Scientific paper

Reductive Heck Reactions and [3+2] Cycloadditions of Unsaturated *N,N'*-Bistricyclic Imides

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Abstract

The C–C coupling of *N,N'*-bis(5-norbornene-2,3-dicarboximide) (**3**) and *N,N'*-bis(7-oxa-5-norbornene-2,3-dicarboximide) (**6**) with aryl and heteroaryl iodides gave under reductive Heck conditions the C-aryl(hetaryl), substituted *N,N'*-bistricyclic imides **7a–f** and **8a**,**b**. The fused spiro-1,3-indandionolylpyrrolidine compounds, **9**, **10** and **11** were also obtained from ninhydrine, sarcosine and **3** or **6** via [3+2]cycloaddition.

Keywords: Alkenes, cycloadditions, heterocycles, hydroarylations, triyclic imides

1. Introduction

A large number of biological activities have been conferred to heterocycles and they play a pivotal role as both pharmaceutical and agrochemical products.[1] Imide moiety is an integral part of structures of various important molecules such as fumaramidmycin, granulatimide, isogranulatimide, rebeccamycin, and thalidomide. These molecules are reported to exhibit wide variety of biological activities such as antitumor, anti-inflammatory, and antimicrobial.[2] In addition, *N*-substituted imides, such as maleimides,[3] isohematinic acids[4] and especially bicyclic and tricyclic derivatives such as tandospirone derivatives[5,6] are known for their broad spectrum of pharmacological properties, thus showing antibiotic, fungicidal, analgesic, anxiolytic and cytostatic effects.

In the last decade, organopalladium-catalyzed C–C bond formation has become one of the most efficient approaches in the synthesis of organic molecules. The Heck reaction, in particular, is widely used as an important method to build biologically active compounds in synthetic chemistry and the pharmaceutical industry.[7,8] As an extension of the Heck reaction, Pd-catalyzed hydroarylation of alkynes and alkenes continues to attract researchers' interest in simple coupling processes and cyclization reactions.[9,10] In the presence of triphenylarsine as a ligand[11] the Pd-catalyzed hydroarylation of the easily accessible starting materials is a versatile and high-yield approach for the synthesis of the corresponding aryl and heteroaryl derivatives.[12,13]

Recently, we were interested in the synthesis of bi-, tri- and tetracyclic imides as epibatidine, epiboxidine and tandospirone analogs via reductive Heck reactions and 1,3-dipolar cycloadditions because of the possible bioactivity of these compounds.[14–20] In this paper, we described the reductive Heck reactions of *N,N'*-bis(5-norbornene-2,3-dicarboximide) and *N,N'*-bis(7-oxa-5-norbornene-2,3-dicarboximide).

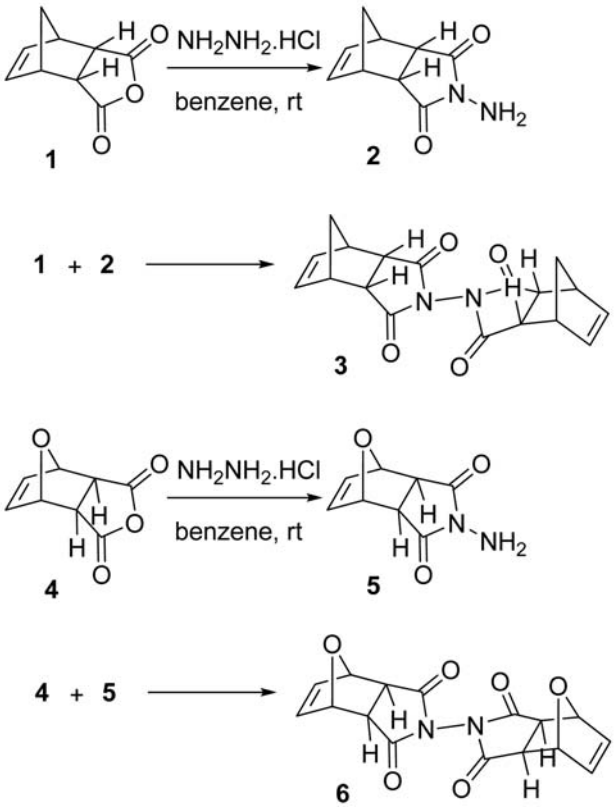
On the other hand, the 1,3-dipolar cycloaddition reaction of azomethine ylides to alkenes is one of the most important and elegant methods for the construction of nitrogen-containing five-membered ring compounds. In addition, we focused on the [3+2] cycloaddition reactions with azomethine ylide[21] to obtain fused spiro-1,3-indandionolylpyrrolidine compounds to have more potentially biologically active molecules available. Spiro compounds are well known to possess varied pharmacological activities and hence their synthesis has always been a challenge and an attraction to organic chemists.[22]

