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FACULTY OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY
GEORGE OLAH DOKTORAL SCHOOL

Synthesis of new isoquinoline derivatives

PhD Thesis

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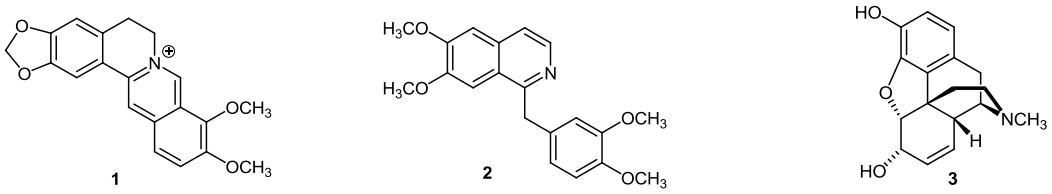
1. Introduction

Numerous isoquinoline derivatives have been described in the literature that play important role both in industry and in medicine. More than 400 members of the naturally occurring isoquinoline-based family of alkaloids are known (*e.g.*; berberine (**1**), papaverine (**2**), morphine (**3**).[1]

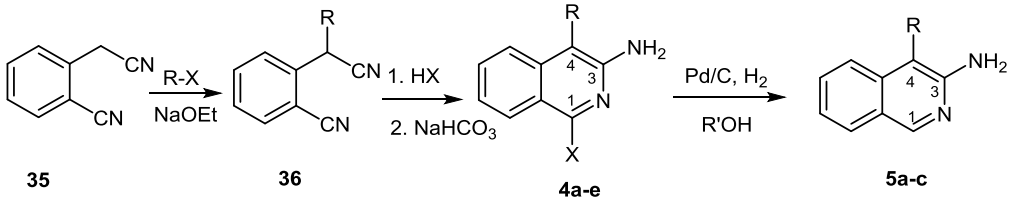


Derivatives of isoquinoline are used as vasodilators, antihypertension agents, anesthetics, antifungal agents, disinfectants in the medical and industrial applications. They are also widely used in the manufacture of dyes and paints.

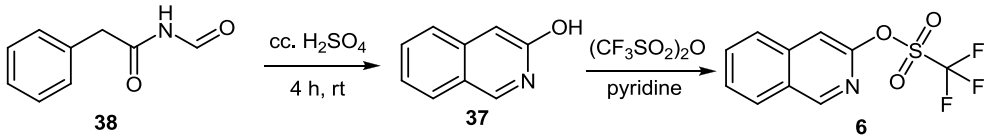
2. Literature background

Our research group has previously dealt with the sythesis of isoquinolines. These researches were focused on the preparation and transformation of 3-subtituted isoquinolines, which is a relatively unexplored area. 1-Bromoisoquinolin-3-amine and its 4-substituted derivatives were synthetized successfully in large scale according to literature procedure.[2]

In the first step, in the synthesis of 4-substituted isoquinolin-3-amine derivatives (**4a-e**), 2-(cyanomethyl)benzonitrile (**35**) was reacted with alkyl halides in the presence of base. 2-(Cyanomethyl)benzonitrile (**35**) and its derivatives (**36**) were cyclized by reaction with HBr or HI. As a result of the ring closure, a halogen atom (X=Br, I) was incorporated in position 1 of isoquinoline (**4a-e**), and hydrogenation of these compounds in the presence of Pd/C afforded isoquinolin-3-amine derivatives (**5a-c**).



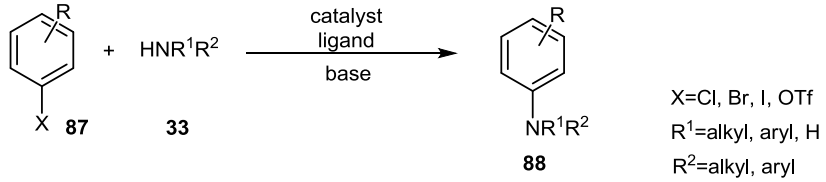
Synthesis of isoquinolin-3-yl trifluoromethanesulfonate has also been elaborated: *N*-formyl-2-phenylacetamide (**38**) was treated with concentrated sulfuric acid to give isoquinolin-3-ol (**37**), which compound was reacted with trifluoromethanesulfonic anhydride in pyridine to yield compound **6**.[3]



