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SYNTHESIS OF 6-CYCLOALKYLCARBONYL-2(3*H*)-BENZOTHIAZOLONES *VIA* 6-TRIBUTYLTIN INTERMEDIATES

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Abstract – 6-Cycloalkylcarbonyl-2(3*H*)-benzothiazolones cannot be prepared by classical Friedel-Crafts acylation with the corresponding cycloalkylcarbonyl chlorides. We have explored new way via stille coupling from the tributyltin intermediates which were synthesised by protection of the NH group with ethylmethyl ether or potassium salt of the corresponding 6-bromo-2-(3*H*)-benzothiazolone. The stille coupling reaction of these tributyltin intermediates with the desired cycloalkylcarbonyl chlorides followed by deprotection of the NH group, afforded the corresponding 6-cycloalkylcarbonyl-2(3*H*)-benzothiazolones.

INTRODUCTION

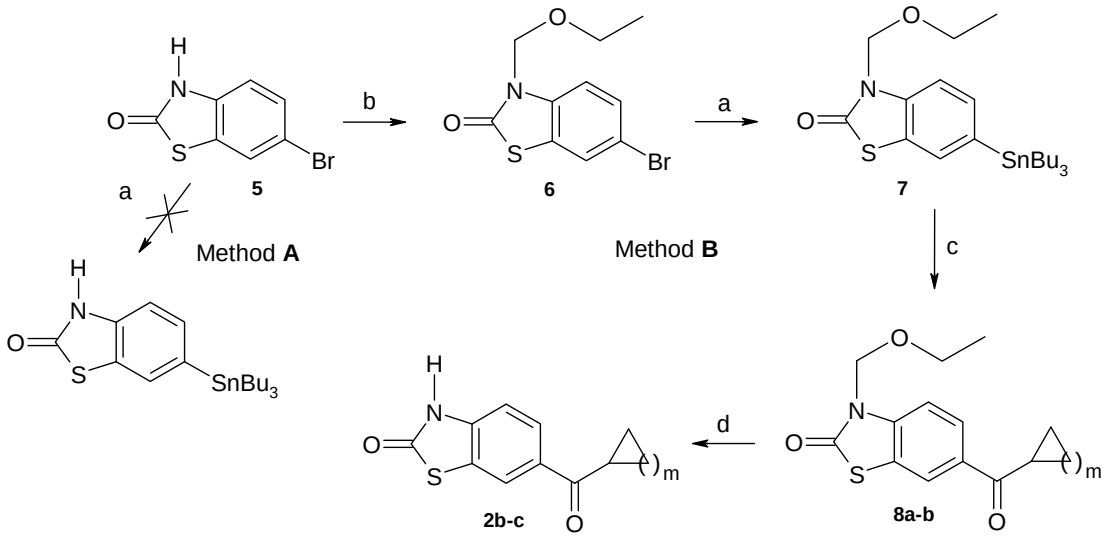
2(*3H*)-Benzothiazolone is a pharmacophore who was usually used to build molecules with medicinal properties or useful as pharmacological tools.[1-3] Friedel-Crafts acylation which used drastic acid conditions as PPA or $AlCl_3$ – DMF complex, was usually employed to give the corresponding products substituted regioselectively in the C-6 position.[4] We showed that introduction of cycloalkylcarbonyl group in *N*-methyl-2-(3*H*)-benzothiazolone cannot be performed in these reaction conditions, the acylium ion is unstable. 6-Cycloalkylcarbonyl-*N*-methyl-2(3*H*)-benzothiazolones were obtained by Stille coupling using stannic intermediates.[5]

In this paper, we have focused our attention on the 2(3*H*)-benzothiazolone ring without substitution on the NH group which seems to be essential structural requirement for activity and receptor selectivity.[6] As for *N*-methyl derivatives, the general approach to synthesize the corresponding 6-cycloalkylcarbonyl compounds with free NH group was explored using stannic intermediates.

