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Selective *N*-alkylation/α-arylation of *N*-heterocycles

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A. INTRODUCTION AND AIMS

The Mannich reaction is an important reaction involving C–C bond formation that is widely used in the syntheses of secondary and tertiary amine derivatives and as a key step in the syntheses of many bioactive molecules and complex natural products. More than one hundred years ago, Mario Betti reported a straightforward synthesis of 1-(α-aminobenzyl)-2-naphthol (the Betti base). The procedure can be interpreted as a modified Mannich reaction (mMR) and the importance of the aminonaphthols prepared via mMRs has recently increased because they have proved to be excellent model compounds for study of the α-arylation/*N*-alkylation of cyclic amines.

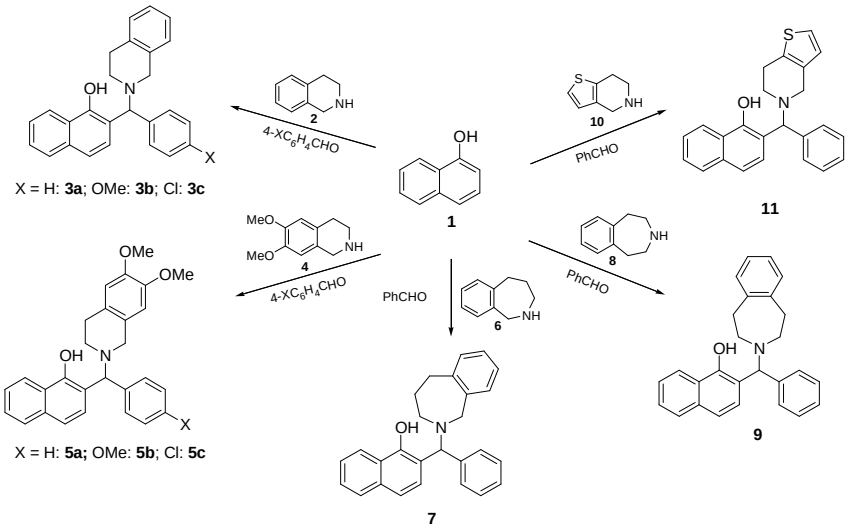
The primary aim of my PhD work was to investigate the application of 1,2,3,4-tetrahydroisoquinoline and analogous secondary amines such as 2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine, 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine and 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole in mMRs. Since recent investigations reflected that by starting from simple cyclic amines both α-arylated and *N*-alkylated products can be formed, a further aim was a systematic study of the mMR starting from tetrahydroisoquinoline, tetrahydrobenzazepine, tetrahydrothieno[3,2-*c*]pyridine or 2,3,4,9-tetrahydropyrido[3,4-*b*]indole by using 1- or 2-naphthol as nucleophile in the presence of benzaldehyde.

The reactions between electron-rich aromatic compounds such as 1- or 2-naphthol and quinolinol or isoquinolinol with 3,4-dihydroisoquinoline, first described by our group, can be interpreted as the aza-Friedel–Crafts alkylation of electron-rich aromatic compounds with cyclic amines containing a polarized double bond (C=N). The synthesis is mostly restricted to the use of 3,4-dihydroisoquinoline as cyclic imine, and the aim of my PhD work was therefore to investigate the possibility of application of other partially saturated cyclic amines such as 4,6-dihydro-3*H*-benz[*c*]azepine, 6,7-dihydrothieno[2,3-*c*]pyridine and 4,9-dihydro-3*H*-β-carboline.

Another goal was to test the scope and limitations of this aza-Friedel–Crafts reaction, starting from the above-mentioned cyclic imines and indole and its derivatives as electron-rich aromatic compounds.

