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Synthesis and transformations of novel precursors via modified Mannich- and *aza*-Friedel-Crafts reaction

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A. INTRODUCTION AND AIMS

The Mannich reaction is one of the most important basic reaction types in organic chemistry for C–C and C–N bond formation. The classical Mannich product arises from the condensation reaction of a compound containing at least one active hydrogen atom with formaldehyde and a secondary amine. A special variation of this latter reaction uses benzaldehyde rather than formaldehyde, ammonia instead of secondary amine and replacing the C–H acid by an electron-rich aromatic compound such as 2-naphthol. The reaction was developed by Mario Betti and the aminonaphthol synthesised in this way is known as Betti base. This modified three-component Mannich reaction (*m*MR) was then extended to apply 1-naphthol, quinolinol or isoquinolinol as electron-rich aromatic compounds.

Mechanistically, the modified *aza*-Friedel–Crafts reaction can be interpreted as a special *m*MR, where electron-rich aromatic compounds such as 1- and 2-naphthol and their *N*-containing analogues are reacted with a wide range of cyclic imines to furnish aminonaphthols, aminoquinolinols or aminoisoquinolinols. The catalyst-free direct coupling of partially saturated cyclic amines and indole as an electron-rich aromatic compound via a modified *aza*-Friedel–Crafts reaction has recently been published by our research group. The reaction has been extended by using indole-2-carboxylic acid as substrate leading to the formation of γ-amino acid derivatives. Most of the methods known already for the synthesis of 3-functionalised 7-azaindole derivatives have applied multistep transformations. Particular efforts have been made to insert other biologically active moieties such as tetrahydroisoquinoline into position 3. In this case, the synthesis of 1-(7-azaindol-3-yl)-1,2,3,4-tetrahydroisoquinoline involved the coupling of 7-azaindole with *N*-protected tetrahydroisoquinoline under iron and copper catalysis. Our first aim was to perform a systematic study of the reactivity of azaindole derivatives (4-, 5-, 6- and 7-azaindole) applying the modified *aza*-Friedel–Crafts reaction using cyclic imine substrates leading to new 3-functionalised azaindole derivatives.

Our next aim was to extend the applicability of the modified *aza*-Friedel–Crafts reaction by using 9-phenanthrol as unique electron-rich aromatic compound and different cyclic

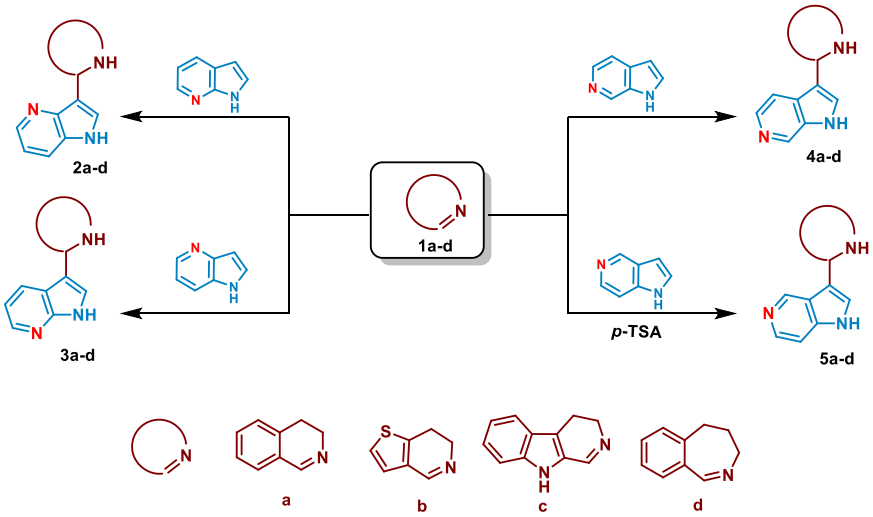
imines such as 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine and 3,4-dihydro-*β*-carboline performing novel aminophenanthrols. As a further aim, the ring-closing ability of the newly synthesised bifunctional aminophenanthrols with formaldehyde was also planned.

