4** (2.0 g, 8.2 mmol) and $Pd(PPh_3)_4$ (0.86 g, 0.8 mmol) in anhyd toluene (20 mL) under dry argon and the mixture was stirred at 110 °C for 16 h. The solvent was then evaporated under reduced pressure and the oily residue was purified by flash column chromatography [PE–EtOAc (9.8:0.2)] to give an oily product; yield: 65%.

IR (KBr): 1678 (CON).

^{1}H NMR ($CDCl_3$): δ = 0.90 [t, *J* = 5.9 Hz, 9 H, $(CH_3)_3$], 1.10 [t, *J* = 6.1 Hz, 6 H, $(CH_2)_3$], 1.30 [m, 6 H, $(CH_2)_3$], 1.55 [m, 6 H, $(CH_2)_3$], 3.45 (s, 3 H, NCH_3), 7.10 (s, 1 H, H_4), 7.40 (d, *J* = 7.6 Hz, 1 H, H_7), 7.40 (d, *J* = 7.6 Hz, 1 H, H_6).

MS (APCI$^+$): *m/z* = 455.1 $[M + H]^+$.

5-Substituted 3-Methyl-1,3-cenzothiazol-2(3*H*)-ones 10–14; General Procedure

An acid chloride (1.8 mmol) was added to a soln of stannyl derivative **9** (0.50 g, 1.2 mmol) and $PdCl_2(PPh_3)_2$ (0.08 g, 0.12 mmol) in anhyd toluene (10 mL) under dry argon, and the mixture was refluxed at 110 °C for 8 h. The soln was evaporated under reduced pressure and the resulting precipitate was purified by flash column chromatography (CH_2Cl_2).

5-Butyryl-3-methyl-1,3-benzothiazol-2(3*H*)-one (10)

Yield: 69%; mp 105–106 °C.

IR (KBr): 1672 (CON, CO).

^{1}H NMR ($CDCl_3$): δ = 1.04 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.82 (sext, *J* = 7.3 Hz, 2 H, CH_2), 3.00 (t, *J* = 7.3 Hz, 2 H, $COCH_2$), 3.53 (s, 3 H, NCH_3), 7.53 (d, *J* = 8.1 Hz, 1 H, H_7), 7.67 (d, *J* = 1.6 Hz, 1 H, H_4), 7.79 (dd, *J* = 8.1, 1.6 Hz, 1 H, H_6).

^{13}C NMR ($CDCl_3$): δ = 13.9, 17.8, 29.3, 40.5, 109.3, 122.3, 123.7, 128.4, 135.5, 138.2, 169.5, 199.7.

MS (APCI$^+$): *m/z* = 236 $[M + H]^+$.

5-(Cyclopropylcarbonyl)-3-methyl-1,3-benzothiazol-2(3*H*)-one (11)
Yield: 84%; mp 113–114 °C,

IR (KBr): 1674 (CON), 1659 (CO).

^{1}H NMR ($CDCl_3$): δ = 1.11 (m, 2 H, CH_2), 1.29 (m, 2 H, CH_2), 2.69 (tt, *J* = 7.8, 4.5 Hz, 1 H, CH), 3.52 (s, 3 H, NCH_3), 7.54 (d, *J* = 8.1 Hz, 1 H, H_7), 7.66 (d, *J* = 1.5 Hz, 1 H, H_4), 7.89 (dd, *J* = 8.1, 1.5 Hz, 1 H, H_6).

^{13}C NMR ($CDCl_3$): δ = 12.1, 17.2, 29.3, 109.3, 122.3, 123.3, 128.2, 136.4, 138.1, 169.5, 199.5.

MS (APCI$^+$): *m/z* = 234.1 $[M + H]^+$

5-(Cyclohexylcarbonyl)-3-methyl-1,3-benzothiazol-2(3*H*)-one (12)
Yield: 76%; mp 92–93 °C.

IR (KBr): 1686 (CON), 1673 (CO).

^{1}H NMR ($CDCl_3$): δ = 1.20–2.00 [m, 10 H, $(CH_2)_5$], 3.28 (tt, *J* = 11.1, 3.1 Hz, 1 H, CH), 3.53 (s, 3 H, NCH_3), 7.53 (d, *J* = 8.3 Hz, 1 H, H_7), 7.66 (d, *J* = 1.5 Hz, 1 H, H_4), 7.77 (dd, *J* = 8.3, 1.5 Hz, 1 H, H_6).

