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Synthesis and microwave-promoted Suzuki-Miyaura cross-coupling reactions of 5-bromo-1,3,3-trimethyl-1,3-dihydro-6′*H*-spiro[indole-2,2′-piperidin]-6′-one

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The aza-Michael addition reaction of 5-bromo-1,3,3-trimethyl-2-methylidene-2,3-dihydro-1*H*-indole with acrylamide and the following cyclization afforded 5-bromo-1,3,3-trimethyl-1,3-dihydro-6'*H*-spiro[indole-2,2'-piperidin]-6'-one. The microwave-promoted Suzuki-Miyaura coupling of the latter compound with arylboronic acids gave the 5-arylated products with good to excellent yields. The reductive ring-opening reaction of 5-(naphthalen-2-yl)spiro[indole-2,2'-piperidin]-6'-one and following chemical transformations yielded the corresponding indoline derivatives possessing 2-[3-(ethoxycarbonyl) propyl]- and 2-(4-aminobutyl)-side chains.

Key words: indole, spiro[indole[2,2']piperidine], Suzuki-Miyaura cross-coupling, microwave, cesium carbonate, fluorescence

INTRODUCTION

Suzuki-Miyaura cross-coupling of arylhalides with organoboronic acids is among the most widely used palladium catalyzed reactions in organic chemistry [1–4]. The particular advantages of this reaction are the wide tolerance of functional groups, low toxicity of arylboronic acids, the air and moisture stability and high yields of the target products. In recent years this method has been used also for the (het) arylation of various halogenated heterocycles, including derivatives of pyrazole [5, 6], pyrimidine [7], pyrido[1,2-*a*] pyrimidine [8]. The coupling of 5-bromoindoline derivatives with heteroaromatic boronic acids was applied for the preparation of sensitizers for solar cells [9] and photochromic materials [10].

Typically Suzuki-Miyaura reactions are carried out by conventional heating of arylhalides with organoboronic acids in an organic solvent in the presence of palladium catalysts such as $Pd(PPh_3)_4$ and inorganic bases such as K_2CO_3 [1]. However, in recent years, microwave-promoted Pd-catalyzed cross-couplings, including the Suzuki-Miyaura reaction, became an area of increasing interest, since this technique is reported to significantly shorten the reaction times and provides high yields of the target products [7, 11–13].

In the present work, we have investigated the synthesis of a halogenated spiro[indole[2,2']piperidine] derivative and its Pd-catalyzed coupling reactions with various (het)aromatic boronic acids in order to obtain new functionalized indoline

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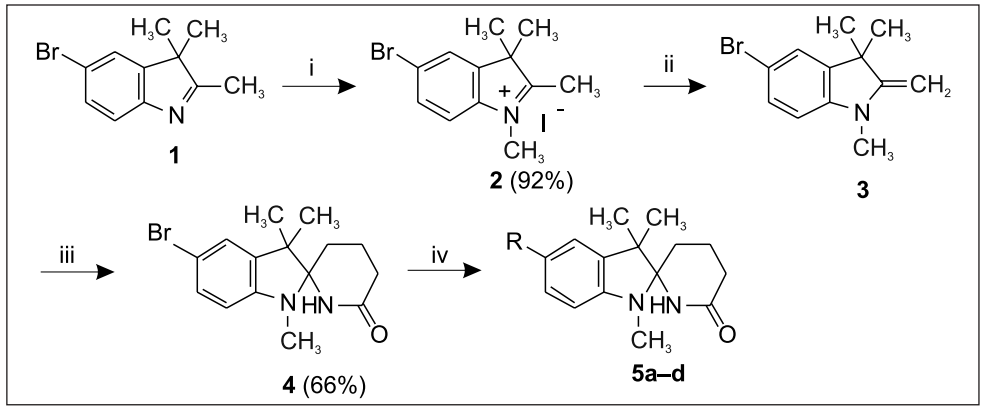
scaffolds. It is known that spiro[indole[2,2']piperidine] system can be easily formed by the reaction of the corresponding 2-methylidene indoline bases with acrylamide [14]. Recently it was shown that structurally similar benzo-annulated spiro[indole[2,2']piperidine] derivatives are useful intermediates for the preparation of fluorescent 2-[3-(ethoxycarbonyl) propyl]- and 2-(4-aminobutyl)benzo[e]indolines [15] as potential molecular probes for biomolecular labelling [16].