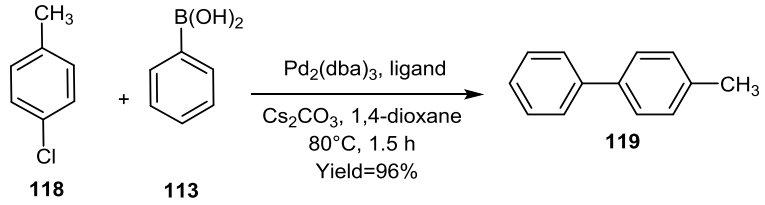
1. Shamma M.: The isoquinoline alkaloids: chemistry and pharmacology, **1972**, New York.
2. Johnson, F.; Nasutavicus, W.A. *J. Orq. Chem*., **1962**, *27*, 3953.
3. Timari, G.; Soos, T.; Hajos, G.; Messmer, A.; Nacsa, J.; Molnar, J. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 2831.

1-Bromoisoquinolin-3-amines (**4a-e**), isoquinolin-3-amines (**5a-c**), and isoquinolin-3-yl trifluoromethanesulfonate (**6**) were used as starting materials in our investigations. Structural modifications in positions 1, 3 and 4 seemed of particular interest. We have also made efforts for the synthesis of new fused ring systems. For this purpose structural modifications of compounds **4-6** have been investigated which allowed construction of novel polycycles.

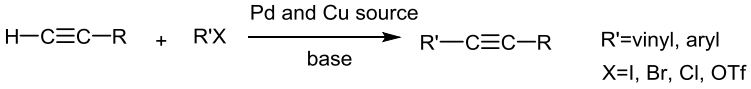
In order to functionalize the isoquinoline ring, different cross-coupling reactions can be applied. The Buchwald-Hartwig amination is used in organic chemistry for the construction of carbon-nitrogen bonds *via* the cross-coupling of amines (**33)** with aryl halides (**87**) to give aniline derivatives (**88**).[4]



Suzuki reaction involves the coupling of an aryl or vinyl boronic acid (**113**) with an aryl, vinyl halide or triflate (**118**). It allows the synthesis of biphenyls (**119**).[5]



The Sonogashira cross-coupling reaction (*Scheme 1*) is used to form carbon-carbon bonds between a terminal alkyne and an aryl or vinyl halide.[6]

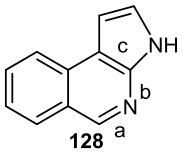


Scheme 1. *General scheme of Sonogashira cross-coupling reactions*

The catalytic systems used in the cross-coupling reactions involve seven factors which can be altered in order to optimize the reaction conditions: substrate, nucleophile partner, Pd source, ligand, base, solvent and temperature.

Our outlined strategy could result in formation of condensed ring systems on the *a,b,c* side of isoquinoline. As a result of our modifications we had the chance to synthesize three different fused ring systems: 3*H*-pyrrolo[2,3-*c*]isoquinoline (**128**), dibenzo[*c,f*][1,8]naphthyridine (**127**), indazolo[3,2-*a*]isoquinoline (**132**). Literature data for the functionalization of these rings sparingly exist.[7,8,9]

4. Guram, A.S.; Buchwald, S.L. *J. Am. Chem. Soc.*, **1994**, *116*, 7901.
5. Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.*, **1979**, *20*, 3437.
6. Sonogashira, K.;Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, **1975**, 4467.
7. Rao, U.N.;Han, X.; Biehl, E. R. *Arkivoc*, **2002**, (*X*), 61.
8. Stanforth, S. P. *J. Het. Chem.*, **1987**, *24*, 531.
9. Blight, B.A.; Camara-Campos, A.; Djurdjevic, S.; Kaller, M.; Leigh, D.A.; McMillan, F.M.; McNab, H.; Slawin, A.M. *J. Am. Chem. Soc.*, **2009**, *131*, 14116.