^{13}C NMR ($CDCl_3$): δ = 25.8, 25.9, 29.3, 29.5, 45.6, 109.8, 122.7, 123.3, 128.3, 134.8, 138.4, 169.5, 202.8.

MS (APCI$^+$): *m/z* = 276.1 $[M + H]^+$.

5-Benzoyl-3-methyl-1,3-benzothiazol-2(3*H*)-one (13)
Yield: 89%; mp 138–139 °C.

IR (KBr): 1683 (CON), 1655 (CO).

^{1}H NMR ($CDCl_3$): δ = 3.50 (s, 3 H, NCH_3), 7.50–7.70 (m, 6 H, H_{Ar}), 7.80–7.85 (m, 2 H, H_{Ar}).

^{13}C NMR ($CDCl_3$): δ = 29.4, 111.3, 122.0, 125.6, 128.1, 128.4, 130.0, 132.7, 135.8, 137.3, 138.1, 169.4, 195.7.

MS (APCI$^+$): *m/z* = 270 $[M + H]^+$.

5-(2-Furoyl)-3-methyl-1,3-benzothiazol-2(3*H*)-one (14)
Yield: 71%; mp 165–166 °C.

IR (KBr): 1685 (CON), 1654 (CO).

^{1}H NMR ($CDCl_3$): δ = 3.55 (s, 3 H, NCH_3), 6.66 (dd, *J* = 3.5, 1.6 Hz, 1 H, H_{Ar}), 7.33 (dd, *J* = 3.5, 0.4 Hz, 1 H, H_{Ar}), 7.57 (d, *J* = 8.1 Hz, 1 H, H_7), 7.70 (d, *J* = 1.5 Hz, 1 H, H_4), 7.76 (dd, *J* = 1.6, 0.4 Hz, 1 H, H_{Ar}), 7.89 (dd, *J* = 8.1, 1.5 Hz, 1 H, H_6).

^{13}C NMR ($CDCl_3$): δ = 29.3, 110.9, 112.5, 120.7, 122.2, 124.5, 128.2, 135.4, 138.1, 147.3, 152.2, 169.5, 181.1.

MS (APCI$^+$): *m/z* = 260 $[M + H]^+$.

5-Vinyl-1,3-benzothiazol-2(3*H*)-ones (15–16); General Procedure
$Pd(PPh_3)_4$ (0.21 g, 0.20 mmol) and tributyl(vinyl)stannane (1.2 mL, 4.0 mmol) were added to a soln of bromo compound **3** or **4** (2.0 mmol) in anhyd toluene (10 mL) under dry argon, and the mixture was stirred at 110 °C for 3 h. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography [CH_2Cl_2–PE (5:5)].

5-Vinyl-1,3-benzothiazol-2(3*H*)-one (15)
Yield: 55%; mp 127–128 °C.

IR (KBr): 1682 (CON).

^{1}H NMR ($CDCl_3$): δ = 5.30 (d, *J* = 11.1 Hz, 1 H, CH_2), 5.77 (d, *J* = 17.5 Hz, 1 H, CH), 6.70 (dd, *J* = 17.5, 11.1 Hz, 1 H, CH), 7.21 (dd, *J* = 7.7, 1.4 Hz, 1 H, H_6), 7.22 (d, *J* = 1.4 Hz, 1 H, H_4), 7.36 (d, *J* = 7.7 Hz, 1 H, H_7), 10.30 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 109.2, 114.7, 121.7, 122.5, 123.2, 135.8, 136.0, 136.6, 173.5.

MS (APCI$^+$): *m/z* = 178.1 $[M + H]^+$.

3-Methyl-5-vinyl-1,3-benzothiazol-2(3*H*)-one (16)
Yield: 65%; mp 61–62 °C.

IR (KBr): 1677 (CON).

^{1}H NMR ($CDCl_3$): δ = 3.49 (s, 3 H, NCH_3), 5.34 (d, *J* = 10.8 Hz, 1 H, CH_2), 5.81 (d, *J* = 17.5 Hz, 1 H, CH_2), 6.75 (dd, *J* = 17.5, 10.8 Hz, 1 H, CH), 7.10 (d, *J* = 1.5 Hz, 1 H, H_4), 7.25 (dd, *J* = 8.1, 1.5 Hz, 1 H, H_6), 7.39 (d, *J* = 8.1 Hz, 1 H, H_7).