RESULTS AND DISCUSSION

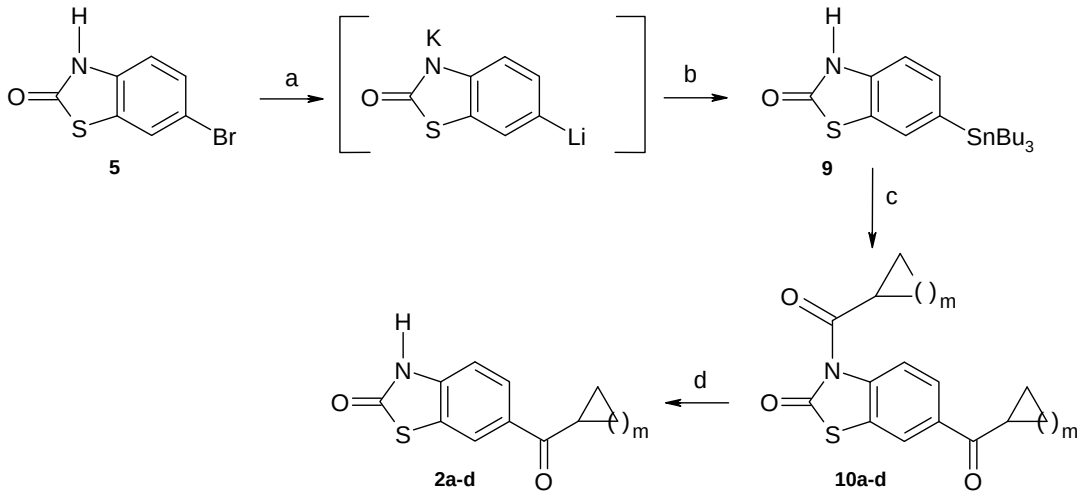
Stille coupling reaction with 6-bromo-2(3*H*)-benzothiazolone (**5**), $Pd(PPh)_3$ and $(Bu_3Sn)_2$ in toluene or

DMF was unsuccessful and all the starting material was recovered (Method A, Scheme 1). As we claimed in a recent publication, some reactions which are successful in the *N*-methyl series cannot be applied in the N-H benzothiazolonic series.[7] Stille reaction is sensible to acid media or acid group as the hydrogen of the thiocarbamate moiety, we have then decided to protect the NH form with ethylmethyl ether group (Method B, Scheme 1).



Scheme 1. Reagents: (a) : $(Bu_3Sn)_2$, $Pd(PPh_3)_4$, toluene, argon (b) : $ClCH_2OCH_2CH_3$, K_2CO_3, DMF, 85%(c) : cycloalkylcarbonyl chloride (m= 2, 4), $PdCl_2(PPh_3)_2$, toluene, argon, 61-76% (d) : TFA, 21-28%.

The 6-bromo-2(*3H*)-benzothiazolone (**5**) [8] in dimethyformamide, in the presence of 2-chloromethylethyl ether and potassium carbonate afforded the *N*-protected compound **6**. Treatment of bromo derivative **6** with $(Bu_3Sn)_2$ and $Pd(PPh_3)_4$ in toluene under argon gave the 3-ethoxymethyl-6-tributyltin-2(3*H*)-benzothiazolone (**7**) with satisfactory yield (58%). Reaction of the stannic intermediate **7** in toluene, under argon, with $PdCl_2(PPh_3)_2$ and the desired cycloalkylcarbonyl chlorides gave compounds **8a-b** with good yields (61-74%). The last step was the cleavage of the protecting group ethylmethyl ether in refluxing TFA of the compounds **8a-b** to afford the corresponding products **2b-c** with low yields (21 and 28 % respectively). Others protecting groups, as acetyl and methanesulfonyl, were introduced to give the N-protected-6-bromo-2(3*H*)-benzothiazolone. These N-protected products were treated according to Stille coupling reaction, but surprisingly we cannot obtain the corresponding N-protected-6-tributyltin-2(3*H*)-benzothiazolones. Considering the weak yields of deprotection and the observed cycloalkyl opening rings in the hard deprotection conditions, we adopted another method of protection to inhibit the interaction of the NH acid group in the stille coupling. Yang have described the introduction of trimethylstannyl group on 5-bromoindole,[9] which was first converted to its potassium salt derivative, subjected to halogen-metal exchange using tert-butyllithium and then introduction of the trimethylstannyl. We have adopted this methodology (Scheme 2).