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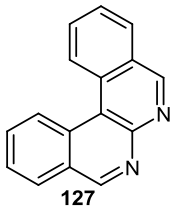

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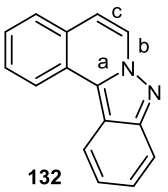

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3. Experimental methods

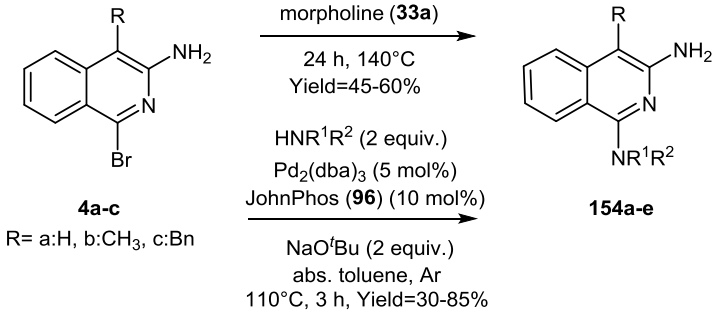
Synthetic organic chemical methods were applied in the course of our work. The progress of the reactions was monitored by thin layer chromatography (TLC).

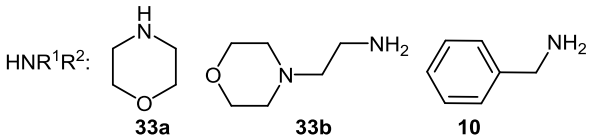
Recrystallization, trituration and flash or column chromatographic methods were applied for purification of the crude products. Identification of the structures was carried out by modern spectroscopic methods (^{1}H, ^{13}C NMR, 2D NMR, IR, and MS) and by elemental analysis. The synthesized crystalline products were also characterized by their melting points.

Argon flow was applied in case of Buchwald-Hartwig cross-coupling reaction to ensure an inert atmosphere and these reactions were carried out in dry solvent. Fluorescence measurements were made on the basis of previous methods.

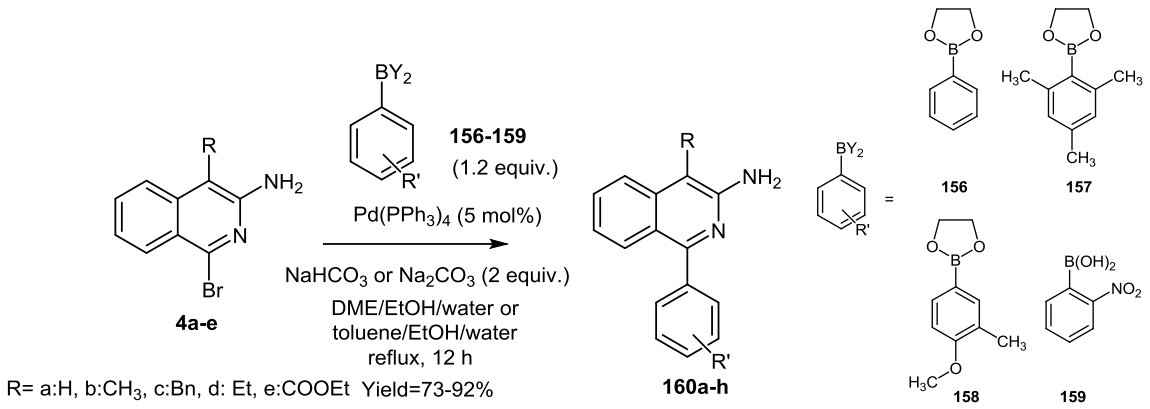
4. New scientific results

In the case of 4-substituted 1-bromoisoquinolin-3-amines, reactions of halogen atom with nucleophilic partners have been carried out easily. Compounds **4a-c** were reacted with morpholine at high temperature for 24 hours and **154a-c** was isolated in moderate yield. To increase the yield and reduce the reaction time, Buchwald-Hartwig cross-coupling condition was used. After optimization of reagents, $Pd_2(dba)_3$ catalyst, JohnPhos (**96**) ligand and NaO^tBu base were applied. With application of this method, morpholine-substituted products (**154a-c**) were synthesized in higher yield, and in the case of primary amines compounds **154d, e** were isolated in moderate yield.