2. Results and Discussion

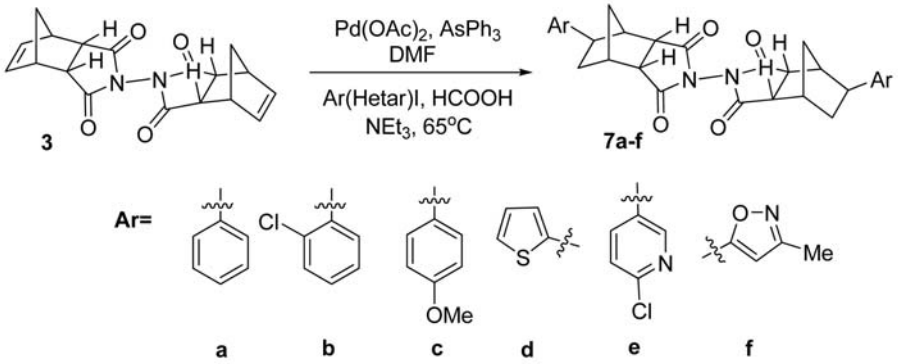
Our synthesis started with the reaction of bicyclo[2.2.1]hept-5-ene-2-*endo*,3-*endo*-dicarboxylic anhydride[23] (**1**) and *N*-aminobicyclo[2.2.1]hept-5-ene-2-*endo*,3-*endo*-dicarboximide[24] (**2**) according to the literature. The reaction occurred in acetic acid at reflux to give *N*,*N*'-bis(bicyclo[2.2.1]hept-5-ene-2-*endo*,3-*endo*-dicarboximide) (**3**) as colorless crystals[25] in a yield of 95%. The same conditions were successfully applied to the reaction of 7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*,3-*exo*-dicarboxylic anhydride (**4**) with *N*-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*,3-e*xo*-dicarboximide (**5**) to give *N*,*N*'-bis(7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*,3-*exo*-dicarboximide) (**6**) as colorless crystals[26] (Scheme 1).

Treatment of **3** with 1-iodobenzene, 2-chloro-1-iodobenzene, 4-methoxy-1-iodobenzene, 2-iodothiophene, 2-chloro-5-iodopyridine and 5-iodo-3-methylisoxazole under reductive Heck conditions and subsequent column chromatography on silica gel gave **7a**–**f** as single diastereomers in isolated yields of 55–72% (Scheme 2).

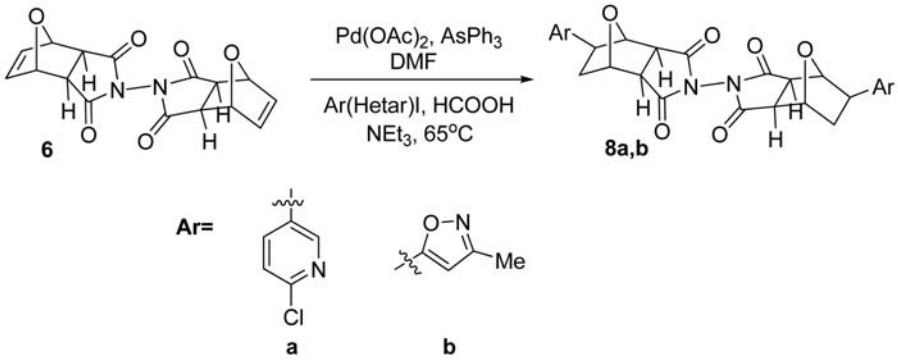
We also synthesized **8a**,**b** from **6** with 2-chloro-5-iodopyridine and 5-iodo-3-methylisoxazole which was prepared according to the literature[27] under the same conditions (Scheme 3). We selected 2-chloro-5-iodopyridine and 5-iodo-3-methylisoxazole as the arylation reagents due to the structures of epibatidine and epiboxidine,[28,29]



Scheme 1. Synthesis of starting materials **3** and **6**.



Scheme 2. Synthesis of compounds **7a**–**f**.



Scheme 3. Synthesis of compounds **8a**,**b**.