The transformation of *ortho*-quinone methide (*o*-QMs) generated from Mannich bases to condensed polyheterocycles is a relatively new area of chemistry. In this case, [4+2] cycloaddition takes place between the *o*-QMs and cyclic imines containing C=N bond. Our research group was the first to develop the reaction of 1-aminoalkyl-2-naphthols with 3,4-dihydroisoquinoline as the cyclic imine. The reaction was then extended starting from 2-aminoalkyl-1-naphthols and other C=N dienophiles preparing naphthoxazino-isoquinoline, -benzazepine and -thienopyridine derivatives. Accordingly, another aim of my PhD work was the synthesis of new 9-phenanthrol and to investigate its reactivity in [4+2] cycloaddition forming new phenanthroxazine derivatives.

To the best of our knowledge, the transformation of bifunctional Mannich bases, which can serve as two different types of *o*-QMs has not been studied. Consequently, our aim was to synthesise new functionalised aminonaphthol derivatives and to study the scope and limitations of the applicability of these aminonaphthols in [4+2] cycloaddition. Furthermore, we wanted to investigate the influence of the relative stability of the formed *o*-QMs and/or the dienophile on the structure of the final products. Our next aim was to synthesise functionalised aminobenzylphenanthrols and to study their reactivity with cyclic imines as novel precursor Mannich bases in [4+2] cycloaddition. Finally, we wanted to explore both the structure and conformational behaviour of the novel polyheterocycles by NMR spectroscopy and theoretical quantum chemical (QC) calculations.

B. RESULTS AND DISCUSSION

1. The modified *aza*-Friedel–Crafts reaction was applied for C-3 substitution of azaindoles. The reactions were carried out by using 3,4-dihydroisoquinoline (**1a**), 6,7-dihydrothieno[3,2-*c*]pyridine (**1b**), 3,4-dihydro-*β*-carboline (**1c**), and 4,5-dihydro-3*H*-benz[*c*]azepine (**1d**) as imine substrates. The transformations of 7-azaindole, 4-azaindole and 6-azaindole led to the formation of new 3-isoquinolyl- (**2a**-**4a**), 3-thieno[3,2-*c*]pyridyl- (**2b**-**4b**), 3-*β*-carbolinyl- (**2c**-**4c**), and 3-benz[*c*]azepinyl-azaindole derivatives (**2d**-**4d**, Scheme 1).

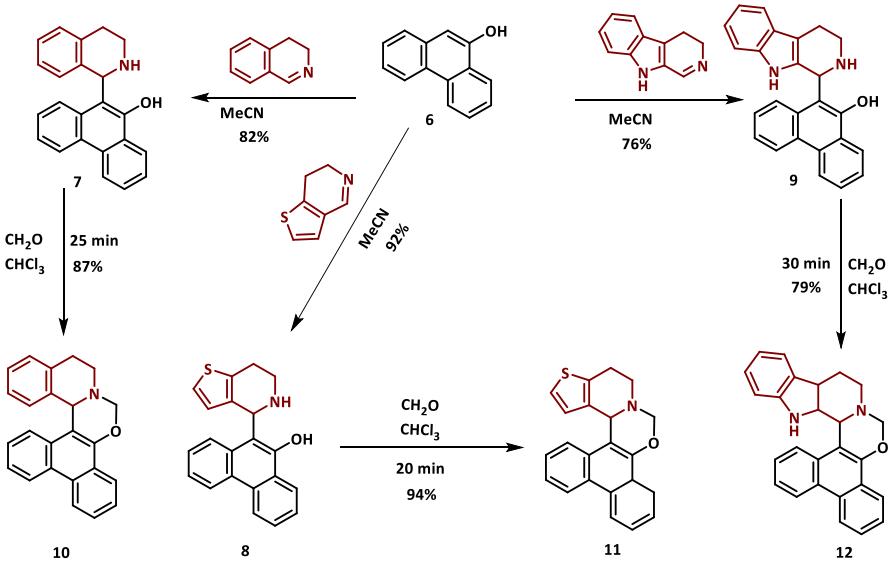


Scheme 1

Starting from 5-azaindole, the modified *aza*-Friedel–Crafts reaction could only be performed by using 10 mol% of *p*-TSA as catalyst (Scheme 1). Systematic correlation was found between the reactivity of azaindoles and their pKa values. This observation allowed to explain why the direct coupling of 5-azaindole underwent only under acidic conditions. Namely, 5-azaindole (pKa=8.42) has the highest basicity in the series of 4-, 5-, 6-, and 7-

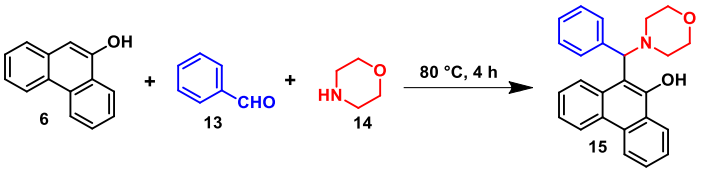
azaindoles. It is important to note that all reactions could be accelerated by using microwave irradiation.

