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Vicinal bromostannanes as novel building blocks for the preparation of di- and trisubstituted imidazoles

Laszlo Revesz*), Frédérique Bonne and Paschalia Makavou

Preclinical Research, Novartis Pharma Ltd., Basel, CH-4002 Switzerland

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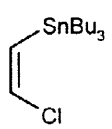
Abstract

Three novel imidazole-based vicinal bromostannanes **5a-c** have been developed for the regioselective preparation of 2,4,5-tri- and 4,5-disubstituted imidazoles. The novel building blocks are particularly attractive for Stille and Suzuki couplings that involve valuable aryl or heteroaryl halides, where conversion to the equivalent stannanes or boranes/boronic acids would represent an inviable option.

Keywords: imidazoles; Suzuki reactions; antiinflammatory compounds; tin and compounds

Molecules containing the trimethylstannyl group as a"metal" along with bromine or chlorine as a leaving group are surprisingly stable and offer a variety of interesting synthetic applications. Olefin **1** e.g. was used as a dienophile in Diels-Alder reactions [1], thiophene **2** and pyrimidine **3** underwent Stille and Suzuki couplings [2, 3], while the norbornene **4** cyclotrimerized upon catalysis [4].



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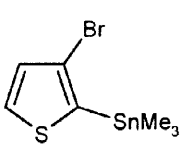

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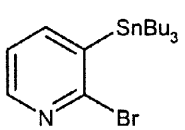

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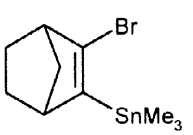

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Our interest in molecules containing the bromostannane functionality was raised by the identification of aryl- and heteroaryl-substituted imidazoles as mitogen activated protein kinase inhibitors and potentially anti-inflammatory drugs [5, 6]. The lack of convenient methods to prepare such compounds rapidly and with high diversity prompted us to investigate bromostannane-based imidazoles as possible starting

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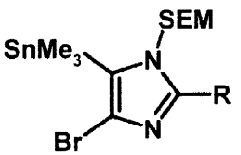
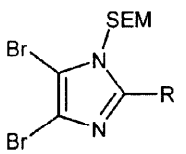
materials for the polyfunctionalization of imidazoles. Here we report our work on the novel imidazole-based bromostannanes **5a-c** and their application in the regioselective synthesis of alkyl-, aryl- and heteroaryl-substituted imidazoles.

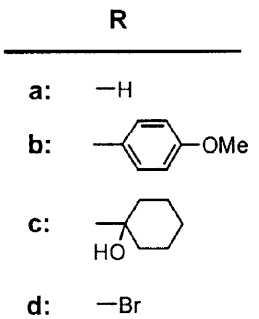
Bromostannes **5a-c** were prepared from the corresponding dibromoimidazoles **6a-c**, which derived from the known SEM-protected 2,4,5-tribromoimidazole **6d** [7]. **6a** and **6c** were prepared in 70% and 85% yield via bromine - lithium exchange from **6d** [8, 9] at -78^0 C and subsequent quenching with isopropyl alcohol or cyclohexanone at the same temperature. Selective 2-arylation provided **6b** from **6d** in 34% yield under conditions of the Suzuki reaction [10] employing 4-methoxyphenylboronic acid as coupling reagent and $PdCl_2(PPh_3)_2$ as catalyst, refluxing 4 h in xylene/methanol (5:1)/2M Na_2CO_3 (2eq.).



5a-c

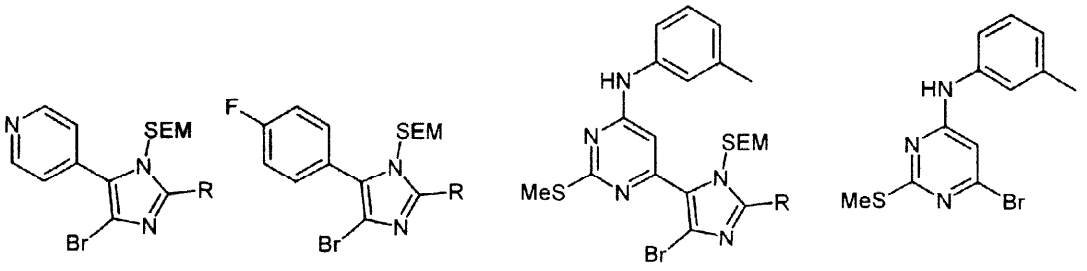


6a-d



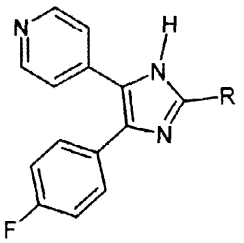
Two different procedures were used for the regioselective monostannylation of dibromides **6a-c**. **6a** gave the desired product **5a** (31%) upon reacting with hexamethyldistannane (3 eq.) in xylene (165^0 C, 5.5 h) and $PdCl_2(PPh_3)_2$ as catalyst. Some destannylated side product (~10%) and starting material were separated by chromatography [11]. The above method proved unsuccessful, when applied to the synthesis of 1-hydroxycyclohexyl substituted bromostannane **5c**. **5c** and **5b** could however be prepared regioselectively in 50% and 34% by bromine-lithium exchange of dibromide **6c** and **6b** at -78^0 C followed by quenching with Me_3SnCl [12].