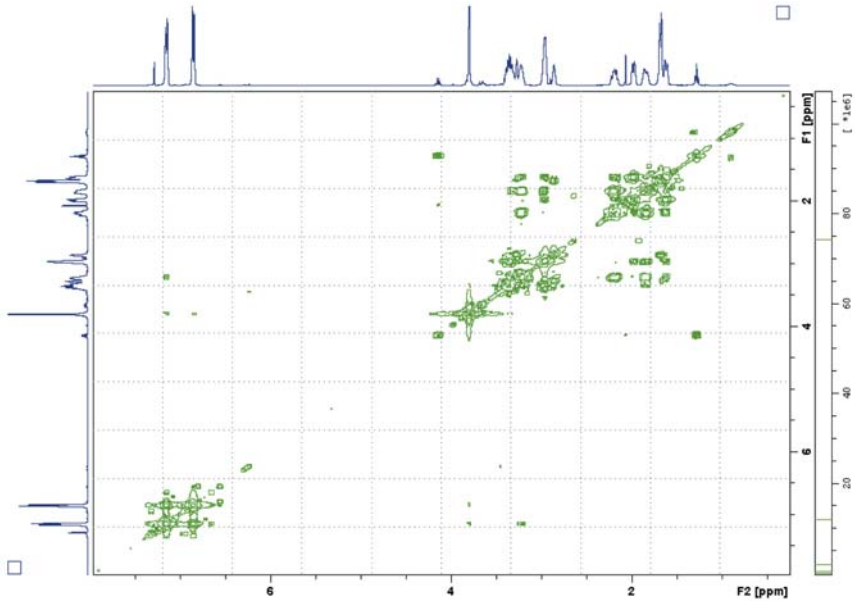
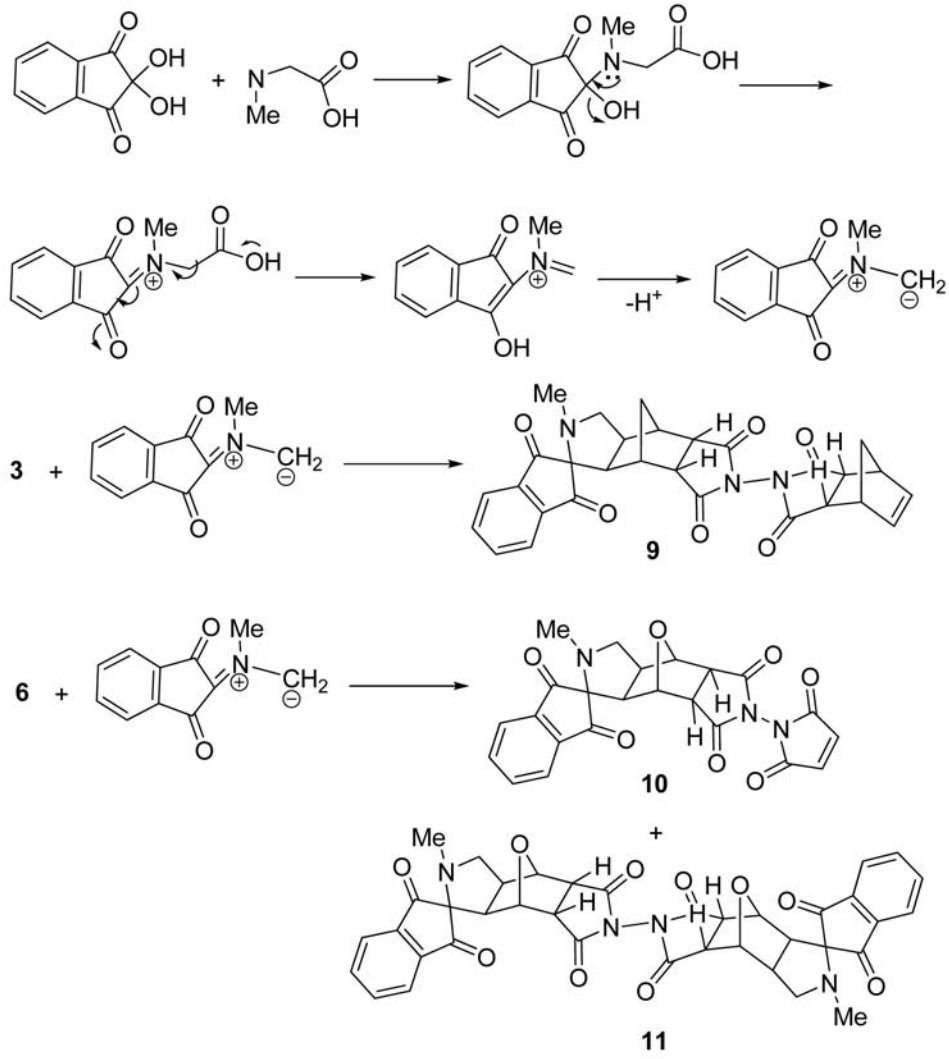


Figure 1. ^{1}H–^{1}H-COSY spectrum of compound **7c**.



Scheme 4. Synthesis of compounds **9**–**11**.

respectively, behaving as potent α4β2 nicotinic receptors to enhance biological activity of new bridged bistricyclic imides.

The *exo*-stereochemistry for each Heck product was inferred from ^{1}H NMR spectra including diagnostic spin–spin interactions. The *exo*-position of the C-5 substituent was confirmed by the fact that H_{5n} showed no significant interaction with H_1. The geminal protons on C-6 were identified by vicinal coupling to H_1. Additionally, ^{1}H–^{1}H-COSY spectra showed cross peaks between H_2 and H_3 and between H_5 and H_6, respectively (Figure 1). In addition to the ^{13}C NMR, HSQC and FTIR spectral data were also in agreement with the proposed structures, the mass spectra of all new compounds showed the expected molecular ion peaks.

The reaction of **3** with azomethine ylide obtained from ninhydrine and sarcosine gave these product **9** instead of the expected dispiro-1,3-indandionolylpyrrolidines. In our experiments, we performed the reactions with 1:1, 1:2 and 1:3 ratios of **3** with the reactants obtaining compound **9** as a single diastereomer in every cases. ^{1}H NMR spectra of **9** showed four aromatic protons at 7.77–7.88 ppm and two alkenic protons at 6.16 and 6.21 ppm. LC-MS result also confirmed the structure of **9** (Figure 2). Upon the treatment of **6** with sarcosine and ninhydrine at the same conditions the retro-Diels–Alder reaction producing **10** beside compound **11** took place. The absent of bridge protons in the ^{1}H NMR spectra of **10** and LC-MS result confirmed the structure of **10**. We also obtained **11** as the expected product from the same reaction after column chromatography purification. The absent of alkenic protons in the ^{1}H and ^{13}C NMR spectrum of **11** and LC-MS result confirmed the structure of **11**. (Scheme 4).