B. RESULTS AND DISCUSSION

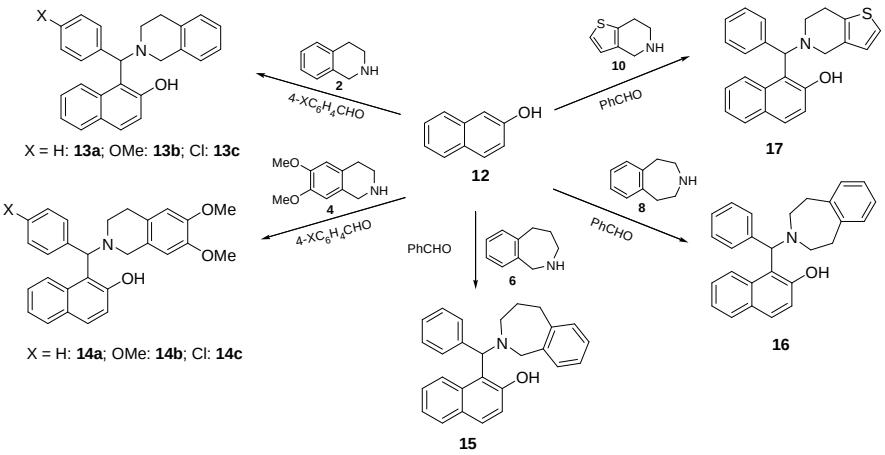
1. Selective *N*-alkylations of tetrahydroisoquinolines, tetrahydrobenz[*d*]azepine, tetrahydrobenz[*c*]azepine and tetrahydrothieno[3,2-*c*]pyridine were achieved by using 1-naphthol and aromatic aldehydes under neat conditions to obtain tertiary aminonaphthols **3a-c**, **5a-c**, **7**, **9** and **11** (Scheme 1).



Scheme 1

The reactions were extended to the synthesis of 1-aminoalkylated 2-naphthol derivatives (**13a-c**, **14a-c**, **15-17**) by mixing 2-naphthol, aromatic aldehydes and the corresponding cyclic amines **2**, **4**, **6**, **8** and **10** according to Scheme 2.

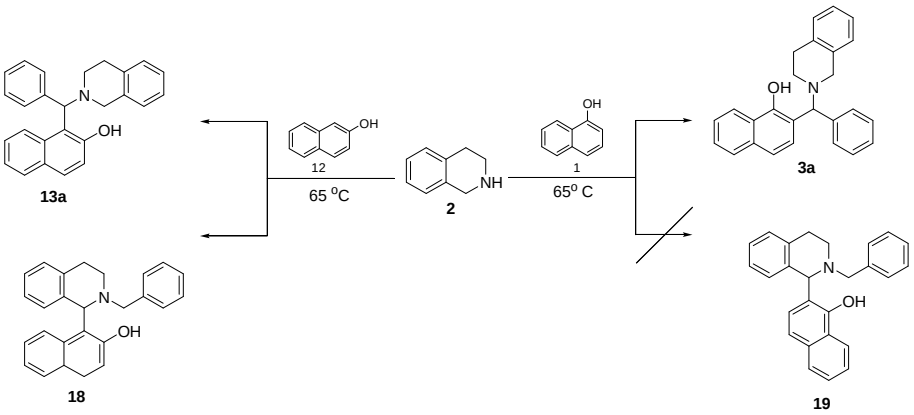
The yields were found to be good with the exception of **13a**, where it was only 46%.



Scheme 2

We conceived that the moderate yield for **13a** can be explained by parallel *N*-alkylation and redox α-arylation, and to prove this a systematic investigation was performed with the reaction of 2-naphthol with 1,2,3,4-tetrahydroisoquinoline in the presence of benzaldehyde at 65 °C. The reaction was followed by comparing the characteristic singlets from the ^{1}H NMR, and it was found that the ratio of **13a:18** is 4:1 during the reaction time (10 h) is 4:1. In contrast, the reaction of 1-naphthol with 1,2,3,4-tetrahydroisoquinoline led to the formation of the *N*-alkylated compound (**3a**) as a single product (Scheme 3).

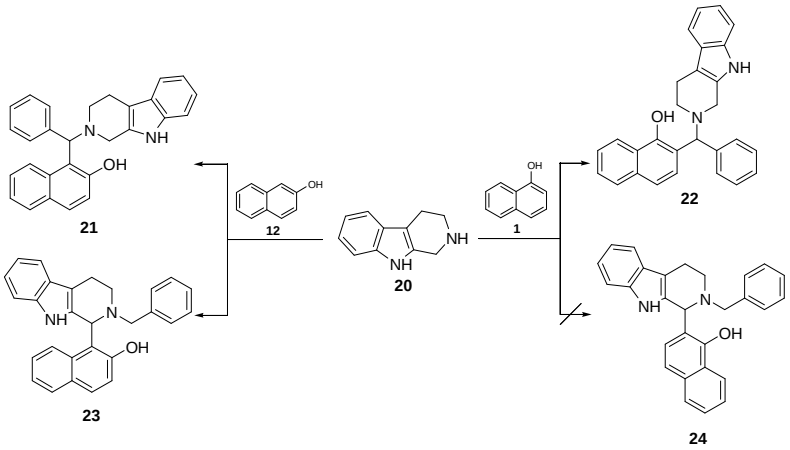
Starting from 2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine, benzaldehyde and 2- or 1-naphthol at 65 °C, formation of the *N*-alkylated product was assumed in each case.