RESULTS AND DISCUSSION

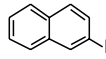
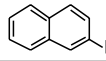
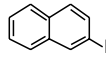
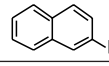
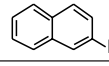
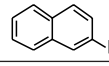
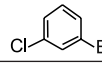
The starting 5-bromo-2,3,3-trimethyl-3*H*-indole **1** was obtained from 4-bromophenylhydrazine and 2-methyl-2-butanone in accordance with the literature procedure [17]. For the preparation of iodide **2**, indole **1** was alkylated with methyl iodide. Treatment of **2** with sodium hydroxide afforded enamine **3**, which was used in the following reaction without further purification. Heating of **3** with acrylamide in 1,2-ethanediol at 110 °C resulted in the formation of 5-bromo-1,3,3-trimethylspiro[indole-2,2'-piperidin]-6'-one (**4**) (Scheme 1). The ^{1}H NMR spectrum of asymmetric molecule **4** revealed two singlets of diastereotopic 3,3-methyl groups 1.19 and 1.26 ppm, while the piperidine ring six methylene protons gave multiplets in the area of 1.85–2.47 ppm. The corresponding ^{13}C NMR spectrum contained a signal of the sp^3-hybridized spiro C-2 atom at 86.8 ppm. The IR spectrum showed the absorption bands at 1 653 (C=O) and 3 176 (N-H) cm^{-1}, characterictic for six-membered lactams.

With the key intermediate in hand, the Suzuki-Miyaura cross-coupling of several (het)aromatic boronic acids was then investigated. The $Pd(PPh_3)_4$ catalyzed reaction of **4** with naphthalene-2-boronic acid was performed under Ar atmosphere in a microwave reactor at 100 °C for 25 min using a variety of bases (Na_2CO_3, K_2CO_3, K_3PO_4) and solvents (dioxane, acetone, ethanol). It furnished product **5a** with low to very good yields (entries 1–5, Table 1). It is known that the cross-



Scheme 1. Reagents and conditions: (i) CH_3I, 40 °C, 19 h; (ii) NaOH, Et_2O, rt, 0.5 h; (iii) CH_2=CHCONH$_2$, 1,2-ethanediol, 110 °C, 5.5 h; (iv) for Suzuki coupling conditions see Table 1

Table 1. **Spiro[indole-2,2'-piperidin]-6'-one 4 Suzuki cross-coupling with organoboronic acids**[a]

Entry	Boronic acid	Solvent	Base	Time	Yield (product)
1.		Dioxane	Na_2CO_3	25 min	20% (**5a**)
2.		Acetone	Na_2CO_3	25 min	53% (**5a**)
3.		EtOH	Na_2CO_3	25 min	88% (**5a**)
4.		EtOH	K_2CO_3	25 min	81% (**5a**)
5.		EtOH	K_3PO_4	25 min	80% (**5a**)
6.		EtOH	Cs_2CO_3	25 min	97% (**5a**)
7.		EtOH	Cs_2CO_3	30 min	81% (**5b**)
8.		EtOH	Cs_2CO_3	40 min	81% (**5c**)
9.		EtOH	Cs_2CO_3	30 min	82% (**5d**)

[a] In all cases 0.07 equiv of $Pd(PPh_3)_4$, 1.3 equiv of boronic acid, 2 equiv of 1M aqueous base solution and microwave heating (100 °C, 50 W) were used.

coupling reaction rate is dependent on the nature of the cation of the applied carbonate [18, 19]. When Cs_2CO_3 was used as a base and the reaction was carried out in ethanol, compound **5a** was obtained in near-quantitative isolated yield (entry 6). The optimized Suzuki-Miyaura reaction conditions [$Pd(PPh_3)_4$, Cs_2CO_3, ethanol, microwave] were then applied to carry out cross-couplings of compound **4** with phenylboronic, 3-chlorophenylboronic and thiophene-3-boronic acids. In all cases the reaction afforded (het)arylated products **5b–d** in very good yields (entries 7–9).

5-Aryl-spiro[indole-2,2'-piperidin]-6'-ones **5a–d** are structurally similar to 4-aminobiphenyls, which fluorescence behavior is well known [20–22]. The optical properties of compounds **5a, b** were investigated by UV–Vis and fluorescence spectroscopy (Table 2). The fluorescence spectra of **5a, b** measured in THF displayed emission maxima (λ_{em}) at 422 and 375 nm, and Stokes' shifts of 105 and 77 nm, respectively. On changing the solvent from THF to toluene, the fluorescence maximum of compound **5a** underwent a 26 nm blue shift (λ_{em} = 396 nm).