3. Experimental Section

3. 1. General

All the reactions were carried out under nitrogen atmosphere unless otherwise indicated. Reactions were monitored using thin-layer chromatography (TLC). Visualization of the developed chromatogram was performed under UV light or with $KMnO_4$ staining. The resulting residues were purified by silica gel chromatography with a solvent gradient of 2:1 (ethyl acetate/*n*-hexane) to afford the title compounds. IR spectra were obtained with a Perkin Elmer FT-IR system and are reported in the terms of frequency of absorption (cm^{-1}). Melting points were determined with a Gallenkamp digital thermometer equipment. All melting points are uncorrected. NMR spectra were determined with a Bruker Ac-400 MHz NMR and Varian-INOVA-500 MHz NMR. 2D NMR experimental studies such as COSY, 2D-NOESY, HMBC, HSQC were measured with a Bruker Ac-400 MHz NMR. TMS (tetramethylsilane) was used as the internal standard and $CDCl_3$ was used as the solvent. Signal multiplicities in the NMR spectra are reported as follows: s-singlet, br s-broad singlet, d-doublet, dd-doublet of doublets, m-multiplet. Mass spectra were measured either with Agillent LC-MSD Trap SL or GC-MS.

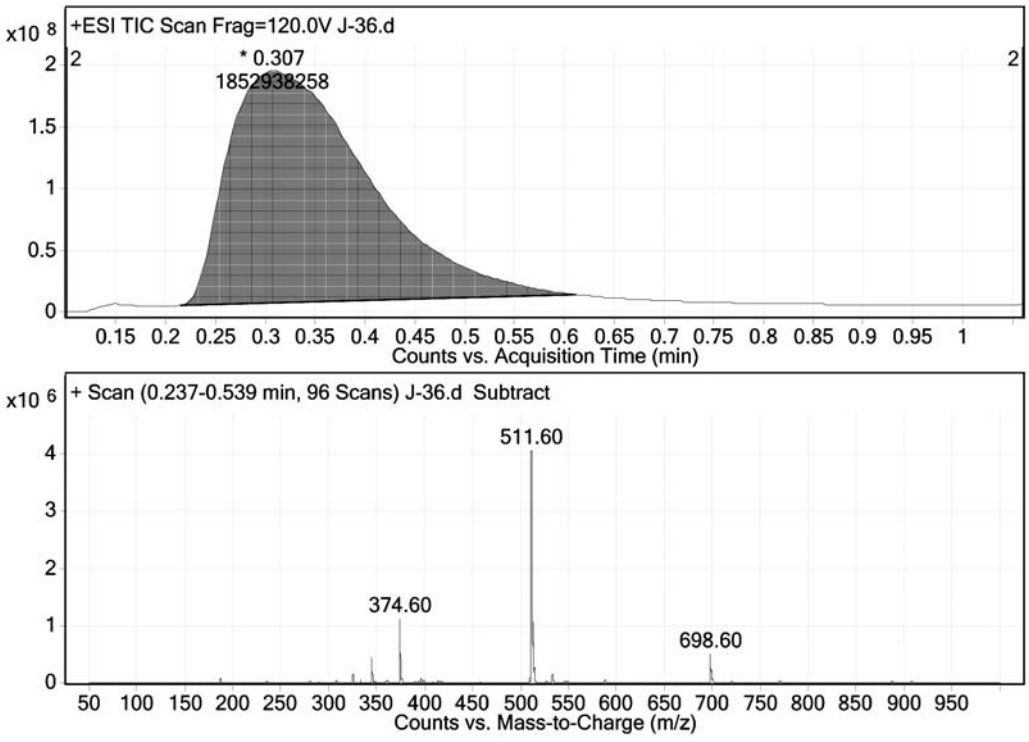
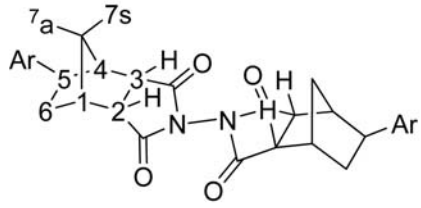


Figure 2. LC-MS result of compound **9**.

3. 1. 1. Typical Experimental Procedure for the Preparation of Arylated Bistricyclicimides

A solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and $AsPh_3$ (33.7 mg, 0.11 mmol) in dry DMF (3 mL) was stirred in a Schlenk flask under nitrogen at 65 °C for 15 min in order to form the catalyst complex. Then aryl or hetaryl iodides (306 mg, 1.5 mmol), **3** or **6** (1.00 mmol), triethylamine (354 mg, 3.5 mmol) and formic acid (138 mg, 3.0 mmol) were added. The mixture was heated to 65 °C for 28 h. After cooling down to rt, brine (50 mL) was added, the reaction mixture was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was evaporated, the residue purified by chromatography.