Scheme 2 Reagents: (a) i : KH, THF ; ii : *tert*-BuLi (b) Bu_3SnCl, 65% (c): KH, cycloalkylcarbonyl chloride derivatives (m= 1, 2, 3, 4), $PdCl_2(PPh_3)_2$, THF, 76-89%(d) NaOH, H_2O, MeOH, 55-81%.

On the first step 6-bromo-2(3*H*)-benzothiazolone (**5**) in THF at 0 °C with KH was converted to the potassium salt compound, the second step was the introduction at -78 °C of *tert*-butyl lithium to realise the halogen-metal exchange, then tributyltin chloride was added to give the desired 6-tributyltin-2(3*H*)-benzothiazolone (**9**). The first attempt of Stille coupling of stannic (**9**) in standard conditions led to the recovery of 2-(3*H*)-benzothiazolone. We decided to convert as previously described, the NH group to its potassium salt for the Stille coupling in presence of KH, $PdCl_2(PPh_3)_2$ and the corresponding cycloalkylcarbonyl chlorides in refluxing THF under argon. In these reaction conditions, the 3,6-diacylated compounds **10a-d** were obtained and the cleavage of the *N*-cycloalkylcarbonyl groups was easily realised in a mixture of water/MeOH in the presence of sodium hydroxide to give the corresponding 6-cycloalkylcarbonyl-2(3*H*)-benzothiazolones (**2a-d**) with free NH group.

In conclusion, in this article we report the synthesis of original 6-cycloalkylcarbonyl-2(3*H*)-benzothiazolones (**2a-d**) which represent powerfull intermediates for the synthesis of a great range of biologically active compounds. These compounds were synthesized by stille coupling via the corresponding 6-tributyltin intermediates. In this article we showed the interaction of the N-H acid group of the 2(3*H*)-benzothiazolone in the Stille reaction, and the necessary to protect via the potassium salt or ethylmethylether group to produce the 6-tributyltin intermediates (**7**, **9**). These protections allowed leading to original compounds **2a-d**, **10a-d**, **and 8a-b**.

EXPERIMENTAL

Melting points were determined on a Büchi SMP-535 apparatus and are uncorrected. IR spectra were recorded on a Brüker Vector 22 spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Brüker AC 300 instrument using TMS as an internal reference.

6-Bromo-3-ethoxymethyl-2(3*H*)-benzothiazolone (**6**): To a solution of 6-bromo-2(3*H*)-benzothiazolone (**5**) (3 g, 13 mmol) in DMF (50 mL), K_2CO_3 (5.4 g, 39 mmol) were refluxed for 30 min and then chloromethyl ethyl ether (1.8 mL, 19 mmol) was added. The mixture was stirred at 100 °C for 4 h. The mixture was allowed to cool, and the reaction was quenched with the addition of water (200 mL). The precipitate was filtered off, dried and recristallised with to give the title compound (2.2 g, 85%). mp 79-80 °C (petroleum ether); IR 1676 (CO); ^{1}H NMR ($CDCl_3$): δ 1.15 (t, 3H, J= 7.0 Hz, CH_3), 3.60 (q, 2H, J= 7.0 Hz, CH_2), 5.40 (s, 2H, NCH_2O), 7.15 (d, 1H, J= 8.5 Hz, H_4), 7.45 (dd, 1H, J= 8.5 Hz, J= 1.7 Hz, H_5), 7.60 (d, 1H, J= 1.7 Hz, H_7). M/z= 289.2. Anal. Calcd for $C_{10}H_{10}NO_2S$: C, 41.68; H, 3.50; N, 4.86. Found: C, 41.89; H, 3.74; N, 4.61.