It is known that protic acids promote the reductive ring-opening reaction of spiro[indole[2,2']piperidin]-6'-ones [23]. When compound **5a** was subjected to hydrogenolysis in acetic acid by treatment with hydrogen in the presence of catalytic palladium, the reaction afforded 2-[(3-carbamoyl) propyl indoline **6** (Scheme 2). Reduction of amide **6** with lithium aluminium hydride in THF gave amine **7**. Heating in ethanol under reflux in the presence of hydrochloric acid afforded ester **8**.

The ^{1}H NMR spectra of indoline derivatives **6–8** revealed a characteristic multiplet for the H-2 proton in the area of 2.88–2.97 ppm, which is due to the coupling with protons of the adjacent methylene group. The corresponding ^{13}C NMR spectra of **6–8** contained signals of the sp^3-hybridized C-2 atom nearby 77.0 ppm. The fluorescence spectra (λ_{ex} = 323 nm) of compounds **6, 7** and **8**, measured in toluene, displayed emission maxima (λ_{em}) at 410, 412 and 410 nm, respectively.

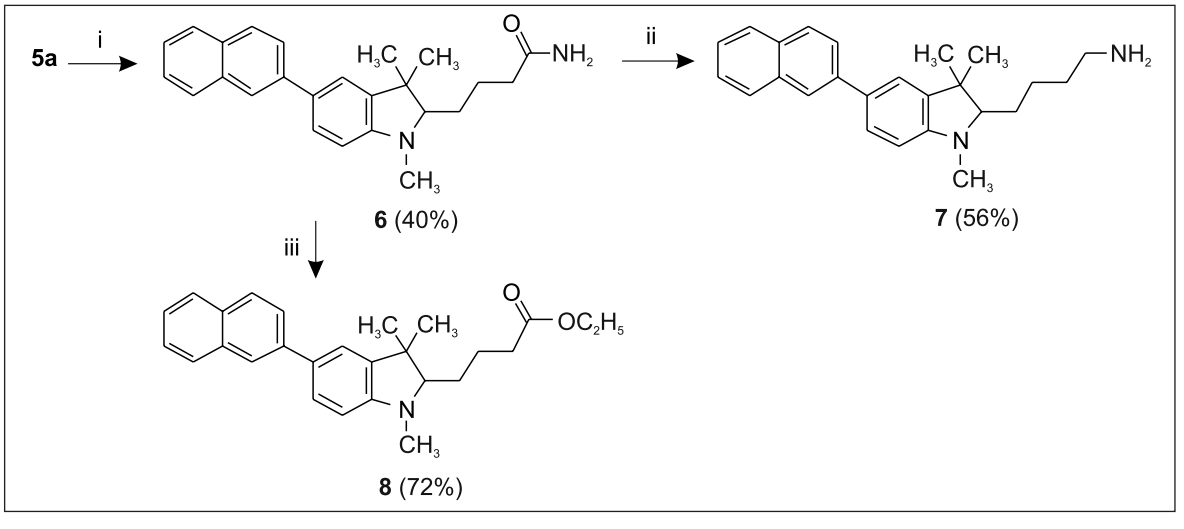
Table 2. **Absorption (λ_{abs} and ε) and fluorescence (λ_{em}) parameters for derivatives 5a, b in THF**

Compound	λ_{abs}, nm	E × 10^4, M^{-1} cm^{-1}	λ_{em}, nm*
5a	230	5.00	422
	282	2.09	
	317	2.48	
5b	211	2.55	375
	298	2.18	

* λ_{ex} = 310 nm.

EXPERIMENTAL

Merck precoated TLC plates (Silica gel 60 F_{254}) were used. Melting points were determined on a Melt-Temp (Capillary Melting point Apparatus) and are uncorrected. ^{1}H NMR spectra were recorded with Varian Unity Inova and Bruker Avance III spectrometers at 300 and 400 MHz. ^{13}C NMR spectra were registered at 75 and 100 MHz, respectively. The chemical shifts, expressed in ppm, were relative to tetramethylsilane (TMS). Infrared spectra were recorded on a Brüker TENSOR 27 spectrometer using potassium bromide pellets. Mass spectra were recorded on a Waters Micromass ZQ 2000 (APCI$^+$, 20 V) instrument or on an Agilent 1100 series mass spectrometer using a direct inlet system (electron spray, 4 000 V). Elemental analyses (C, H, and N) were recorded with a CE-440 elemental analyser, Model 440 CHN/O/S at the Microanalytical Laboratory, Department of Organic Chemistry, Kaunas University of Technology, and were in good agreement (±0.4%) with the calculated values. UV-Vis spectra were recorded on a Perkin Elmer Lambda 35 UV/Vis spectrometer. Fluorescence spectra were recorded on a Hitachi MPF-4 spectrometer. Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. The reaction was performed in glass vessels (capacity 10 mL) sealed