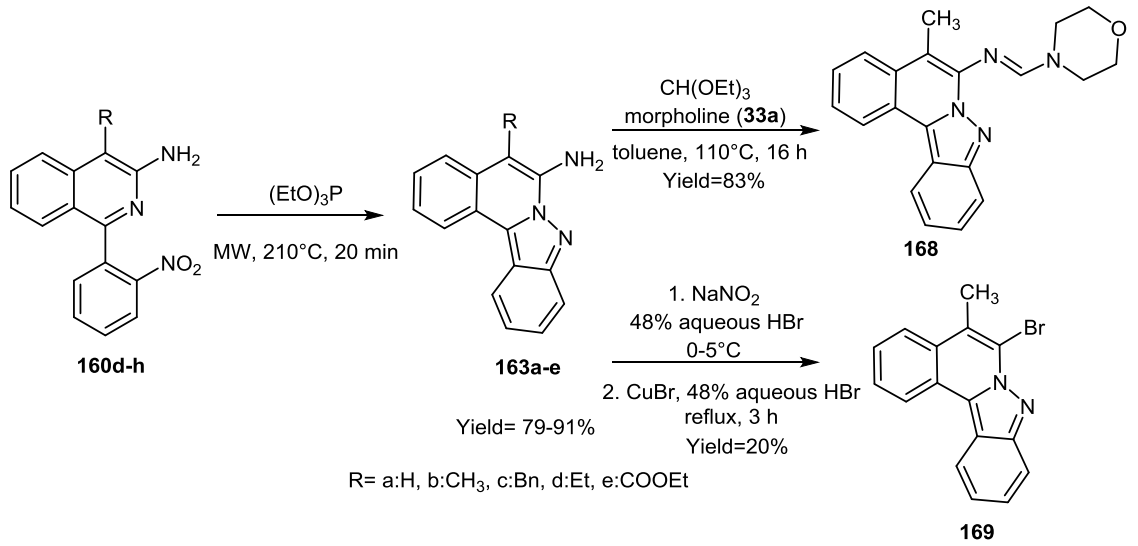
Suzuki cross-coupling reaction was used to form new carbon-carbon bonds in position 1 of isoquinolin-3-amine derivatives. Compounds **154a-e** were reacted with different organic boronic acids (**156-159**) in aqueous mixture of DME/EtOH or toluene/ethanol, in the presence of $Pd(PPh_3)_4$ catalyst, and $NaHCO_3/Na_2CO_3$ base. The products **160a-h** were isolated in high yields. The aromatic phenyl ring of boronic acids contained electron donating and electron withdrawing groups.



We have investigated the cyclization of 1-(2-nitrophenyl)isoquinolin-3-amine derivatives. With retrosynthetic analysis we found that the synthesis of indazolo[3,2-*a*]isoquinolin-6-amines (**163a-e**) is possible *via* Suzuki intermediates (**160d-b**). Investigation of the literature revealed that relatively few derivatives of this heteroaromatic ring system have been published and the described compounds did not include functional groups on the ring other than a halogen atom.[8,10,11,12]

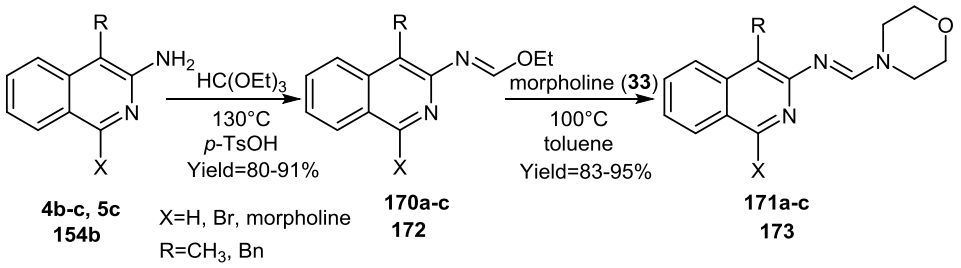
We have found that 1-(2-nitrophenyl)isoquinolin-3-amine derivatives participated in Cadogan cyclization with triethyl-phosphite under microwave irradation (220°C, 20 min) to yield indazolo[3,2-*a*]isoquinolin-3-amines.

