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Reductive Heck reactions of *N*-arylamino-substituted tricyclic imides

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Abstract: The C–C coupling of (3a*R*,4*S*,7*R*,7a*S*)-*rel*-2-[(3-chloro-4-fluorophenyl)amino]-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione (**3**) which was prepared as a new starting material and (3a*R*,4*S*,7*R*,7a*S*)-*rel*-2-[(2,4-dinitrophenyl)amino]-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-isoindole-1,3-(2*H*)-dione (**6**) with aryl- and heteroaryl iodides gave the aryl(hetaryl), *N*-arylamino tricyclic imides **4a**–**d** and **7a**–**d** under reductive Heck conditions.

Keywords: hydroarylation reactions; cyclic hydrazines; imides; C–C coupling with $Pd(OAc)_2$.

INTRODUCTION

Hydrazine derivatives are widely applied as pharmaceuticals, *e.g.*, as tuberculoci--dal, anti-tumor and psychotherapeutic agents.[1] They are also used in agriculture as herbicides and protection agents for plants.[2] Kas'yan and co-workers studied the reactions of an endic anhydride with alkyl- and arylhydrazines and reported the products as biologically active compounds.[3] These kinds of products also have imide forms. Cyclic imides are also important intermediates of many pharmaceutical drugs, such as human therapeutic agents, and are reported to exhibit cytostatic, antibacterial, herbicide and antimicrobial activities. In addition, they can cross biological membranes *in vivo* due to the imide bonds.[4–8]

Organopalladium-catalyzed C–C bond formation has become one of the most efficient approaches in the synthesis of organic molecules. Due to its broad synthetic potential as a stereoselective C–C coupling method, the Heck reaction has been the subject of several synthetic and mechanistic studies over the last 30 years. The Heck reaction is widely used as an important method to build biologically active compounds in synthetic chemistry and the pharmaceutical indus-

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try.[9–11] Reductive Heck reactions of unsaturated *N*-substituted tricyclic imides, which have possible biological activities, were studied previously.[12–18]

The palladium-catalyzed hydroarylations of several *N*-substituted tricyclic imides were studied in order to find a new stereoselective access to a series of new *exo*-aryl(hetaryl)-substituted tricyclic imides in the presence of triphenylarsine using the Kaufmann reductive Heck procedure.[19–21]

In this study, the endic anhydride (**1**)[22] was combined with 3-chloro-4-fluorophenylhydrazine (**2**), which was chosen for the active groups on the aromatic ring, and 2,4-dinitrophenylhydrazine (**5**), which was chosen for many applications of this group in medicinal chemistry, using the Kas'yan method.[3] Then, their hydroarylation reactions with aryl and heteroaryl iodides were studied to obtain new possibly bioactive molecules.

EXPERIMENTAL

General

All the reactions were performed under a nitrogen atmosphere unless otherwise indicated. Reactions were monitored using thin-layer chromatography (TLC). Visualization of the developed chromatogram was performed under UV light or using $KMnO_4$ stain. The IR spectra were obtained with a Perkin Elmer FT-IR system and are reported in terms of frequency of absorption (cm^{-1}). The melting points were determined using a Gallenkamp digital thermometer. All melting points are uncorrected. The NMR spectra were determined with a Bruker AC-500 (500 MHz) NMR spectrometer. TMS (tetramethylsilane) was used as the internal standard and $CDCl_3$ (or DMSO-d_6, CD_3OCD_3 and CD_3OD) were used as the solvents. Signal multiplicities in the NMR spectra are reported as follows: *s*, singlet, *brs*, broad singlet, *d*, doublet, *dd*, doublet of doublets and *m*, multiplet. Mass spectra were measured with either an Agilent LC/MSD Trap SL or GC–MS (Agilent 6890N GC-System-5973 IMSD) or an Agilent 6460 Triple Quad LC/MS instruments.

*The synthesis of (3a*R*,4*S*,7*R*,7a*S*)-*rel*-2-[(3-Chloro-4-fluorophenyl)amino]-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione (**3**)*

A mixture of **1** (164 mg, 1 mmol) and **2** (160.5 mg, 1 mmol) in CH_3CN (5 mL) was stirred at r.t. for 4 h. The solid was filtered and recrystallized from 2-propanol to afford **3** in 80 % yield. The characterization data for **3** are given in the Supplementary material to this paper.

General procedure for the hydroarylation reactions

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 **3** (306 mg, 1.5 mmol) 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 to r.t., brine (50 mL) was added, the reaction mixture was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was evaporated, and the residue purified by chromatography to afford **4a**–**d** or **7a**–**d**. The characterization data for the synthesized compounds are given in the Supplementary material together with their IR and NMR spectra.

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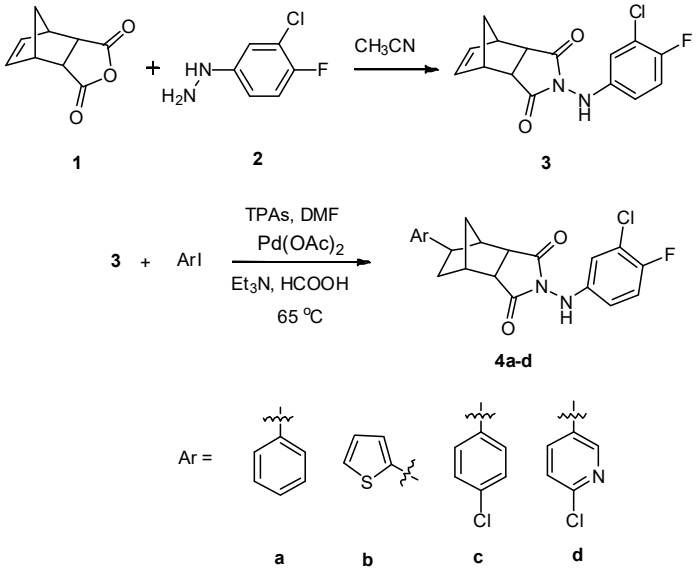
RESULTS AND DISCUSSION