Scheme 2. Reagents and conditions: (i) AcOH, Pd/C, H_2, 20 bar, rt, 4 h; (ii) $LiAlH_4$, THF, reflux, 3 h; (iii) 6M HCl_{aq}, EtOH, reflux, 4 h

with a septum. The pressure was controlled by a load cell connected to the vessel. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

5-Bromo-1,2,3,3-tetramethyl-3*H*-indolium iodide (2)

To 5-bromo-2,3,3-trimethyl-3*H*-indole (**1**) (2.37 g, 10 mmol) methyl iodide (7.1 g, 50 mmol) was added and the mixture was heated at 40 °C for 19 hours. Upon cooling to room temperature the crystalline was filtered and washed with cold Et_2O to give the pure product **2** (yield 3.5 g, 92%) as brownish solid, mp 228.2–230.0 °C. ^{1}H NMR (400 MHz, $DMSO_{d6}$): δ 1.54 (s, 6H, 3-$(CH_3)_2$), 2.77 (s, 3H, 2-CH_3), 3.96 (s, 3H, 1-CH_3), 7.84–7.90 (m, 2H, 6-H and 7-H), 8.18 (s, 1H, 4-H); ^{13}C NMR (100 MHz, $DMSO_{d6}$): δ 14.4 (2-CH_3), 21.5 (2 × C, 3-$(CH_3)_2$), 35.0 (1-CH_3), 54.2 (C-3), 117.1 (CH_{Ar}), 122.7 (C_{quat}), 126.7 (CH_{Ar}), 131.8 (CH_{Ar}), 141.5 (C_{quat}), 143.9 (C_{quat}), 196.6 (C-2); MS (API-ES, pos mode), *m/z* (%): 252/254 ($M\text{-}I^-+H^+$, 100). Anal. calcd. for $C_{12}H_{15}BrIN$: C, 37.92; H, 3.98; N, 3.69. Found: C, 38.17; H, 3.61; N, 3.46.

5-Bromo-1,3,3-trimethyl-1,3-dihydro-6'*H*-spiro[indole-2,2'-piperidin]-6'-one (4)

To a suspension of 5-bromo-1,2,3,3-tetramethyl-3*H*-indolium iodide **2** (3.8 g, 10 mmol) in Et_2O (50 mL) an aqueous 1 M NaOH solution (30 mL) was added and the reaction mixture was stirred at rt for 0.5 h. The organic layer was separated and the aqueous layer was additionally extracted with Et_2O (2 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. To the residue ethylene glycol (15 mL) and acrylamide (1.07 g, 15 mmol) were added and the mixture was stirred at 110 °C for 5.5 h. The reaction mixture was cooled to rt and diluted with water (50 mL). The crystalline product was filtrated and recrystallized from EtOAc to give the desired compound **4** (yield 1.93 g, 66%) as pink crystals, mp 183.6–185.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 3H, 3-CH_3), 1.26 (s, 3H, 3-CH_3), 1.85–2.11 (m, 4H, 4'-CH_2 and 3'-CH_2), 2.24–2.47 (m, 2H, 5'-CH_2), 2.69 (s, 3H, 1-CH_3), 5.72 (brs, 1H, NH), 6.30 (d, *J* = 8.3 Hz, 1H, 7-H), 7.07 (d, *J* = 2.0 Hz, 1H, 4-H), 7.18 (dd, *J* = 8.3 Hz, *J* = 2.0 Hz, 1H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.4 (C-4'), 21.7 (3-CH_3), 25.0 and 25.3 (3-CH_3 and C-3'), 28.8 (1-CH_3), 31.3 (C-5'), 48.7 (C-3), 86.8 (C-2), 108.9 (C-7), 110.8 (C-5), 125.3 (C-4), 130.8 (C-6), 138.1 (C-3a), 147.0 (C-7a), 173.1 (C=O); IR (KBr, ν_{max}, cm^{-1}): 3 176 (N-H), 1 653 (C=O); MS (API-ES, pos mode), *m/z* (%): 323/325 ($M+H^+$, 100). Anal. calcd. for $C_{15}H_{19}BrN_2O$: C, 55.74; H, 5.92; N, 8.67. Found: C, 55.37; H, 6.21; N, 8.46.