^{13}C NMR ($CDCl_3$): δ = 29.0, 107.8, 114.5, 121.5, 122.0, 122.5, 136.2, 136.4, 138.1, 170.0.

MS (APCI$^+$): *m/z* = 192 $[M + H]^+$.

5-Aryl-1,3-benzothiazol-2(3*H*)-ones (17–24); General Procedure
Bromo compound **3** or **4** (1.2 mmol) and $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol) were stirred in dry toluene (10 mL) at r.t. under dry argon for 10 min. A soln of K_2CO_3 (0.49 g, 3.6 mmol) in H_2O (3 mL) and the desired boronic acid (1.8 mmol) dissolved in 95% EtOH (5 mL) were added. The mixture was refluxed for 4 h then concentrated under a reduced pressure. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography [CH_2Cl_2–PE (5:5)].

5-(3-Acetylphenyl)-1,3-benzothiazol-2(3*H*)-one (17)
Yield: 76%; mp 212–213 °C.

IR (KBr): 1685 (CON), 1654 (CO).

^{1}H NMR (DMSO-d_6): δ = 2.66 (s, 3 H, $COCH_3$), 7.38 (d, *J* = 1.8 Hz, 1 H, H_4), 7.51 (dd, *J* = 8.1, 1.8 Hz, 1 H, H_6), 7.63 (t, *J* = 7.4 Hz, 1 H, H_{Ar}), 7.71 (d, *J* = 8.1 Hz, 1 H, H_7), 7.91 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1 H, H_{Ar}), 7.98 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1 H, H_{Ar}), 8.15 (t, *J* = 1.7 Hz, 1 H, H_{Ar}), 12.02 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ =27.4, 110.0, 121.9, 123.6, 123.8, 126.7, 127.9, 130.0, 131.8, 137.5, 138.0, 138.3, 140.5, 170.6, 198.4.

MS (APCI$^+$): *m/z* = 270.0 $[M + H]^+$.

5-(3-Methoxyphenyl)-1,3-benzothiazol-2(3*H*)-one (18)
Yield: 75%; mp 169–170 °C.

IR (KBr): 1659 (CON).

^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3 H, OCH_3), 6.94 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1 H, H_{Ar}), 7.12 (dd, *J* = 2.6, 1.6 Hz, 1 H, H_{Ar}), 7.17 (ddd, *J* = 7.6, 1.7, 1.0 Hz, 1 H, H_{Ar}), 7.35–7.43 (m, 3 H, H_4, H_6, H_{Ar}), 7.47 (d, *J* = 8.0 Hz, 1 H, H_7), 9.91 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 55.4, 110.3, 112.9, 113.1, 119.6, 122.5, 122.8, 123.0, 130.0, 135.7, 140.1, 141.7, 160.0, 173.0.

MS (APCI$^+$): *m/z* = 258.1 $[M + H]^+$.

3-Methyl-5-phenyl-1,3-benzothiazol-2(3*H*)-one (19)
Yield: 96%; mp 95–96 °C.

IR (KBr): 1688 (CON).

^{1}H NMR ($CDCl_3$): δ = 3.55 (s, 3 H, NCH_3), 7.24 (d, *J* = 1.6 Hz, 1 H, H_4), 7.38–7.42 (m, 2 H, H_6, H_{Ar}), 7.46–7.54 (m, 3 H, H_7, H_{Ar}), 7.62 (m, 2 H, H_{Ar}).

^{13}C NMR ($CDCl_3$): δ = 29.1, 109.2, 121.6, 122.4, 122.8, 127.2, 127.8, 129.0, 138.2, 140.2, 140.5, 170.5.

MS (APCI$^+$): *m/z* = 242 $[M + H]^+$.

5-(3-Acetylphenyl)-3-methyl-1,3-benzothiazol-2(3*H*)-one (20)
Yield: 76%; mp 174–175 °C.

IR (KBr): 1674 (CON).

^{1}H NMR ($CDCl_3$): δ = 2.68 (s, 3 H, $COCH_3$), 3.52 (s, 3 H, NCH_3), 7.24 (d, *J* = 1.7 Hz, 1 H, H_4), 7.42 (dd, *J* = 8.0, 1.7 Hz, 1 H, H_6), 7.52 (d, *J* = 8.1 Hz, 1 H, H_7), 7.58 (t, *J* = 7.7 Hz, 1 H, H_{Ar}), 7.81 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1 H, H_{Ar}), 7.97 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1 H, H_{Ar}), 8.20 (t, *J* = 1.7 Hz, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$): δ = 26.8, 29.2, 109.1, 122.2, 122.4, 122.9, 126.7, 127.8, 129.3, 131.8, 137.7, 138.4, 139.0, 141.0, 170.1, 198.0.