Two new derivatives were prepared with the modification of amine group of **163b**. The reaction of **163b** with triethyl orthoformate afforded the amidine compound (**168**) in the presence of morpholine (**33a**) and toluene, whereas diazotation of **163b** in the presence of HBr led to the formation of **169**.

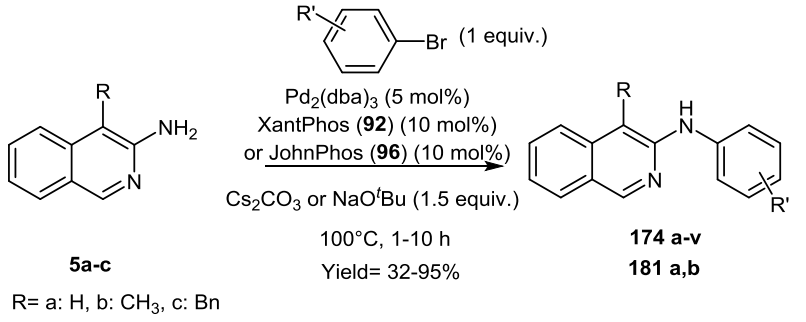


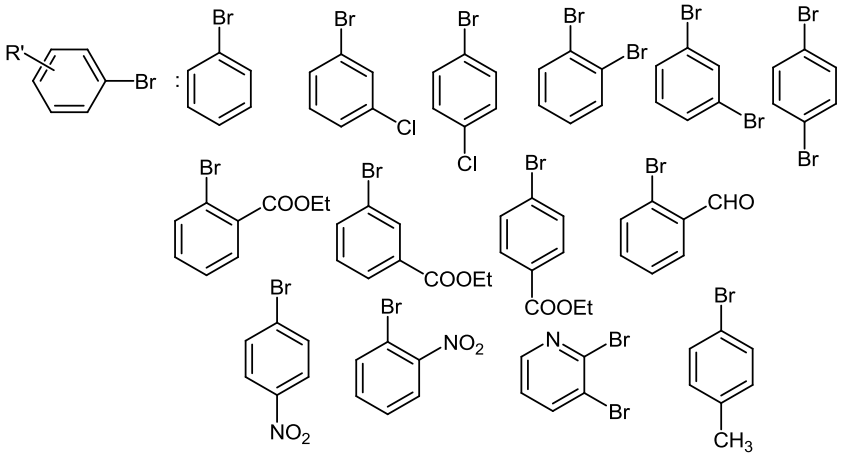
We continued the structural modification of isoquinoline in position 3. With conversion of the amino group we aimed at the synthesis of the earlier unknown formimidate and amidine derivatives. The different primary amines (**4b,c, 5c, 154b**) were treated with triethyl orthoformate to give formimidates (**170a-c, 172)** in good yields. These compounds were reacted with morpholine (**33a**) to give amidines (**171a-c, 173**) in high yields.

10. Stanley, A.L., Stanforth, S.P. *J. Heterocycl. Chem.*, **1994**, *31*, 1399.
11. Qing-Zhong, Z.; Peng, F.; Yu-Feng, L.; Ning, J. *Orq. Lett.*, **2013**, *15*, 4262.
12. Zhao, J.; Wu, C.; Li, P.; Ai, W.; Chen, H.; Wang, C.; Larock, R.C.; Shi, F. *J. Org. Chem*., **2011**, *76*, 6837.