To exemplify the efficient reactivity of the novel bromostannanes **5a-c** with aryl bromides or heteroaryl bromides, **5a** and **5b** were coupled with 4-bromopyridine under Stille conditions (xylene, $PdCl_2(PPh_3)_2$, reflux 5 h) to render **7a** and **7b** in 74% and 55% yield [13]. When 4-fluorobromobenzene was used, the yields of **8a** and **8b** were lower (36% and 24%) [14]. Bromopyrimidine **10** [15, 16] and **5c** were similarly coupled to generate the cyclohexanol analogue **9c** in 34% [17].



7a,b **8a,b** **9c** **10**

Examples of 4,5-disubstituted imidazoles and 2,4,5-trisubstituted imidazoles of biological interest prepared by this new procedure are represented by **11a** [6] and **11b** [18]. They were obtained in 65% and 68% by Suzuki coupling of **7a** and **7b** with 4-fluorophenylboronic acid followed by cleaving the SEM-group quantitatively by $EtOH/HCl_{conc.}$ (1:1) at room temperature.



11a,b

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[11] Typical procedure, method A, preparation of **5a**: **6a** (5.89 g; 16.7 mmol), hexamethyldistannane (10.35 ml; 50 mmol) and $PdCl_2(PPh_3)_2$ (1.16 g; 1.67 mmol) were dissolved in xylene (116 ml) and refluxed for 5.5 h, filtered, evaporated and purified over SiO_2 (acetone/hexanes 2/98) to yield 3.6 g of a colorless oil consisting of **5a** in approx. 80% purity accompanied by each 10% of **6a** and 4-bromo-1-SEM protected destannylated imidazole **12**. Further purification was performed by preparative HPLC on LiChrospher RP-18 (Gilson HPLC system; column tube: 125 mm x 25 mm ID) with MeCN/water as elution system, 40:60 to 100:0 as gradient and a flow rate of 10 ml/min. Retention times and amounts isolated after repetitive runs and automatic fraction-collection (Gilson 215 liquid handler) were as follows: **12** (0.3 g; 17 min.), **6a** (0.25 g; 19 min.), **5a** (2.3 g; 24 min., 31 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) of **5a**: 0.01 (s, 9H); 0.46 (s, 9H); 0.91 (dd, 2H, J=7Hz); 3.40 (dd, 2H, J=7Hz); 5.20 (s, 2H); 7.58 (s, 1H). 2D NMR and 1D-ROE ($NCH_2O/SnMe_3$) are in agreement with the regiochemistry of **5a**. MS (m/z) of **5a**: 440 (2, M+); 425 (10); 394 (20); 368 (29); 366 (35); 364 (21); 73 (100).

[12] Typical procedure, method B, preparation of **5c**: **6c** (14 g; 31 mmol) was dissolved in THF (490 ml) and cooled to -78^0 C. nBuLi (79 ml of a 1.6 M solution in hexane; 65.3 mmol) was added dropwise. After completed addition the reaction mixture was stirred at -78^0 C for a further 10 min., then Me_3SnCl (41 ml of a 1 M solution in THF; 40.4 mmol) was added dropwise. The cooling bath was removed and stirring continued for 1.5 h. The reaction mixture was poured on a saturated solution of NaCl and extracted three times with EtOAc. The organic phases were dried over Na_2SO_4, evaporated to dryness and purified over SiO_2 (acetone/hexanes 10/90) to yield 12.3 g of a colorless oil consisting of the desired bromostannane **5c** in ca 60% purity, accompanied by starting material **6c** and destannylated 4-bromo-1-SEM protected imidazole **13**. Further purification was performed by preparative HPLC on LiChrospher RP-18 (Gilson HPLC system; column tube: 125 mm x 25 mm ID) with the elution system MeCN/water, a gradient of 40:60 to 100:0 and a flow rate of 10 ml/min. Retention times and amounts isolated after repetitive runs and automatic fraction-collection (Gilson 215 liquid handler) were as follows: **13** (3.1 g; 21.5 min.), **6c** (0.5 g; 25.1 min.), **5c** (8.1 g, 24 min., 50 %) as colorless crystals, m.p.: 96-97^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) of **5c:** 0.02 (s, 9H); 0.42 (s, 9H); 0.95 (dd, 2H, J=7Hz); 1.27-1.40 (m, 2H); 1.65-1.73 (m, 4H); 1.87-1.95 (bd, 2H); 2.03-2.14 (m, 2H); 2.19 (s, 1H. OH); 3.51 (dd, 2H, J=7Hz); 5.51 (s, 2H). MS (m/z) of **5c**: 523 (15, M-CH3); 521 (10); 495 25; 493 (35); 491 (20); 465 (35); 463 (25); 405 (12); 377 (30); 375 (45); 373 (35); 165 (40); 163 (30); 73 (100).