***General procedure for the Suzuki couplings giving spiro[indole-2,2'-piperidin]-6'-ones* (5a–d)**. To a solution of spiro[indole-2,2'-piperidin]-6'-one **4** (323 mg, 1 mmol) in EtOH (5 mL) in a sealed vessel under Ar atmosphere at rt an appropriate boronic acid (1.3 mmol), 1 M aqueous Cs_2CO_3 solution (2 mL) and $Pd(PPh_3)_4$ (81 mg, 7 mol%) were added and the reaction mixture was irradiated at 100 °C for the given time. After cooling to rt the reaction mixture was filtered over Celite®, the filter cake was washed with EtOAc and DCM. The filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with brine (2 × 15 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using an appropriate eluent and recrystallized from Hex / DCM.

1,3,3-Trimethyl-5-(naphthalene-2-yl)-1,3-dihydro-6'*H*-spiro[indole-2,2'-piperidin]-6'-one (5a)

The coupling was performed with naphthalene-2-boronic acid (224 mg, 1.3 mmol), reaction time 25 min. Purified by column chromatography on silica gel (DCM/MeOH, 100 : 2 v/v). Yield 358 mg (97%); white crystals, mp 157.4–158.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H, 3-CH_3), 1.39 (s, 3H, 3-CH_3), 1.91–2.19 (m, 4H, 4'-CH_2 and 3'-CH_2), 2.29–2.50 (m, 2H, 5'-CH_2), 2.80 (s, 3H, 1-CH_3), 5.81 (brs, 1H, NH), 6.56 (d, *J* = 8.3 Hz, 1H, 7-H), 7.38 (d, *J* = 1.9 Hz, 1H, 4-H), 7.47–7.52 (m, 3H, 3 × CH_{naph}), 7.71 (dd, *J* = 8.3 Hz, *J* = 1.9 Hz, 1H, 6-H), 7.83–7.90 (m, 3H, 3 × CH_{naph}), 7.95–7.97 (m, 1H, CH_{naph}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5 (C-4'), 21.8 (3-CH_3), 25.3 and 25.4 (3-CH_3 and C-3'), 29.0 (1-CH_3), 31.4 (C-5'), 48.7 (C-3), 86.9 (C-2), 107.8 (C-7), 121.4 (CH_{Ar}), 124.7 (CH_{Ar}), 125.5 (CH_{Ar}), 125.6 (CH_{Ar}), 126.3 (CH_{Ar}), 127.5 (CH_{Ar}), 127.7 (CH_{Ar}), 128.1 (CH_{Ar}), 128.4 (CH_{Ar}), 132.3 (C_{quat}), 132.5 (C_{quat}), 133.9 (C_{quat}), 136.6 (C_{quat}), 139.0 (C-3a), 147.6 (C-7a), 173.2 (C=O); IR (KBr, ν_{max}, cm^{-1}): 3 234 (N-H), 1 654 (C=O); MS (API-ES, pos mode), *m/z* (%): 371 ($M+H^+$, 100). Anal. calcd. for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56. Found. C, 81.32; H, 7.01; N, 7.49.

1,3,3-Trimethyl-5-phenyl-1,3-dihydro-6'*H*-spiro[indole-2,2'-piperidin]-6'-one (5b)

The coupling was performed with phenylboronic acid (159 mg, 1.3 mmol), reaction time 30 min. Purified by column chromatography on silica gel (DCM/MeOH, 100 : 1 v/v). Yield 259 mg (81%); brownish crystals, mp 144.7–146.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 3H, 3-CH_3), 1.36 (s, 3H, 3-CH_3), 1.93–2.18 (m, 4H, 4'-CH_2 and 3'-CH_2), 2.28–2.49 (m, 2H, 5'-CH_2), 2.78 (s, 3H, 1-CH_3), 5.77 (brs, 1H, NH), 6.52 (d, *J* = 8.1 Hz, 1H, 7-H), 7.24–7.30 (m, 2H, 2 × CH_{Ar}), 7.34–7.43 (m, 3H, 3 × CH_{Ar}), 7.51–7.54 (m, 2H, 2 × CH_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5 (C-4'), 21.8 (3-CH_3), 25.3 and 25.4 (3-CH_3 and C-3'), 29.0 (1-CH_3), 31.4 (C-5'), 48.7 (C-3), 86.9 (C-2), 107.7 (C-7), 121.2 (CH_{Ar}), 126.4 (CH_{Ar}), 126.7 (2 × CH_{Ph}), 127.2 (CH_{Ar}), 128.8 (2 × CH_{Ph}), 132.7 (C_{quat}), 136.4 (CH_{quat}), 141.7 (C-3a), 147.5 (C-7a), 173.2 (C=O); IR (KBr, ν_{max}, cm^{-1}): 3 191 (N-H), 1 657 (C=O); MS (API-ES, pos mode), *m/z* (%): 321 ($M+H^+$, 100). Anal. calcd. for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found. C, 78.82; H, 7.61; N, 8.52.