3-Ethoxymethyl-6-tri-n-butyltin-2(3*H*)-benzothiazolone (**7**): To a mixture of 6-bromo-3-ethyoxymethyl-2(3*H*)-benzothiazolone (**6**) (5.2 g, 18 mmol) in dry toluene (50 mL) under argon, tetrakis(triphenylphosphine)palladium (2.1 g, 1.8 mmol) and bis(tributyltin) (13.6 mL, 27 mmol) were added. The reaction was stirred at 90 °C for 16h. The solution was evaporated under reduced pressure. The oily residue was purified by flash column chromatography with petroleum ether/EtOAc (9.7/0.3) to give an oily product. Yield 58%; IR 1677 (CO); ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 9H, J= 6.8 Hz, $(CH_3)_3$), 1.10 (t, 6H, J= 6.0 Hz, $(CH_2)_3$),1.20 (t, 3H, J= 7.0 Hz, CH_3), 1.35 (m, 6H, $(CH_2)_3$), 1.55 (m, 6H, $(CH_2)_3$), 3.60 (q, 2H, J= 7.0 Hz, OCH_2), 5.40 (s, 2H, NCH_2), 7.25 (d, 1H, J= 7.9 Hz, H_4), 7.40 (dd, 1H, J= 7.9 Hz, J= 0.9 Hz, H_5), 7.50 (s, 1H, H_7). M/z= 499.1.

General procedure for the preparation of products 8a-b: Compounds **7** (1.15 g, 2.3 mmol) in dry toluene (10 mL) was placed under argon, $PdCl_2(PPh_3)_2$ (0.16 g, 0.23 mmol) and the desired cycloalkylcarbonyle chloride (4.6 mmol) was added. The reaction was refluxed for 4 h. The solution was evaporated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (8/2).

6-Cyclobutylcarbonyl-3-ethoxymethyl-2(3*H*)-benzothiazolone (**8a**): Yield 61%; mp 76-77 °C; IR 1673 (CO) 1660 (CO); ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 3H, J= 7.0 Hz, CH_3), 1.90 (m, 1H, CH_2), 2.10 (m, 1H, CH_2), 2.30 (m, 2H, CH_2), 2.45 (m, 2H, CH_2), 3.60 (q, 2H, J= 7.0 Hz, OCH_2), 4.00 (m, 1H, CH), 5.45 (s, 2H, NCH_2), 7.35 (d, 1H, J= 8.5 Hz, H_4), 7.90 (dd, 1H, J= 8.5 Hz, J= 1.8 Hz, H_5), 8.05 (d, 1H, J= 1.8 Hz, H_7). M/z= 292.1. Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.95; H, 5.96; N, 4.67.

6-Cyclohexylcarbonyl-3-ethoxymethyl-2(3*H*)-benzothiazolone (**8b**): Yield 76%; mp 115-116 °C; IR 1672 (CO); ^{1}H NMR ($CDCl_3$): δ 1.15 (t, 3H, J= 7.0 Hz, CH_3), 1.40 (m, 5H, CH_2), 1.85 (m, 5H, CH_2), 3.25 (m, 1H, CH), 3.60 (q, 2H, J= 7.0 Hz, CH_2), 5.40 (s, 2H, NCH_2O), 7.35 (d, 1H, J= 8.5 Hz, H_4), 7.95

(dd, 1H, J= 8.5 Hz, J= 1.7 Hz, H_5), 8.10 (d, 1H, J= 1.7 Hz, H_7). M/z= 320.2. Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 64.15; H, 6.78; N, 4.50.