***N,N'*-Bis[5-phenylbicyclo[2.2.1]heptane-2-*endo*,3-*endo*-dicarboximide] (7a).**

Colorless solid, 55% yield, R_f 0.43 (1:2 *n*-hexane/ethyl acetate), mp 99–97 °C, IR (KBr) ν 3063, 2969, 2884, 1774, 1731, 1599, 1583 1474, 1454, 1170, 785, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (d, *J* 10.3 Hz, 2H, H_{7s}-H_{7s}^1), 1.85–1.88 (m, 2H, H_{7a}-H_{7a}^1), 1.96–1.99 (dd, *J* 10.3; 5.2 Hz, 2H, H_{6x}-H_{6x}^1), 2.17–2.22 (m, 2H, H_{6n}– H_{6n}^1), 2.83 (brs, 2H, H_4-H_4^1), 2.96–3.01 (m, 2H, H_{5n}-H_{5n}^1), 3.23–3.24 (m, 2H, H_1-H_1^1), 3.31–3.35 (m, 2H H_3-H_3^1), 3.36–3.39 (m, 2H, H_2-H_2^1), 7.17–7.22 (m, 4H, ArH), 7.28–7.31 (m, 6H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.36 and 33.42 (2C, C_6-C_6^1), 38.43 and 38.47 (2C, C_7-C_7^1), 39.77 and 39.94 (2C, C_1-C_1^1), 41.53 and 41.86 (2C, C_4-C_4^1), 46.63 and 46.89 (2C, C_5-C_5^1), 46.96 and 47.32 (2C, C_3-C_3^1), 47.59 and 47.67 (2C, C_2-C_2^1), 126.11, 126.98 and 128.49 (10C, ArC), 144.83 and 144.87 (2C, Csubst.), 172.28, 172.32, 172.38 and 172.44 (4C, C=O), ppm GCMS *m/z* (relative intensity): 481 (M+H, 65), 142 (M–subst, 100).

***N,N'*-Bis[5-(2-chlorophenyl)bicyclo[2.2.1]heptane-2-*endo*,3-*endo*-dicarboximide] (7b).** Colorless solid, yield 65%, R_f 0.47 (1:2 *n*-hexane/ethyl acetate), mp 95–93 °C, IR (ATR) ν 3058, 2969, 2887, 1782, 1734, 1592, 1471, 1459, 1171, 740, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.61–1.63 (m, 2H, H_{7a}-H_{7a}^1), 1.81 (d, *J* 12.8 Hz, 2H, H_{7s}-H_{7s}^1), 2.01–2.03 (m, 2H, H_{5n}-H_{5n}^1), 2.94 (br s, 4H, H_{6x}-H_{6n}, H_{6x}^1–H_{6n}^1), 3.23 (br s, 2H, H_4-H_4^1), 3.31–3.38 (m, 2H, H_1-H_1^1), 3.41–3.46 (m, 2H, H_3-H_3^1), 3.47–3.52 (m, 2H, H_2-H_2^1), 7.14–7.16 (m, 2H, ArH), 7.27–7.28 (m, 3H, ArH), 7.34 (d, *J* 4.0 Hz, 1H, ArH), 7.36 (d, *J* 8.0 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.13 (2C, C_6-C_6^1), 39.51 and 39.85 (2C, C_7-C_7^1), 41.60 and 41.81 (2C, C_1-C_1^1), 44.40 and 44.46 (2C, C_4-C_4^1), 45.40 and 45.83 (2C, C_5-C_5^1), 46.81 and 47.27 (2C, C_3- C_3^1), 47.57 and 47.65 (2C, C_2-C_2^1), 126.46, 126.98, 127.12, 127.45, 127.77, 128.48, 129.81 and 130.03 (8C, ArC), 134.98 and 135.11 (2C, Csubst.), 141.80 and 141.86 (2C, C-Cl), 172.32, 172.45, 172.63 and 172.88 (4C, C=O) ppm. LC-MSD *m/z* (relative intensity): 550.0 (M+H, 100), 549.02 (M^+, 75), 480 (M–2Cl, 25).

***N,N'*-Bis[5-(4-methoxyphenyl)bicyclo[2.2.1]heptane-2-*endo*,3-*endo*-dicarboximide] (7c).** Colorless solid, 72% yield, R_f 0.52 (1:2 *n*-hexane/ethyl acetate), mp 97–95 °C, IR (KBr) ν 3051, 3005, 2964, 2887, 1786, 1726, 1610, 1582, 1457, 1169, 772, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (d, *J* 10.4 Hz, 2H, H_{7s}-H_{7s}^1), 1.83–1.88 (m, 2H, H_{7a}-H_{7a}^1), 2.21–2.25 (m, 2H, H_{5n}-H_{5n}^1), 2.94 (br s, 4H, H_{6x}-H_{6n}, H_{6x}^1 -H_{6n}^1), 3.21–3.29 (m, 4H, H_1-H_1^1 and H_4-H_4^1), 3.37–3.42 (m, 4H, H_2-H_2^1 and H_3-H_3^1), 3.74 (s, 6H, -OCH_3), 6.93 (d, *J* 6.9 Hz, 4H, ArH), 7.33 (d, *J* 6.9 Hz, 4H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.30 and 33.41 (2C, C_6-C_6^1) 39.29 and 39.47 (2C, C_7-C_7^1), 40.69 and 41.85 (2C, C_1-C_1^1), 46.61 and 46.88 (2C, C_4-C_4^1), 46.94 and 47.16 (2C, C_5-C_5^1), 47.30 and 47.47 (2C, C_3-C_3^1), 47.51 and 47.64 (2C, C_2-C_2^1), 55.30 (2C, OCH_3), 113.80 and 127.96 (8C, ArC), 136.96 and 157.88 (4C, Csubst.), 172.29, 172.40, 172.58 and 172.63 (4C, C=O) ppm. LC-MSD *m/z* (relative intensity): 540.2 (M^+, 100).