2. 9-Phenanthrol as a unique electron-rich aromatic compound was tested in the modified *aza*-Friedel–Crafts reaction. The application of 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine or 3,4-dihydro-*β*-carboline as cyclic imines led to the formation of the corresponding bifunctional phenanthrol derivatives (**7-9**) that were further transformed to new phenanthr[9,10-*e*][1,3]oxazines (**10-12**, Scheme 2).



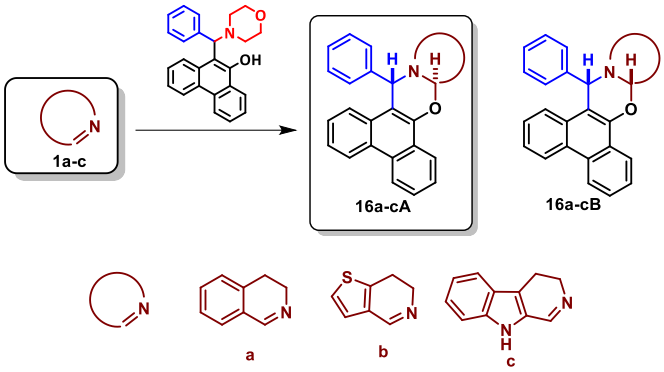
Scheme 2

3. 9-Phenanthrol was aminoalkylated by using morpholine in the presence of benzaldehyde. Aminophenanthrol (**15**, Scheme 3) prepared in this way was reacted with 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine and 3,4-dihydro-*β*-carboline as dienophiles (Scheme 4).



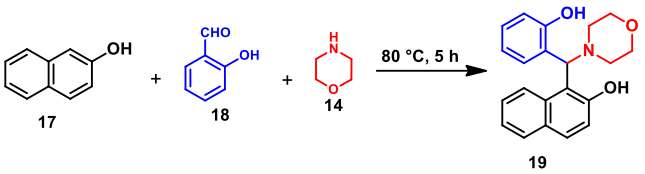
Scheme 3

The reaction was performed in 1,4-dioxane under microwave irradiation at three different temperatures (60°C, 80°C and 100°C). Since during the reaction two new stereogenic centres are generated during the transformation, two epimeric structures (**a** and **b**) can be obtained (Scheme 4). The reactions were monitored by TLC, and the compositions of the crude reaction mixtures were verified by ^{1}H-NMR analysis. All reactions were diastereoselective, and, on the basis of detailed NMR studies, relative configurations were found to be *trans*, based on the detailed NMR studies.



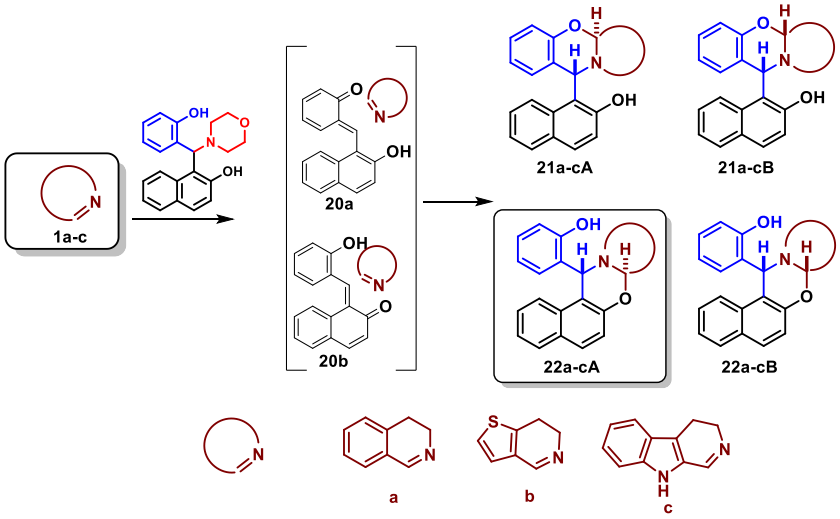
Scheme 4

4. Starting from salicylaldehyde and 2-naphthol in the presence of morpholine, functionalised Mannich base could be synthesised in the presence of morpholine affording (**19**, Scheme 5) two types of *o*-QM intermediates.