Scheme 3

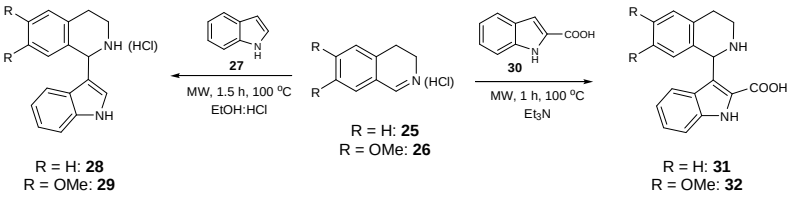
2. The reaction of 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole as secondary cyclic amine with 2- or 1-naphthol as nucleophile in the presence of benzaldehyde led to the formation of 1-((3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(phenyl)methyl)naphthalen-2-ol (**21**) and 2-((3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(phenyl)methyl)naphthalen-1-ol (**22**) (Scheme 4).

The reaction of 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole with 1-naphthol as nucleophile in the presence of benzaldehyde proved to be regioselective for the formation of the *N*-alkylated derivative **22** as a single product. With 2-naphthol as nucleophile, both of the possible *N*-alkylated and α-arylated products **21** and **23** were detected; the ratio was found to depend on the temperature and the heating technique (Scheme 4).



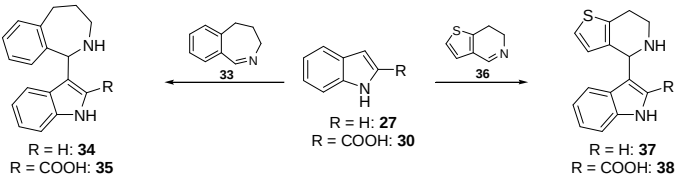
Scheme 4

3. A simple synthesis of 3-(1,2,3,4-tetrahydroisoquinolin-1-yl)indole (**28**) and 3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)indole (**29**) has been developed, involving the reaction of 3,4-dihydroisoquinoline or 6,7-dimethoxy-3,4-dihydroisoquinoline and indole. The reaction was tested by starting from the latter cyclic imines and indole-2-carboxylic acid. The new γ-amino acids (**31**, **32**) prepared in this way were obtained in good yields (Scheme 5).



Scheme 5

4. The synthetic applicability of this aza-Friedel–Crafts reaction was extended to the preparation of 3-(2,3,4,5-tetrahydro-1*H*-benz[*c*]azepin-1-yl)indole (**34**), 3-(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-4-yl)indole (**37**), 3-(2,3,4,5-tetrahydro-1*H*-benz[*c*]azepin-1-yl)indole-2-carboxylic acid (**35**) and 3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-4-yl)indole-2-carboxylic acid (**38**) from cyclic imines such as 4,6-dihydro-3*H*-benz[*c*]azepine and 6,7-dihydrothieno[2,3-*c*]pyridine. All the reactions could be accelerated dramatically by using microwave irradiation (Scheme 6).