MS (APCI$^+$): *m/z* = 283.9 $[M + H]^+$.

3-(3-Methyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-yl)benzonitrile (21)
Yield: 89%; mp 197–198 °C.

IR (KBr): 2230 (CN), 1693 (CON).

^{1}H NMR ($CDCl_3$): δ = 3.54 (s, 3 H, NCH_3), 7.20 (d, *J* = 1.7 Hz, 1 H, H_4), 7.38 (dd, *J* = 8.1, 1.7 Hz, 1 H, H_6), 7.54 (d, *J* = 8.1 Hz, 1 H, H_7), 7.60 (t, *J* = 7.7 Hz, 1 H, H_{Ar}), 7.68 (dt, *J* = 7.7, 1.5 Hz, 1 H, H_{Ar}), 7.85 (dt, *J* = 7.7, 1.5 Hz, 1 H, H_{Ar}), 7.89 (t, *J* = 1.5 Hz, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$): δ = 29.2, 109.0, 113.2, 118.7, 122.2, 123.0, 123.1, 129.9, 130.7, 131.1, 131.5, 137.7, 138.5, 141.7, 170.0.

MS (APCI$^+$): *m/z* = 266.2 $[M + H]^+$.

5-(3-Aminophenyl)-3-methyl-1,3-benzothiazol-2(3*H*)-one (22)
Yield: 83%; mp 166–167 °C.

IR (KBr): 3351 (NH_2), 1665 (CON).

^{1}H NMR ($CDCl_3$): δ = 3.52 (s, 3 H, NCH_3), 3.75 (br s, 2 H, NH_2), 6.73 (ddd, *J* = 7.7, 1.9, 1.0 Hz, 1 H, H_{Ar}), 6.92 (t, *J* = 1.9 Hz, 1 H, H_{Ar}), 7.00 (ddd, *J* = 7.7, 1.9, 1.0 Hz, 1 H, H_{Ar}), 7.21 (d, *J* = 1.7 Hz, 1 H, H_4), 7.27 (t, *J* = 7.7 Hz, 1 H, H_{Ar}), 7.38 (dd, *J* = 8.0, 1.7 Hz, 1 H, H_6), 7.48 (d, *J* = 8.0 Hz, 1 H, H_7).

^{13}C NMR ($CDCl_3$): δ = 29.1, 109.1, 113.7, 114.5, 117.5, 121.4, 122.3, 122.6, 129.9, 138.1, 140.4, 141.7, 147.0, 170.3.

MS (APCI$^+$): *m/z* = 257 $[M + H]^+$.

5-(3-Hydroxyphenyl)-3-methyl-1,3-benzothiazol-2(3*H*)-one (23)
Yield: 72%; mp 182–183 °C.

IR (KBr): 3304 (OH), 1660 (CON)

^{1}H NMR (DMSO-d_6): δ = 3.48 (s, 3 H, NCH_3), 6.80 (ddd, *J* = 8.0, 2.3, 1.0 Hz, 1 H, H_{Ar}), 7.10 (t, *J* = 1.9 Hz, 1 H, H_{Ar}), 7.15 (dt, *J* = 8.0, 1.6 Hz, 1 H, H_{Ar}), 7.28 (t, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.44 (dd, *J* = 8.1, 1.7 Hz, 1 H, H_6), 7.50 (d, *J* = 1.5 Hz, 1 H, H_4), 7.71 (d, *J* = 8.2 Hz, 1 H, H_7), 9.57 (br s, 1 H, OH).

^{13}C NMR (DMSO-d_6): δ = 29.5, 110.0, 114.2, 115.1, 118.2, 120.9, 122.1, 123.5, 130.4, 138.7, 139.7, 141.6, 158.3, 169.4.

MS (APCI$^+$): *m/z* = 257.9 $[M + H]^+$.

5-(3-Methyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-yl)-2-furaldehyde (24)
Yield: 54%; mp 150–151 °C.

IR (KBr): 1687 (CON), 1662 (CHO).