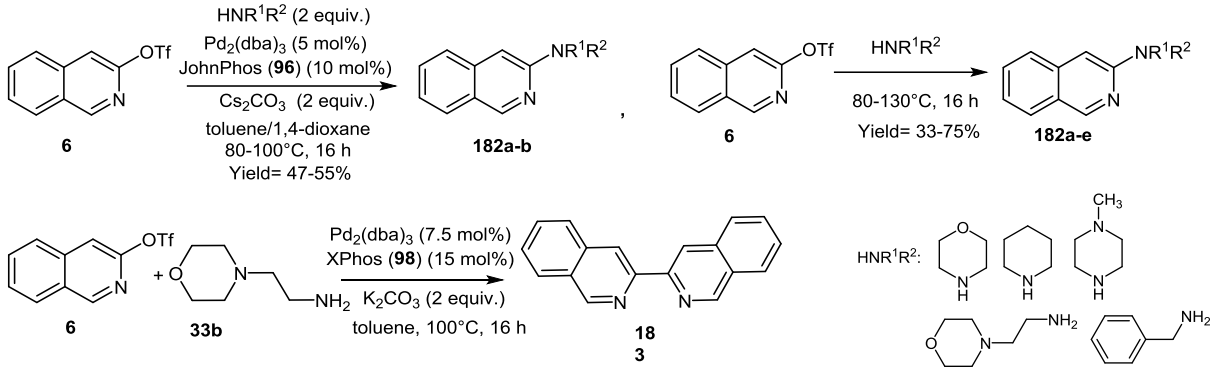


Amino group of **5a-c** derivatives were reacted with variously substituted aryl halides. Buchwald-Hartwig method was used in these reactions, which has been already applied in our earlier work.

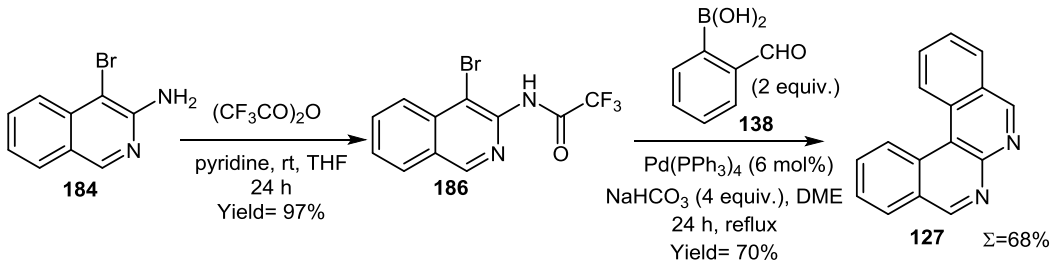




Isoquinolin-3-triflate (**6**) is a highly suitable electrophilic partner in such reactions. The Buchwald-Hartwig cross-coupling reactions with secondary amines took place in acceptable yields (**182a,b**). In case of reactions with secondary amines, no cross-coupling products (**182d,e**) could be isolated, whereas cross-coupling reactions of 2-(morpholin-4-yl)ethan-1-amine and isoquinolin-3-triflate resulted side products only. When the amine reagent was used as a solvent and the reaction was heated, the desired compounds were isolated in good yields in the case of secondary amines, while the reactions of primary amines gave the isoquinoline derivatives in medium yields.



Only one example for synthesis of dibenzo[*c,f*][1,8]naphthyridine (**127**) can be found in the literature[13]: it is a three-step method, the starting material is 4-bromoisoquinoline, gross yield is 58% and in the final step the authors used a special flash vacuum pyrolytic process. Based on our work, the tetracyclic product (**127**) was synthesized starting from 4-bromo-isoquinolin-3-amine in a two-step reaction under simple reaction conditions. When the *N*-protected compound (**186**) was transformed to **127**, the yield was higher and the reaction was cleaner.