6-Tributyltin-2(3*H*)-benzothiazolone (**9**): In dry THF (40 mL) under argon atmosphere, KH (0.8g, 8.70 mmol) was added dropwise at 0 °C and 6-bromo-2(3*H*)-benzothiazolone (**5**) (1 g, 4.35 mmol) in 10 mL of dry THF. The solution was cooled to -78 °C and a 1.5 M solution of *tert*-BuLi (5.8 mL, 8.70 mmol) in pentane was added. After the addition, the solution was strirred for 15 mn and a solution of tributyltin chloride (3.5 mL, 13.05 mmol) was added dropwise at -7 8°C. The mixture was stirred for 1 h at -78 °C and then the reaction mixture was allowed to warm to rt. A solution of 10% H_3PO_4 (100 mL) was added to the reaction and the mixture was extracted with Et_2O. The extracts were washed with water, dried, and concentrated to give a residue. The resulting crude product was purified by flash column chromatography eluting with petroleum ether/EtOAc (9.5/0.5) to give an oily product. Yield 65%; IR 1681 (CO); ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 9H, J= 6.7 Hz, $(CH_3)_3$), 1.10 (m, 6H, J= 6.0 Hz, $(CH_2)_3$), 1.25 (m, 6H, $(CH_2)_3$), 1.50 (m, 6H, $(CH_2)_3$), 7.15 (d, 1H, J= 7.6 Hz, H_4), 7.35 (dd, 1H, J= 7.6 Hz, J= 0.9, H_5), 7.45 (s, 1H, H_7), 9.55 (brs, 1H, NH). M/z= 231.2.

General procedure for the preparation of products 10a-d: In dry THF (40 mL) under argon atmosphere, KH (0.4 g, 4.54 mmol) was added dropwise at 0 °C and 6-tributyltin-2(3*H*)-benzothiazolone (**7**) (1 g, 2.27 mmol) in 10 mL of dry THF. After the addition of dichlorobis(triphenyl phosphine) palladium (0.08 g, 0.114 mmol), the mixture was stirred for 10 mn and the desired cycloalkylcarbonyl chloride was added (3.41 mmol). The reaction mixture was refluxed for 3 h. The solution was evaporated. The resulting crude product was purified by flash column chromatography eluting with petroleum ether/EtOAc (9.5/0.5) to give the 3,6-dicycloalkylcarbonyl intermediates **10a-d**.

3,6-Dicyclobutylcarbonyl-2(3*H*)-benzothiazolone (**10b**): Yield (85%), mp 83-84 °C, IR 1713(CO), 1671 (CO); ^{1}H NMR ($CDCl_3$): δ 2.05 (m, 4H, CH_2), 2.40 (m, 8H, CH_2), 4.00 (m, 1H, CH), 4.20 (m, 1H, CH), 7.85 (dd, 1H, J= 8.8 Hz, J= 1.9 Hz, H_5), 8.00 (d, 1H, J= 1.5 Hz, H_7), 8.35 (d, 1H, J= 8.8 Hz, H_4). M/z= 316.3.

3,6-Dicyclopentylcarbonyl-2(3*H*)-benzothiazolone (**10c**): Yield (76%), mp 97-98 °C, IR 1702 (CO), 1665 (CO); ^{1}H NMR ($CDCl_3$): δ 1.70 (m, 8H, $(CH_2)_2$), 2.05 (m, 8H, CH_2), 3.65 (m, 1H, CH), 4.00 (m, 1H, CH), 7.90 (dd, 1H, J= 8.8 Hz, J= 1.8 Hz, H_5), 8.05 (d, 1H, J= 1.8 Hz, H_7), 8.20 (d, 1H, J= 8.8 Hz, H_4). M/z= 344.1.