***N,N'*-Bis[5-(2-thienyl)bicyclo[2.2.1]heptane-2-*endo*,3-*endo*-dicarboximide] (7d).** Colorless solid, 55% yield, R_f 0.45 (1:2 *n*-hexane/ethyl acetate), mp 96–94 °C, IR (KBr) ν 3075, 2977, 2932, 2887, 1772, 1733, 1528, 1474, 1458, 1168, 782, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (d, *J* 10.5 Hz, 2H, H_{7s}-H_{7s}^1), 1.87–1.91 (m, 2H, H_{7a}-H_{7a}^1), 2.05 (d, *J* 10.6 Hz, 2H, H_{6x}-H_{6x}^1), 2.23–2.28 (m, 2H, H_{6n}-H_{6n}^1), 2.95–2.98 (m, 4H, H_4-H_4^1 and H_{5n}-H_{5n}^1), 3.29–3.33 (m, 2H, H_1-H_1^1), 3.36–3.39 (m, 2H H_3-H_3^1), 3.43–3.45 (m, 2H, H_2-H_2^1), 6.82 (d, *J* 4.4 Hz, 2H, ArH), 6.92 (dd, *J* 4.4; 2.3 Hz, 2H, ArH), 7.14 (d, *J* 4.5 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.06 (2C, C_6-C_6^1), 37.57 (2C, C_5-C_5^1), 39.57 (2C, C_7-C_7^1), 39.66 (2C, C_4-C_4^1), 46.73 (2C, C_1-C_1^1), 47.13 (2C, C_3-C_3^1), 47.19 (2C, C_2-C_2^1), 123.31, 123.57 and 126.75 (6C, ArC), 149.41 (2C, Csubst.), 172.08 and 172.21 (4C, C=O) ppm. GCMS *m/z* (relative intensity): 492 (M^+, 75), 149 (M–subst, 100).

***N,N'*-Bis[5-(6-chloropyridin-3-yl)bicyclo[2.2.1]heptane-2-*endo*,3-*endo*-dicarboximide] (7e).** Colorless solid, 45% yield, R_f 0.25 (1:5 *n*-hexane/ethyl acetate), mp 223–224 °C, IR (KBr) ν 3059, 2963, 2888, 1783, 1733, 1582, 1564, 1458, 1302, 1282, 1171, 1107, 818, 740 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.50–1.65 (m, 6H, H_{6x}, $H_{6n,}$ $H_{7a,}$ H_{7a}^1, H_{7s}, H_{7s}^1), 1.90–2.01 (d, *J* 11.71 Hz, 1H, H_{6n}^1), 2.43–2.45 (d, *J* 10.73 Hz, 1H, H_{6x}^1), 2.81–2.83 (d, *J* 11.71

Hz , 2H, H_{5n}-H_{5n}^1), 3.14 (br s, 2H, H_3-H_3^1), 3.26 (br s, 2H, H_2-H_2^1), 3.46 (br s, 2H, H_1-H_1^1), 3.66–3.67(d, *J* 4.88 Hz, 2H, H_4-H_4^1), 6.92–6.94 (dd, *J* 1.95; 7.80 Hz, 2H, ArH), 7.00–7.02 (dd, *J* 1.95; 7.80 Hz, 2H, ArH), 7.90–7.92 (dd, *J* 1.95; 8.78 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.64 and 23.70 (2C, C_6-C_6^1), 38.45 and 38.54 (2C, C_5-C_5^1), 39.62 and 40.89 (2C, C_7-C_7^1), 43.28 and 43.33 (2C, C_4-C_4^1), 44.77 and 44.79 (2C, C_1-C_1^1), 46.25 (2C, C_3-C_3^1), 46.49 and 46.62 (2C, C_2-C_2^1), 122.71 2C, ArC), 133.28 (2C, Csubst.), 137.76 (2C, ArC), 148.05 (2C, ArC) 148.68 (2C, Csubst.), 170.37, 170.66, 171.57 and 172.29 (4C, C=O) ppm. LC-MSD *m/z* (relative intensity): 550.5 (M+H, 100).

***N,N'*-Bis[5-(3-methylisoxazol-5-yl)bicyclo[2.2.1]heptane-2-*endo*,3-*endo*-dicarboximide] (7f).** Colorless solid, 40% yield, R_f 0.66 (1:3 *n*-hexane/ethyl acetate), mp 216–218°C, IR (KBr) ν 318, 2966, 2888, 1777, 1732, 1600, 1456, 1417, 1304, 1281, 1172, 1125, 833, 819, 749 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49–1.51 (d, *J* 8.78 Hz, 1H, H_{7s}), 1.56–1.60 (m, 2H, H_{7a}- H_{7a}^1), 1.71–1.73 (d, *J* 8.78 Hz, 1H, H_{7s}^1), 1.77–2.09 (m, 4H, H_{6x}-H_{6n}-H_{6n}^1-H_{6x}^1), 2.17 (s, 6H, CH_3), 2.76 (br s, 1H, H_{5n}), 3.12 (br s, 1H, H_{5n}^1), 3.16–3.31 (m, 4H, H_3-H_3^1-H_2-H_2^1), 3.35–3.40 (m, 4H, H_1-H_1^1-H_4-H_4^1), 6.18–6.21 (m, 2H, =CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.62 (2C, CH_3), 31.53 (2C, C_6-C_6^1), 35.21 (2C, C_5-C_5^1), 39.47 (2C, C_4-C_4^1), 40.09 (2C, C_7-C_7^1), 44.87 (2C, C_1-C_1^1), 45.35 (2C, C_3-C_3^1), 46.70 (2C, C_2-C_2^1), 101.83 and 101.86 (2C, =CH), 159.92, 171.02, 171.26 and 171.87 (4C, Csubst), 172.09, 172.27, 174.83 and 174.88 (4C, C=O) ppm GCMS *m/z* (relative intensity): 490 (M^+, 54), 409 (M–isoxazole, 100).