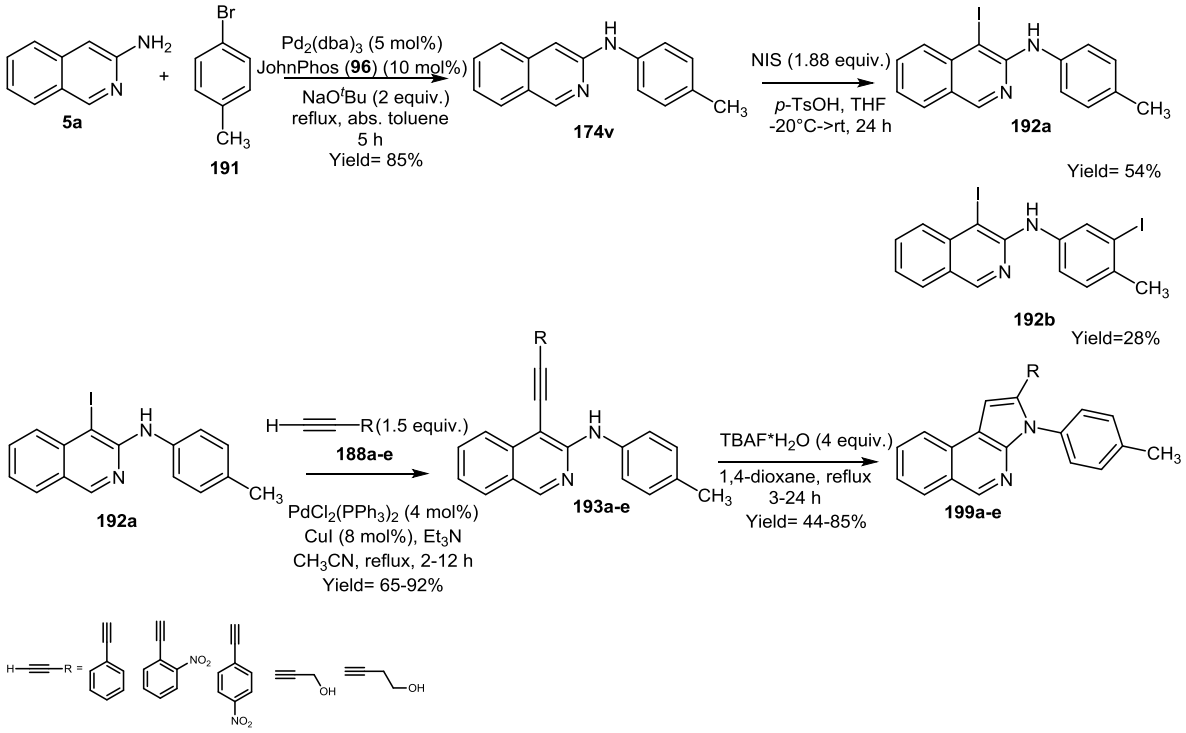


Formation of the 3*H*-pyrrolo[2,3-*c*]isoquinoline ring system was earlier investigated by Biehl and co-workers. Our retrosynthetic analysis revealed that this ring-closed product could be synthesized by starting from an isoquinolin-3-amine intermediate containing an acetylic moiety in position 4. This transformation can be carried out by Sonogashira coupling.

Using Buchwald-Hartwig cross-coupling, isoquinolin-3-amine (**5a**) was reacted with 1-bromo-4-methylbenzene (**191**) to give product (**174v**) in good yield. This compound (**174v)** was subjected to iodination to result in formation of two compounds (**192a,b**). Thus, iodination of the phenyl ring (**192b**) - in *ortho* to the methyl group - was also experienced. Sonogashira coupling of **192a** with various acetylenic compounds (**188a-e**) was carried out succesfully to give 4-ethynyl derivatives (**193a-e**) in the presence of $PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_3CN.

4-Ethynyl derivatives (**193a-e**) were treated with 4 equivalents of TBAF*H_2O reagent,[14] the mixture was refluxed in 1,4-dioxane and the final products (**199a-e**) were obtained in acceptable to excellent yield.

13. Djurdjevic, S.; Leigh, D.A.; McNab, H.; Parsons, S.; Teobaldi, G.; Zerbetto, F. *J. Am. Chem. Soc.*, **2007**, *129*, 476.
14. Hiroya, K.; Jouka, R.; Kameda, M.; Yasuhara, A.; Sakamoto, T. *Tetrahedron*, **2001**, *57*, 9697.



Some of the synthesized compounds were tested by fluorescence measurements. The quantum yields were usually high values (Φ=0,16-0,45) whereas lifetime of the fluorescence (4,6-14,4 ns) corresponded to the expected values.

5. Theses

1. 1-Bromoisoquinolin-3-amine derivatives were reacted with various amines using both Buchwald-Hartwig cross-coupling and thermal conditions, which resulted unknown 1-substituted isoquinolin-3-amine compounds [1].

2. The Suzuki cross-coupling reaction was used successfully to form new carbon-carbon bonds between 1-bromoisoquinolin-3-amine derivatives and different organic boronic acids [4].

3. Syntheses of new indazolo[3,2-*a*]isoquinolin-3-amines were accomplished by using a new method starting from 1-bromoisoquinolin-3-amine derivatives. Amidine and bromo derivatives were prepared by transformation of amino group [4].