5-(3-Chlorophenyl)-1,3,3-trimethyl-1,3-dihydro-6'*H*-spiro[indole-2,2'-piperidin]-6'-one (5c)

The coupling was performed with 3-chlorophenylboronic acid (203 mg, 1.3 mmol), reaction time 40 min. Purified by column chromatography on silica gel (Hex / acetone, 3 : 2 v/v) and recrystallized from Et_2O/DCM. Yield 276 mg (81%); grey crystals, mp 168.3–169.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 3H, 3-CH_3), 1.35 (s, 3H, 3-CH_3), 1.89–2.15 (m, 4H, 4'-CH_2 and 3'-CH_2), 2.29–2.47 (m, 2H, 5'-CH_2), 2.78 (s, 3H, 1-CH_3), 5.77 (brs, 1H, NH), 6.50 (d, J = 8.1 Hz, 1H, 7-H), 7.21–7.50 (m, 6H, 6 × CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5 (C-4'), 21.8 (3-CH_3), 25.2 and 25.4 (3-CH_3 and C-3'), 28.9 (1-CH_3), 31.4 (C-5'), 48.6 (C-3), 86.9 (C-2), 107.6 (C-7), 121.0 (C-4), 124.7 (CH_{Ph}), 126,3 and 126.6 (CH_{Ph} and C-6), 127.2 (CH_{Ph}), 130.0 (CH_{Ph}), 131.0.5 (C_{quat}), 134.6 (C_{quat}), 136.6 (C-3a), 143.5 (C_{quat}), 148.0 (C-7a), 173.1 (C=O); IR (KBr, ν_{max}, cm^{-1}): 3 180 (N-H), 1 654 (C=O); MS (API-ES, pos mode), *m/z* (%): 342.5 ($M+H^+$, 100). Anal. calcd. for $C_{21}H_{23}ClN_2O$: C, 71.07; H, 6.53; N, 7.89. Found: C, 71.01; H, 6.86; N, 7.97.

1,3,3-Trimethyl-5-(thiophen-3-yl)-1,3-dihydro-6'*H*-spiro[indole-2,2'-piperidin]-6'-one (5d)

The coupling was performed with thiophene-3-boronic acid (166 mg, 1.3 mmol), reaction time 40 min. Purified by column chromatography on silica gel (Hex / acetone, 3 : 2 v/v). Yield 268 mg (82%); pink crystals, mp 160.2–161.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 3H, 3-CH_3), 1.35 (s, 3H, 3-CH_3), 1.94–2.16 (m, 4H, 4'-CH_2 and 3'-CH_2), 2.29–2.47 (m, 2H, 5'-CH_2), 2.77 (s, 3H, 1-CH_3), 5.75 (brs, 1H, NH), 6.47 (d, J = 8.0 Hz, 1H, 7-H), 7.23–7.37 (m, 5H, 5 × CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4 (C-4'), 21.6 (3-CH_3), 25.1 and 25.3 (3-CH_3 and C-3'), 28.8 (1-CH_3), 31.3 (C-5'), 48.5 (C-3), 86.7 (C-2), 107.5 (C-7), 118.1 (CH_{thioph}), 120.5 (C-4), 125.9 (CH_{Ar}), 126.3 (CH_{Ar}), 126.5 (CH_{Ar}), 127.5 (C_{quat}), 136.3 (C-3a), 142.8 (C_{quat}), 147.2 (C-7a), 173.1 (C=O); IR (KBr, ν_{max}, cm^{-1}): 3 437 (N-H), 1 653 (C=O); MS (API-ES, pos mode), *m/z* (%): 312 ($M+H^+$, 100). Anal. calcd. for $C_{19}H_{22}N_2OS$: C, 69.90; H, 6.79; N, 8.58. Found: C, 69.71; H, 6.68; N, 8.49.