^{1}H NMR ($CDCl_3$): δ = 3.55 (s, 3 H, NCH_3), 6.91 (d, *J* = 3.7 Hz, 1 H, H_{Ar}), 7.37 (d, *J* = 3.7 Hz, 1 H, H_{Ar}), 7.50 (d, *J* = 8.2 Hz, 1 H, H_7), 7.51 (d, *J* = 1.6, 1 H, H_4), 7.61 (dd, *J* = 8.2, 1.6 Hz, 1 H, H_6), 9.68 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$): δ = 29.4, 106.8, 108.1, 120.4, 123.0, 124.0, 124.4, 127.5, 138.5, 152.1, 158.6, 169.8, 177.1.

MS (APCI$^+$): *m/z* = 260.1 $[M + H]^+$.

Acknowledgment

The 300 MHz NMR facilities were funded by the Région Nord-Pas de Calais (France), the Ministère de la Jeunesse, de l'Education Nationale et de la Recherche (MJENR), and the Fonds Européens de Développement Régional (FEDER).

References

(1) Yous, S.; Poupaert, J.-H.; Lesieur, I.; Depreux, P.; Lesieur, D. *J. Org. Chem.* **1994**, *59*, 1574.
(2) Diouf, O.; Carato, P.; Depreux, P.; Bonte, J.-P.; Caignard, D.-H.; Guardiola-Lemaître, B.; Rettori, M. C.; Belzung, C.; Lesieur, D. *Bioorg. Med. Chem. Lett.* **1997; 7**, 2579.
(3) Diouf, O.; Carato, P.; Lesieur, I.; Rettori, M. C.; Caignard, D.-H. *Eur. J. Med. Chem.* **1999**, *34*, 9.
(4) Lesieur, D.; Carato, P.; Bonte, J.-P.; Depreux, P.; Caignard, D.-H.; Millan, M.; Newman-Tancredi, A.; Renard, P.; Rettori, M. C. EP0841330 **1998**; *Chem. Abstr.* **1998**, *129*, 4662x.
(5) Carato, P.; Depreux, P.; Lesieur, D.; Millan, M.; Newman-Tancredi, A.; Rettori, M. C.; Caignard, D.-H. *Drug Des. Discovery* **2000**, *17*, 73.
(6) Blanc-Delmas, E.; Lebegue, N.; Wallez, V.; Leclerc, V.; Yous, S.; Carato, P.; Farce, A.; Bennejean, C.; Renard, P.; Caignard, D.-H.; Audinot-Bouchez, V.; Chomarat, P.; Boutin, J.; Hennuyer, N.; Louche, K.; Carmona, M. C.; Staels, B.; Penicaud, L.; Casteilla, L.; Lonchampt, M.; Dacquet, C.; Chavatte, P.; Berthelot, P.; Lesieur, D. *Bioorg. Med. Chem.* **2006**, *14*, 7377.
(7) Takao, T.; Hisashi, T. EP0120589 **1984**.
(8) Aichaoui, H.; Poupaert, J. H.; Lesieur, D.; Hénichart, J.-P. *Tetrahedron* **1991**, *47*, 6649.
(9) Aichaoui, H.; Lesieur, I.; Hénichart, J.-P. *Synthesis* **1990**, *8*, 679.
(10) Tzanova, T.; Gerova, M.; Petrov, O.; Karaivanova, M.; Bagrel, D. *Eur. J. Med. Chem.* **2009**, *44*, 2724.
(11) Nishiguchi, I.; Konishi, K.; Hirashima, T. *Heterocycles* **1984**, *21*, 455.
(12) Konishi, K.; Nishiguchi, I.; Hirashima, T. *Synthesis* **1984**, 254.
(13) Hodgson, W. *J. Chem. Soc.* **1925**, *127*, 442.
(14) Zhifang, L.; Yongmin, Z. *Heteroat. Chem.* **2003**, *14*, 46.
(15) Heiss, C.; Andersson, J.; Phillips, R. *Org. Biomol. Chem.* **2003**, *1*, 288.
(16) Carato, P.; Cherry, K.; Lebegue, N.; Berthelot, P.; Yous, S. *Heterocycles* **2007**, *71*, 2041.
(17) Cherry, K.; Lebegue, N.; Leclerc, V.; Carato, P.; Yous, S.; Berthelot, P. *Tetrahedron Lett.* **2007**, *48*, 5751.