***N,N'*-Bis[5-(6-chloropyridin-3-yl)-7-oxabicyclo[2.2.1]heptane-2-*exo*,3-*exo*-dicarboximide] (8a).** Colorless solid, 51% yield, R_f 0.25 (1:5 *n*-hexane/ethyl acetate), mp 180 °C (decomp.), IR (KBr) ν 3059, 2988, 2959, 1783, 1738, 1583, 1564, 1457, 1311, 1289, 1183, 1105, 826, 814 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.92–1.97 (m, 2H, H_{6x}-H_{6x}^1), 2.50–2.54 (dd, *J* 9.1; 12.6 Hz, 2H, H_{6n}-H_{6n}^1), 3.46–3.49 (m, 2H, H_{5n}-H_{5n}^1), 3.53–3.57 (m, 2H, H_2-H_2^1), 3.60–3.63 (m, 2H H_3-H_3^1), 4.73–4.75 (m, 2H, H_1-H_1^1), 5.06–5.09 (m, 2H, H_4-H_4^1), 7.40–7.43 (m, 2H, ArH), 7.78–7.82 (m, 2H, ArH), 8.35–8.36 (m, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.11 and 39.16 (2C, C_6-C_6^1), 43.03 and 47.43 (2C, C_2-C_2^1), 47.54 and 47.69 (2C, C_3-C_3^1), 47.79 (2C, C_5-C_5^1), 78.02 and 78.07 (2C, C_1-C_1^1), 83.25 and 83.28 (2C, C_4-C_4^1), 123.59 (ArC), 136. 34 (ArC), 137.09 (Csubst), 137.11 (Csubst), 147.50 (ArC), 149.37 (Csubst.), 168.23, 168.50, 169.12 and 169.39 (4C, C=O) ppm. GCMS *m/z* (relative intensity): 327 (M–2pyridine, 54), 289 (M/2, 100).

***N,N'*-Bis[5-(3-methylisoxazol-5-yl)-7-oxabicyclo[2.2.1]heptane-2-*exo*,3-*exo*-dicarboximide] (8b).** Colorless solid, 47% yield, R_f 0.38 (1:5 *n*-hexane/ethyl acetate), mp 167–168 °C, IR (KBr) ν 3134, 2996, 2972, 2936, 1787, 1740, 1603, 1418, 1316, 1294, 1184, 1008, 833, 817 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07–2.12 (m, 2H, H_{6x}-H_{6x}^1), 2.22 (d, *J* 9.4 Hz, 2H, H_{6n}-H_{6n}^1), 2.26 (s, 6H, CH_3), 3.19 (d, *J* 7.2 Hz, 2H, H_2-H_2^1), 3.27 (d, *J* 7.2 Hz, 2H, H_3-H_3^1), 3.30–3.33 (dd, *J* 4.7; 9.1 Hz, 2H, H_{5n}-H_{5n}^1), 5.01–5.02 (m, 2H H_1-H_1^1), 5.11 (d, *J* 5.3 Hz, 2H, H_4-H_4^1), 5.92 (d, *J* 2.8 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.64 (2C, CH_3), 36.81 (2C, C_6-C_6^1), 39.90 (2C, C_5-C_5^1), 48.41 and 48.50 (2C, C_3-C_3^1), 48.52 and 48.62 (2C, C_2-C_2^1), 79.14 and 79.19 (2C, C_1-C_1^1), 82.62 and 82.67 (2C, C_4-C_4^1), 101.75 and 101.79 (2C, =CH), 160.28, 169.44, 169.73 and 170.36 (4C, Csubst), 170.65, 173.24, 173.26 and 173.28 (4C, C=O) ppm. GCMS *m/z* (relative intensity): 494 (M^+, 23), 329 (M–isoxazole, 92).

3. 1. 2. Typical Experimental Procedure for the Preparation of Fused Spiro-1,3-indandionolylpyrrolidine Compounds

A sealed tube containing ninhydrine (1 mmol), sarcosine (1 mmol) and 3 or 6 (1 mmol) in EtOH/dioxane (1:1, 6 mL) was heated at 65 °C for 6 h under nitrogen atmosphere. After completion of the reaction with TLC control, the solvent was evaporated under vacuum, and the residue purified by chromatography on silica gel.