3,6-Dicyclohexylcarbonyl-2(3*H*)-benzothiazolone (**10d**): Yield (89%), mp 93-95 °C, IR 1728(CO), 1703 (CO), 1654 (CO); ^{1}H NMR ($CDCl_3$): δ 1.30 (m, 10H, CH_2), 1.65 (m, 8H, CH_2), 2.00 (m, 2H, CH_2),

3.35 (m, 1H, CH), 3.50 (m, 1H, CH), 7.95 (dd, 1H, J= 8.7 Hz, J= 1.6 Hz, H_5), 8.05 (d, 1H, J= 8.7 Hz, H_4), 8.40 (d, 1H, J= 1.6 Hz, H_7). M/z= 372.2.

General procedure for the preparation of products 2a-d: The products **10a-d** were dissolved in MeOH (15mL), and a solution of 5% aqueous NaOH (10 mL) was added. The mixture was refluxed for 1h. MeOH was epavorated under reduced pressure. The basic solution was diluted with water (30 mL), and washed with ethyl acetate. The aqueous layer was acidified to pH 1 with 12N HCl, and extracted with CH_2Cl_2. The organic layer was dried, and concentrated to give the corresponding products **2a-d**. The compound was recrystallized with the appropriated solvent.

6-Cyclopropylcarbonyl-2(3*H*)-benzothiazolone (**2a**): Yield 75% (EtOH); mp 203-204 °C; IR 1688 (CO), 1668 (CO); ^{1}H NMR (DMSO-d_6): δ 1.00 (m, 4H, $(CH_2)_2$), 2.90 (m, 1H, CH), 7.20 (d, 1H, J= 8.5 Hz, H_4), 8.00 (dd, 1H, J= 8.5 Hz, J= 1.5 Hz, H_5), 8.30 (d, 1H, J= 1.5 Hz, H_7), 12.30 (brs, 1H, NH). M/z= 220.1. Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39. Found: C, 60.49; H, 4.25; N, 6.51.

6-Cyclobutylcarbonyl-2(3*H*)-benzothiazolone (**2b**): Yield 55% (EtOH); mp 151-152 °C; IR 3135 (NH), 1685 (CO), 1663 (CO); ^{1}H NMR (DMSO-d_6): δ 1.70 (m, 1H, CH_2), 2.00 (m, 1H, CH_2), 2.20 (m, 4H, CH_2), 4.10 (m, 1H, CH), 7.20 (d, 1H, J= 8.5 Hz, H_4), 7.80 (dd, 1H, J= 8.5 Hz, J= 1.8 Hz, H_5), 8.15 (d, 1H, J= 1.8 Hz, H_7), 12.30 (brs, 1H, NH). M/z= 234.1. Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.61; H, 4.94; N, 5.85.

6-Cyclopentylcarbonyl-2(3*H*)-benzothiazolone (**2c**): Yield 62% (EtOH); mp 137-138 °C; IR 3225 (NH), 1712 (CO), 1653 (CO); ^{1}H NMR (DMSO-d_6): δ 1.70-2.00 (m, 8H, CH_2), 3.80 (m, 1H, CH), 7.20 (d, 1H, J= 8.2 Hz, H_4), 7.90 (dd, 1H, J= 8.2 Hz, J= 1.8 Hz, H_5), 8.30 (d, 1H, J= 1.8 Hz, H_7), 12.30 (brs, 1H, NH). M/z= 248. Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.42; H, 5.51; N, 5.41.

6-Cyclohexylcarbonyl-2(3*H*)-benzothiazolone (**2d**): Yield 81% (EtOH); mp 195-196 °C; IR 1714 (CO), 1648 (CO); ^{1}H NMR (DMSO-d_6): δ 1.30 (m, 5H, CH_2), 1.70 (m, 5H, CH_2), 3.25 (m, 1H, CH), 7.20 (d, 1H, J= 8.3 Hz, H_4), 7.90 (dd, 1H, J= 8.3 Hz, J= 1.6 Hz, H_5), 8.30 (d, 1H, J= 1.6 Hz, H_7), 12.30 (brs, 1H, NH). M/z= 262. Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.61; H, 5.88; N, 5.51.

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