First, (3a*R*,4*S*,7*R*,7a*S*)-*rel*-2-[(3-chloro-4-fluorophenyl)amino]-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione (**3**) was synthesized as a new compound in the reaction of the endic anhydride **1** and 3-chloro-4-fluorophenylhydrazine (**2**) as a new compound. Reactions of **3** with iodobenzene, 2-iodothiophene, 4-chloro-1-iodobenzene and 2-chloro-5-iodopyridine under reductive Heck conditions gave the pure products **4a**–**d** after chromatographic separation on silica gel as single diastereomers in isolated yields (Scheme 1).



Scheme 1. Synthesis of **3** and **4a**–**d**.

Furthermore, (3a*R*,4*S*,7*R*,7a*S*)-*rel*-2-[(2,4-dinitrophenyl)amino]-3a,4,7,7a--tetrahydro-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione (**6**) was prepared in a known procedure[3] from the reaction of the same endic anhydride (**1**) and 2,4-dinitrophenylhydrazine (**5**) as the second starting material. The same reductive Heck arylation conditions were successfully applied to the reactions of **6** with iodobenzene, 2-iodothiophene, 4-chloro-1-iodobenzene and 2-chloro-5-iodopyridine to give the new *exo*-arylated heterocycles **7a**–**d** in moderate yields after chromatographic separation (Scheme 2).

The stereochemistry of the compounds was investigated from their NMR spectra including diagnostic spin–spin interactions. The *exo*-position of the C-5 substituent was confirmed by the fact that *endo*-H5 showed no significant interaction with H7 but did show a cross-peak because of W-coupling to H8-syn. The geminal protons on C8 were identified by vicinal coupling to H7 and W-coupling to H3a-*exo*, respectively. In addition, the ^{13}C-NMR and HSQC spectral data

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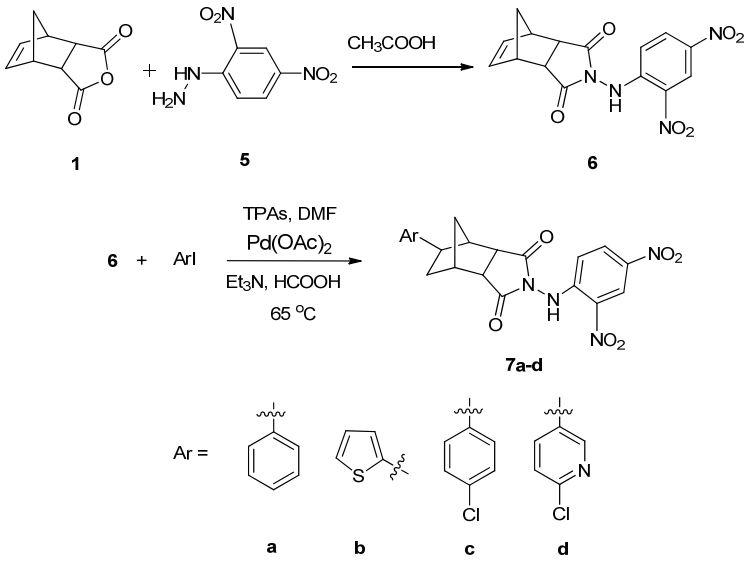
were in agreement with the proposed structures and the mass spectra of all new compounds showed the expected molecular ion peaks. IR spectra of the starting materials and hydroarylation products exhibited strong absorption bands due to the symmetric and asymmetric stretching vibrations of the C=O and NH bonds in the expected areas.



Scheme 2. Synthesis of **7a**–**d**.

CONCLUSIONS

In summary, the palladium(II) acetate catalyzed hydroarylation of readily accessible tricyclic hydrazino imides in the presence of triphenylarsine as ligand was shown to be a stereoselective, versatile and high yield approach to the synthesis of the aryl and heteroaryl derivatives of tricyclic hydrazino imides **4a**–**d** and **7a**–**d**. From the results, it was possible to observe that these compounds may be suitable for effective description of their biological activity.

SUPPLEMENTARY MATERIAL

Characterization data and selected spectra of the synthesized compounds are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

РЕДУКТИВНА ХЕКОВА РЕАКЦИЈА *N*-АРИЛАМИНО-СУПСТИТУИСАНИХ ТРИЦИКЛИЧНИХ ИМИДА

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(3a*R*,4*S*,7*R*,7a*S*)-*rel*-2-[(4-флуор-3-хлорфенил)амино]-3a,4,7,7a-тетрахидро-4,7-метано-1*H*-изоиндол-1,3(2*H*)-дион (**3**), који је припремљен као ново полазно једињење, и (3a*R*,4*S*,7*R*,7a*S*)-*rel*-2-[(2,4-динитрофенил)амино]-3a,4,7,7a- тетрахидро-4,7-метано-1*H*-изоиндол-1,3(2*H*)-дион (**6**) у редуктивној Хековој реакцији са арил- и хетероарил- јодидима, као производе дају *N*-ариламинотрицикличне имиде **4a**–**d** и **7a**–**d**.

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