Compound 9. Yellow crystals, yield 65%, R_f 0.67 (20:1 dichloromethane/methanol), mp 262–263 °C, IR (ATR) ν 2939, 2855, 2663, 1737, 1702, 1595, 1462, 1176, 781, 746 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44–1.47 (m, 1H, H_{7a}), 1.54 (d, *J* 6.8 Hz, 1H, H_{7a}^1), 1.69 (d, *J* 8.8 Hz, 1H, H_{7s}^1), 2.12 (t, *J* 6.8 Hz, 2H, CH_2), 2.32 (d, *J* 7.8 Hz, 1H, H_{7s}), 2.61 (d, *J* 4.8 Hz, 1H, H_{6n}), 2.68–2.73 (m, 2H, H_2^1, H_6^1), 2.78 (s, 1H, H_4), 2.81 (s, 1H, H_1), 2.86 (dd, *J* 1.9; 6.8 Hz, 1H, H_{5n}), 3.02–3.09 (m, 2H, H_2-H_3), 3.30 (s, 3H, CH_3), 3.37 (s, 1H, H_4^1), 3.41 (s, 1H, H_1^1), 6.16 (dd, *J* 2.9; 4.8 Hz, 1H, =CH), 6.21 (dd, *J* 2.9; 4.8 Hz, 1H, =CH), 7.78 (dd, *J* 3.9; 7.8 Hz, 2H, ArH), 7.87 (dd, *J* 3.9; 7.8 Hz, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.93 (N-CH_3), 38.81 (C_7), 42.36 (C_6), 42.66 (C_5), 44.75 (C_1), 45.15 (C_4), 45.30 (C_1^1), 45.35 (C_4^1), 45.40 (C_2), 46.39 (C_3), 46.70 (C_2^1), 50.68 (C_3^1), 51.73 (C_7^1), 61.08 (N-CH_2), 123.34 (C_5^1), 123.64 (C_6^1), 134.86 (ArC), 135.24 (ArC), 136.21 (ArC), 136.62 (ArC), 139.97 (Csubst.), 142.01 (Csubst.), 153.09 (Csubst.) 171.18, 171.35, 172.05, 172.28, 201.00 and 202.85 (6C, C=O) ppm. LC-MSD *m/z* (relative intensity): 511.5 (M+H, 100).

Compound 10. Yellow oil, yield 43%, R_f 0.64 (20:1 dichloromethane/methanol), IR (ATR) ν 3073, 2924, 2854, 2801, 1737, 1705, 1593, 1465, 1376, 1185, 756, 716 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (t, *J* 6.8 Hz, 2H, CH_2), 2.21 (d, *J* 3.9 Hz, 1H, H_{6n}), 2.93 (dd, *J* 2.9; 6.8 Hz, 1H, H_{5n}), 3.55–3.60 (m, 2H, H_2-H_3), 3.62 (s, 3H,

CH_3), 5.23 (s, 1H, H_4), 5.31 (d, *J* 4.8 Hz, $1H_1$), 6.50 (dd, *J* 4.8; 8.8 Hz, 1H, =CH), 7.85 (dd, *J* 3.9; 7.8 Hz, 2H, ArH), 7.93 (dd, *J* 3.9; 7.8 Hz, 2H, ArH) ppm. LC-MSD *m/z* (relative intensity): 447.5 (M^+, 100).

Compound 11. Yellow oil, yield 45%, R_f 0.20 (20:1 dichloromethane/methanol), ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (t, *J* 3.9 Hz, 4H, CH_2), 2.48 (dd, *J* 1.9; 7.8 Hz, 2H, H_{6n}), 2.80–2.87 (m, 4H, H_2-H_3), 3.03 (dd, *J* 3.9; 7.8 Hz, 2H, H_{5n}), 3.40 (s, 6H, CH_3), 4.75 (d, *J* 5.8 Hz, 2H, H_4), 4.81 (d, *J* 4.8 Hz, 2H, H_1), 7.85–7.89 (m, 6H, ArH), 7.93 (m, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.49 (N-CH_3), 34.61 (N-CH_3), 46.87, 46.93, 47.06, 47.12, 54.27, 54.44, 54.77, 54.84, 57.91 (N-CH_2), 58.02 (N-CH_2), 78.13, 78.27, 81.21, 81.57, 122.24 (ArC), 122.28 (ArC), 122.59 (ArC), 122.67 (ArC), 135.53 (ArC), 135.74 (ArC), 135.84 (ArC), 135.86 (ArC), 138.81 (Csubst.), 138.89 (Csubst.), 138.98 (Csubst.), 139.07 (Csubst.), 140.70 (Csubst.), 140.75 (Csubst.), 167.90, 167.96, 169.26, 169.28, 198.07, 198.17, 201.72 and 201.98 (8C, C=O) ppm. LC-MSD *m/z* (relative intensity): 702.80 (M^+, 100).

4. Conclusion

In the presence of triphenylarsine as a ligand the palladium-catalyzed hydroarylation of the readily accessible unsaturated *N*,*N'*-bistricyclic imides, **3** and **6** was shown to be a stereoselective, versatile and high-yield approach to the synthesis of aryl and heteroaryl derivatives of bistricyclic imides (**7a–f, 8a,b**). Additionally, the stereoselective synthesis of fused spiro-1,3-indandionolylpyrrolidines (**9–11**) was demonstrated. The above approach has been proved to be very useful for the construction of novel heterocycles of potential pharmacological interest. During pharmaceutical research and development, solubility of compounds also is important, therefore implying easier applicability of our new compounds due to their good solubilities.

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6. References

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Povzetek

S tvorbo nove C–C vezi s pripajanjem *N,N'*-bis(5-norbornen-2,3-dikarboksimidov) (**3**) oz. *N,N'*-bis(7-oksa-5-norbornen-2,3-dikarboksimidov) (**6**) z aril oz. heteroaril jodidi pod pogoji reduktivne Heckove reakcije smo pripravili C-aril(hetaril) substituirane *N,N'*-bistriciklične imide **7a**–**f** in **8a**,**b**. Pripojeni spiro-1,3-indandionolilpirolidinske spojine **9**, **10** in **11** smo pripravili iz ninhidrina, sarkozina in **3** oz. **6** s pomočjo [3+2] cikloadicije.