5b was prepared in analogy to **5c**, except that only 1.2 equivalents of nBuLi were used instead of 2.1 equivalents. Separation of **5c** from its destannylated side product was performed as above by the same preparative HPLC-method and yielded pure **5b** (yield: 34 %) as pale pink oil with a retention time of 28 min. ^{1}H NMR (400 MHz, $CDCl_3$) of **5b**: 0.00 (s, 9H); 0.48 (s, 9H); 0.84 (dd, 2H, J=7Hz); 3.29 (dd, 2H, J=7Hz); 3.87 (s, 3H); 5.19 (s, 2H); 6.98 (d, 2H, J=9Hz); 7.53 (d, 2H, J=9Hz). 1D-ROE ($NCH_2O/SnMe_3$ and NCH_2O/H_{Ar}) is in agreement with the regiochemistry of **5b.** MS(m/z) of **5b**: 547 (8, M+1); 545 (15, M-1); 543 (10); 532 (20); 531 (25); 529 (20); 503 (40); 501 (45); 498 (35); 475 (25); 473 (38); 471 (25); 429 (100); 376 (40); 374 (60); 372 (40).

[13] ^{1}H NMR (400 MHz, $CDCl_3$) of **7a**: 0.02 (s, 9H); 0.97 (dd, 2H, J=8Hz); 3.58 (dd, 2H, J=8Hz); 5.23 (s, 3H); 7.58 (d, 2H, J=7Hz); 7.67 (s, 1H); 8.73 (d, 2H, J=7Hz). 1D-ROE (NCH_2O/H_{Pyr}) is in agreement with the regiochemistry of **7a.** MS (m/z) of **7a:** 355 (5, M+1); 353 (5, M+); 297 (18); 295 (18); 231 (20); 130 (20); 129 (18); 103 (40); 73 (100). ^{1}H NMR (400 MHz, $CDCl_3$) of **7b**: 0.04 (s, 9H); 0.99 (dd, 2H, J=9Hz); 3.48 (dd, 2H, J=9Hz); 3.90 (s, 3H); 5.05 (s, 2H); 7.02 (d, 2H, J=8Hz); 7.64 (d, 2H, J=6Hz); 7.78 (d, 2H, J=8Hz); 8.75 (d, 2H, J=6Hz). 1D-ROE (NCH_2O/H_{Ar} and NCH_2O/H_{Pyr}) are in agreement with the regiochemistry of **7b.** MS (m/z) of **7b:** 461 (41, M+1); 459 (39); 431 (35); 429 (25); 403 (75); 401 (73); 330 (35); 329 (33); 322 (65); 73 (100).

[14] ^{1}H NMR (200 MHz, $CDCl_3$) of **8a**: 0.03 (s, 9H); 0.90 (dd, 2H, J=8Hz); 3.52 (dd, 2H, J=8Hz); 5.16 (s, 2H); 7.18 (dd, 2H, J=9Hz); 7.42-7.58 (m, 2H); 7.63 (s, 1H). ^{1}H NMR (400 MHz, $CDCl_3$) of **8b**: 0.03 (s, 9H); 0.93 (dd, 2H, J=9Hz); 3.39 (dd, 2H, J=9Hz); 3.90 (s, 3H); 5.03 (s, 2H); 7. 01 (d, 2H, J=8Hz); 7.20 (dd, 2H, J=7Hz); 7.57-7.63 (m, 2H); 7.78 (d, 2H, J=8Hz). 1D-ROE (NCH_2O/H_{Ar}) is in agreement with the regiochemistry of **8b.** MS (m/z) of **8b:** 478 (33, M+1); 476 (30); 420 (30); 418 (29); 339 (70); 73 (100).

[15] Prepared from 4,6-dibromo-2-methylthiopyrimidine [16] and m-toluidine/$KN(TMS)_2$ in THF at -78^{0}C in 68%.

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[17] ^{1}H NMR (400 MHz, $CDCl_3$) of **9c**: -0.07 (s, 9H); 0.81 (dd, 2H, J=9Hz), 1.21-1.43 (m, 2H); 1.64-1.82 (m, 4H); 1.91-2.00 (bd, 2H); 2.05-2.18 (bt, 2H); 2.40 (s, 3H); 2.59 (s, 3H); 2.86 (s, 1H, OH); 3.46 (dd, 2H, J=9Hz); 6.02 (s, 2H); 6.83 (s, 1H); 6.87 (s, 1H, NH); 7.03 (d, 1H, J=8Hz); 7.17 (d, 1H, J=8Hz); 7.25 (s, 1H); 7.30 (dd, 1H, J=8Hz). MS (m/z) of **9c:** 605 (4, M+); 603 (3); 505 (20); 504 (80); 502 (75); 474 (70); 472 (65); 458 (60); 456 (65); 91 (50); 84 (75); 73 (100).

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