4-(1,3,3-Trimethyl-5-(naphthalen-2-yl)-2,3-dihydro-1*H*-indol-2-yl)butanamide (6)

To a solution of compound **5a** (370 mg, 1 mmol) in acetic acid (2 mL) under Ar atmosphere a powder of 10% palladium on activated carbon (74 mg, 20 wt% of starting compound) was added and the reaction mixture was stirred under a 20 bar hydrogen atmosphere for 4 h at rt. The mixture was filtered over Celite®, the filter cake was washed with ethyl acetate and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with a saturated aqueous $NaHCO_3$ solution (3 × 15 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The target product was purified by column chromatography on silica gel (DCM / MeOH, 50 : 1 v/v). Yield 149 mg, 40%; yellow residue; R_f = 0.25 (DCM / MeOH, 20 : 1 v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 3H, 3-CH_3), 1.46 (s, 3H, 3-CH_3), 1.73–1.95 (m, 4H, CHCH_2CH_2), 2.30–2.34 (m, 2H, COCH_2), 2.80 (s, 3H, 1-CH_3), 2.93–2.97 (m, 1H, 2-H), 5.52 (brs, 1H, N(*H*)H), 5.67 (brs, 1H, N(H)*H*), 6.61 (d, J = 8.3 Hz, 1H, 7-H), 7.38 (d, J = 1.8 Hz, 1H, 4-H), 7.41–7.50 (m, 3H, 3 × CH_{naph}), 7.73 (dd, J = 8.3 Hz, J = 1.8 Hz, 1H, 6-H), 7.82–7.88 (m, 3H, 3 × CH_{naph}), 7.96–7.98 (m, 1H, CH_{naph}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2 and 23.6 (CH_2 and 3-CH_3), 27.6 (3-CH_3), 28.4 (CH_2), 35.0 (NCH_3), 36.4 ($COCH_2$), 43.3 (C-3), 76.9 (C-2), 108.2 (C-7), 120.8 (CH_{Ar}), 124.5 (CH_{Ar}), 125.4 (CH_{Ar}), 125.7 (CH_{Ar}), 126.2 (CH_{Ar}), 126.9 (CH_{Ar}), 127.7 (CH_{Ar}), 128.0 (CH_{Ar}), 128.3 (CH_{Ar}), 131.7 (C_{quat}), 132.2 (C_{quat}), 134.0 (C_{quat}), 139.3 (C_{quat}), 140.3 (C-3a), 151.2 (C-7a), 175.0 (C=O); IR (KBr, ν_{max}, cm^{-1}): 3 368, 3 187 (N-H), 1 672 (C=O); MS (API-ES, pos mode), *m/z* (%): 373 ($M+H^+$, 100). Anal. calcd. for $C_{25}H_{28}N_2O$: C, 80.61; H, 7.58; N, 7.52. Found: C, 80.74; H, 7.38; N, 7.83.

4-(1,3,3-Trimethyl-5-(naphthalen-2-yl)-2,3-dihydro-1*H*-indol-2-yl)butan-1-amine (7)

A solution of indole **6a** (186 mg, 0.5 mmol) in dry THF (1 mL) was added to a suspension of $LiAlH_4$ (57 mg, 1.5 mmol) in dry THF (2 mL) under Ar atmosphere and the reaction mixture was stirred at reflux under Ar atmosphere. After 3 h the mixture was cooled to 0 °C, an aqueous 3M NaOH solution (5 mL) was added and the resulting mixture was stirred at rt. After 2 h the reaction mixture was filtered over Celite®, the filter cake was washed with ethyl acetate and the filtrate was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined, washed with brine (3 × 15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM/MeOH, 9 : 1 v/v). Yield 100 mg, 56%; a yellow viscous substance; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 3H, 3-CH_3), 1.43 (s, 3H, 3-CH_3), 1.50–1.92 (m, 8H, NH_2CH_2CH_2CH_2CH_2), 2.76 (s, 3H, NCH_3), 2.88–2.91 (m, 1H, 2-H), 3.01–3.08 (m, 2H, NH_2CH_2), 6.56 (d, J = 8.1 Hz, 1H, 7-H), 7.34–7.47 (m, 4H, 4-H and 3 × CH_{naph}), 7.69–7.94 (m, 5H, 6-H and 4 × CH_{naph}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5 (3-CH_3), 24.4 (CH_2), 27.5 (3-CH_3), 28.4 (CH_2), 29.3 (CH_2), 34.9 (NCH_3), 40.1 (NH_2CH_2), 43.1 (C-3), 76.8 (C-2), 108.0 (C-7), 120.6 (CH_{Ar}), 124.4 (CH_{Ar}), 125.2 (CH_{Ar}), 125.6 (CH_{Ar}), 126.1 (CH_{Ar}), 126.8 (CH_{Ar}), 127.6 (CH_{Ar}), 127.9 (CH_{Ar}), 128.2 (CH_{Ar}), 131.5 (C_{quat}), 132.0 (C_{quat}), 133.8 (C_{quat}), 139.1 (C_{quat}), 140.0 (C-3a), 151.2 (C-7a); IR (KBr, ν_{max}, cm^{-1}): 3 352, 3 205 (N-H); MS (API-ES, pos mode), *m/z* (%): 359 ($M+H^+$, 100). Anal calcd. for $C_{25}H_{30}N_2$: C, 83.75; H, 8.43; N, 7.81. Found: C, 83.79; H, 8.26; N, 8.04.