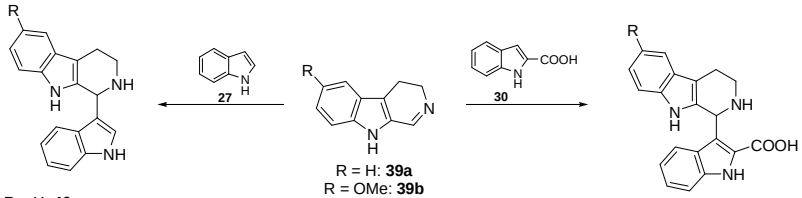
R = H: **34**
R = COOH: **35**

R = H: **27**
R = COOH: **30**

R = H: **37**
R = COOH: **38**

Scheme 6

5. 4,9-Dihydro-3*H*-β-carboline and 6-methoxy-4,9-dihydro-3*H*-β-carboline were subjected to catalyst-free one-pot α-arylation with indole or indole-2-carboxylic acid to prepare 1-(1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**40a**), 1-(1*H*-indol-3-yl)-6-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**40b**), 3-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-1*H*-indole-2-carboxylic acid (**41a**) and 3-(6-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-1*H*-indole-2-carboxylic acid (**41b**) in good yields. The reactions were performed under neat conditions, using microwave agitation (Scheme 7).



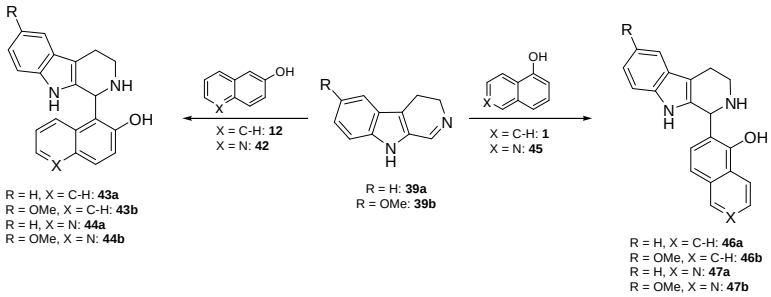
R = H: **40a**
R = OMe: **40b**

R = H: **39a**
R = OMe: **39b**

R = H: **41a**
R = OMe: **41b**

Scheme 7

6. A simple synthesis of 1-hydroxynaphthyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles (**43a**, **43b**, **46a** and **46b**) has been developed, involving the reaction of **39a**, **39b** and 2- or 1-naphthol. The synthetic pathway was extended to the preparation of 5-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)quinolin-6-ol and 6-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)isoquinolin-5-ol derivatives (**44a**, **44b**, **47a** and **47b**) from *N*-containing naphthol analogues (6-quinolinol or 5-isoquinolinol). The yields of the reactions were improved by the use of microwave irradiation, and the reactions were accelerated (Scheme 8).



Scheme 8

C. PUBLICATIONS

I. István Szatmári, **Judit Sas**, Ferenc Fülöp
Catalyst-free coupling of indole derivatives with 3,4-dihydroisoquinoline and related compounds
Tetrahedron Lett., 2013, *54*, 5069-5071. **IF: 2.391**

II. **Judit Sas**, István Szatmári, Ferenc Fülöp
Selective *N*-alkylation of isoquinolines, benzazepines and thienopyridines with aromatic aldehydes and naphthols
Tetrahedron, 2015, *71*, 7216-7221. **IF: 2.641**

III. **Judit Sas**, István Szatmári, Ferenc Fülöp
One-pot α-arylation of β-carboline with indole and naphthol derivatives
Curr. Org. Synth., in press **IF: 2.117**

IV. István Szatmári, **Judit Sas**, Ferenc Fülöp
C-3 functionalization of indole derivatives with isoquinolines
Curr. Org. Chem., submitted

D. CONFERENCE LECTURES

V. **Sas Judit**
Új indolilizokinolin- és indolilbenzazepin-származékok szintézise
XXXV. Kémiai Előadói Napok
Szeged, 2012. október 29-31. Absztr.: 205.

VI. **Sas Judit,** Szatmári István, Ferenc Fülöp
Új indolilizokinolin-, indolilbenzazepin- és indoliltienopiridin-származékok szintézise
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése
Balatonszemes, 2013. június 5-7.

VII. **Judit Sas**, István Szatmári and Ferenc Fülöp
Catalyst-free coupling of indole derivatives with 3,4-dihydroisoquinoline and related compounds
15th Blue Danube Symposium on Heterocyclic Chemistry
1-5th September, 2013 Olomouc, Czech Republic, Abstr.: PO-1

VIII. **Judit Sas**, István Szatmári and Ferenc Fülöp
Catalyst-free coupling of partially unsaturated β-carboline with indole and naphthol derivatives
15th Tetrahedron Symposium, Challenges in Bioorganic and Organic Medicinal Chemistry
24-27th June, 2014 London, UK, Abstr.: P2.35