4. Buchwald-Hartwig cross coupling method was succesfully applied in reaction of isoquinolin-3-amines and aromatic halides, and new *N*-substituted-phenylisoquinolin-3-amine derivatives were produced [2]. Isoquinolin-3-triflate was reacted with different primary and secondary amines by using thermal and Buchwald-Hartwig cross-coupling conditions; new 3-substituted isoquinolines derivatives were synthesized.

5. A new, more effective synthetic route has been elaborated for preparation of dibenzo[*c*,*f*][1,8]naphtiridine starting from 4-bromoisoquinolin-3-amine.

6. Synthesis of substituted 3*H*-pirrolo[2,3-*c*]isoquinoline ring system was carried out [3].

7. Fluorescence properties of the synthesized compounds were examined in many cases. These derivatives were characterized by basic photophysical parameters [1] [2].

6. Application possibility

Our fluorescence studies revealed that a great number of actively fluorescent compounds can easily be obtained by some simple and well reproducible methods starting from derivatives of isoquinolin-3-amine in high yields. Fluorescent measurement data can be valuable starting points for further photochemical studies. Our elaborated methods for the synthesis of new ring systems may result in formation of many new, potentially biologically active compounds.

7. Publications

7.1. Papers in periodicals

[1] József Balog, Zsuzsanna Riedl, György Hajós, Zsombor Miskolczy, László Biczók: **New fluorescent isoquinoline derivatives**, *Tetrahedron Letters*, **2011**, *52*, 5264-5266.

[2] József Balog, Zsuzsanna Riedl, György Hajós, Zsombor Miskolczy, László Biczók: **Novel fluorescent isoquinoline derivatives obtained *via* Buchwald-Hartwig coupling of isoquinolin-3-amines**, *Arkivoc*, **2012**, *V*, 109-119.

[3] Bharat Dixit, József Balog, Zsuzsanna Riedl, László Drahos, György Hajós: **New approach for the synthesis of 3*H*-pyrrolo[2,3-*c*]isoquinoline derivatives**, *Tetrahedron*, **2012**, *68*, 3560-3565.

[4] József Balog, Zsuzsanna Riedl, György Hajós: **A straightforward synthesis of indazolo[3,2-*a*]isoquinolin-6-amines**, *Tetrahedron Letters*, **2013**, *54*, 5338-5340.

7.2. Oral lectures

1. József Balog, Zsuzsanna Riedl, László Biczók, György Hajós: **Új izokinolin származékok szintézise palládium-katalizált reakciókkal** MTA KK Tudományos Intézeti napok, 2010.

2. József Balog, Zsuzsanna Riedl, György Hajós: **Új izokinolin származékok szintézise palládium-katalizált reakciókkal** MTA KK Kálmán Erika Doktori Konferencia, 2011.

3. József Balog, Zsuzsanna Riedl, György Hajós: **Új izokinolin származékok előállítása Sonogashira kapcsolással** Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2012.

4. József Balog, Zsuzsanna Riedl, György Hajós: **Új izokinolin származékok előállítása Sonogashira kapcsolással** MTA TTK Szerves Kémiai Intézet szemináriuma, Budapest, 2012.

5. József Balog, Zsuzsanna Riedl, György Hajós: **Új izokinolin származékok előállítása** MTA TTK SZKI, Szerves Kémiai Szeminárium 2013.

7.3. Posters

1. József Balog, Zsuzsanna Riedl, László Biczók, György Hajós: **Új fluoreszcens izokinolin származékok szintézise** Vegyészkonferencia és 53. Magyar Spektrokémiai Vándorgyűlés, Hajdúszoboszló, 2010.

2. József Balog, Zsuzsanna Riedl, László Biczók, György Hajós: **Synthesis of new isoquinoline derivatives by palladium catalyzed reactions** 14th Blue Danube Symposium of Heterocyclic Chemistry, Podbanské, 2011.

3. József Balog, Zsuzsanna Riedl, László Biczók, György Hajós: **Synthesis of new isoquinoline derivatives** 15th Blue Danube Symposium of Heterocyclic Chemistry, Olomouc, 2013.