Ethyl 4-(1,3,3-trimethyl-5-(naphthalen-2-yl)-2,3-dihydro-1*H*-indol-2-yl)butanoate (8)

To a solution of amide **6** (186 mg, 0.5 mmol) in EtOH (2 mL) 6M aqueous HCl solution (4 mL) was added and the mixture was stirred under reflux. After 4 h the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with a saturated $NaHCO_3$ solution (2 × 10 mL). The organic layer was separated, dried over Na_2SO_4, filtered, concentrated under reduced pressure and

purified by flash chromatography on silica gel (Hex/EtOAc, 5 : 1 v/v). Yield 117 mg (72%), a brown viscous substance, R_f = 0.34 (Hex/EtOAc, 5 : 1 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (s, 3H, 1-CH_3), 1.27 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.44 (s, 3H, 1-CH_3), 1.68–1.87 (m, 4H, 2-CH_2CH_2), 2.37–2.42 (m, 2H, CH_2CO), 2.77 (s, 3H, NCH_3), 2.90–2.92 (m, 1H, 2-H), 4.15 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 6.58 (d, *J* = 8.1 Hz, 1H, 7-H), 7.36–7.47 (m, 4H, 4-H and 3 × CH_{naph}), 7.70–7.96 (m, 5H, 6-H and 4 × CH_{naph}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (CH_2CH_3), 22.7 (1-CH_3) 23.5 (CH_2), 27.5 (1-CH_3), 28.3 (CH_2), 34.8 and 34.9 (CH_2CO and NCH_3), 43.2 (C-1), 60.5 (CH_2CH_3), 76.8 (C-2), 108.0 (C-7), 120.7 (CH_{Ar}), 124.5 (CH_{Ar}), 125.3 (CH_{Ar}), 125.7 (CH_{Ar}), 126.2 (CH_{Ar}), 126.9 (CH_{Ar}), 127.7 (CH_{Ar}), 128.0 (CH_{Ar}), 128.3 (CH_{Ar}), 131.5 (C_{quat}), 132.1 (C_{quat}), 134.0 (C_{quat}), 139.3 (C_{quat}), 140.2 (C-3a), 151.4 (C-7a), 173.5 (C=O); IR (KBr, ν_{max}, cm^{-1}): 1733 (C=O); MS (API-ES, pos mode), *m/z* (%): 402 ($M+H^+$, 100). Anal. calcd. for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 80.95; H, 7.61; N, 3.28.

CONCLUSIONS

In conclusion, an efficient method for the Suzuki-Miyaura cross-coupling of 5-bromo-1,3,3-trimethylspiro[indole-2,2'-piperidin]-6'-one with (het)arylboronic acids was developed. $Pd(PPh_3)_4$ catalyzed coupling, performed in a microwave reactor (25–40 min at 100 °C), using Cs_2CO_3 as a base and ethanol as a solvent, afforded the 5-arylated products with good to excellent yields. Reductive ring-opening reaction of 5-(naphthalen-2-yl)spiro[indole-2,2'-piperidin]-6'-one and the following chemical transformations yielded the corresponding indoline derivatives possessing 2-[3-(ethoxycarbonyl)propyl]- and 2-(4-aminobutyl)-side chains.

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5-BROM-1,3,3-TRIMETIL-1,3-DIHIDRO-6'*H*-SPIRO[INDOLO-2,2'-PIPERIDIN]-6'-ONO SINTEZĖ IR MIKROBANGŲ SKATINAMOS SUZUKI-MIYAURA KRYŽMINIO JUNGIMO REAKCIJOS

S a n t r a u k a

5-Brom-1,3,3-trimetil-2-metiliden-2,3-dihidro-1*H*-indolui reaguojant su akrilamidu susidaro 5-brom-1,3,3-trimetil-1,3-dihidro-6'*H*-spiro[indolo-2,2'-piperidin]-6'-onas. Ištirta šio junginio Suzuki-Miyaura kryžminio jungimo reakcija su arilboro rūgštimis panaudojant mikrobangų reaktorių. Vienas iš tokiu būdu gautų produktų – 1,3,3-trimetil-5-(naftalen-2-il)-1,3-dihidro-6'*H*-spiro-[indolo-2,2'-piperidin]-6'-onas – toliau buvo transformuotas į indolino darinius, turinčius 2-[3-(etoksikarbonil)propilo] arba 2-(4-aminobutilo) šonines grandines.