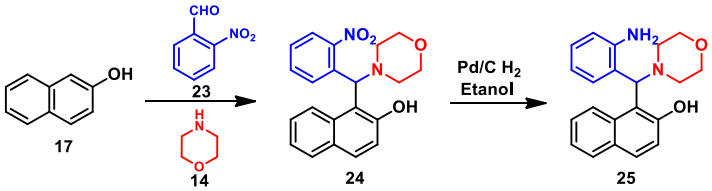
Scheme 5

While the relative stability of the formed *o*-QM intermediates was postulated to influence the formation of the products in subsequent [4+2] cycloaddition, the highly functionalised aminodiols were reacted under heating with different cyclic imines such us 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-c]pyridine, and 3,4-dihydro-*β*-carboline. The latter reactions were found to be diastereo- and regioselective leading to *trans* naphthoxazines (**22a-cA**, Scheme 6). Its structure was proved by DFT computed structures in comparison with the experimental $^{1}H/^{13}C$-NMR spectra, and a detailed analysis of the spatial magnetic properties of the preferred diastereomers.



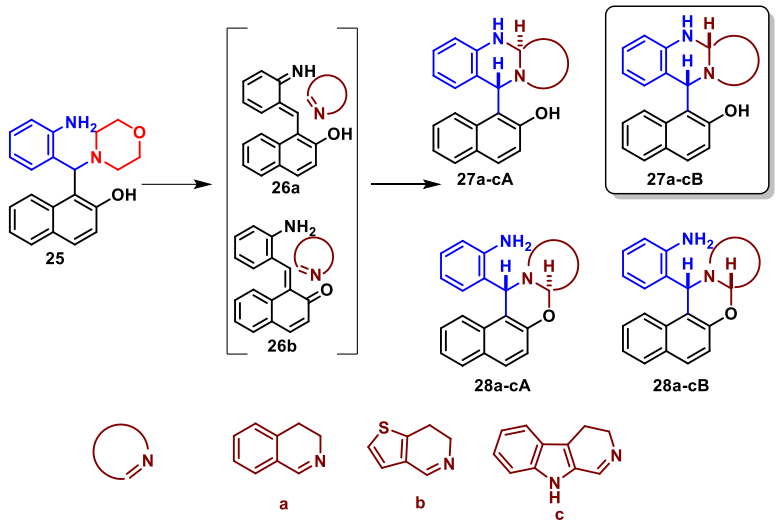
Scheme 6

5. Mannich base **25** was synthesisd as a unique substrate that can form *o*-QM and *aza*-*o*-QM after thermal elimination. Accordingly, 2-naphthol was reacted with morpholine in the presence of 2-nitrobenzaldehyde. After a reaction time of 5 hours at 80 °C, aminonaphthol derivative **24** was isolated (Scheme 7). The next step was the reduction of nitro compound **24** via hydrogenation in the presence of Pd/C. The desired diaminonaphthol (**25**, Scheme 7**)** was isolated after 1 hour reaction time, by crystallization in a yield of 77 %.



Scheme 7

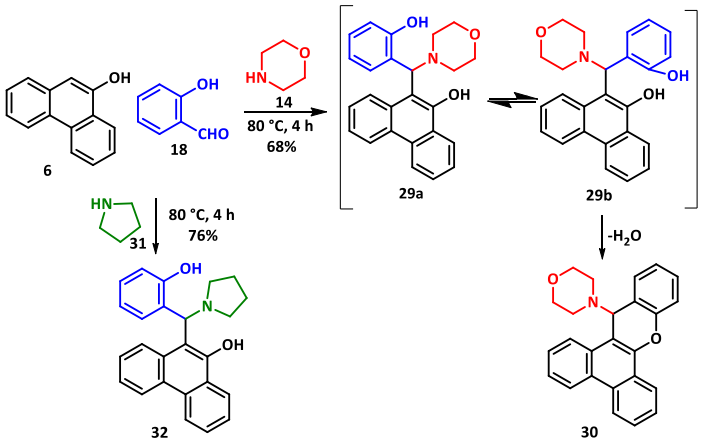
The functionalised diaminonaphthol was tested in [4+2] cycloaddition with cyclic imines. The regio- and diastereoselectivity of the reactions were examined by computational and $^{1}H/^{13}C$ NMR analysis indicating the formation of *cis*-quinazolines as single products (**27a-cB**, Scheme **8**).



Scheme 8

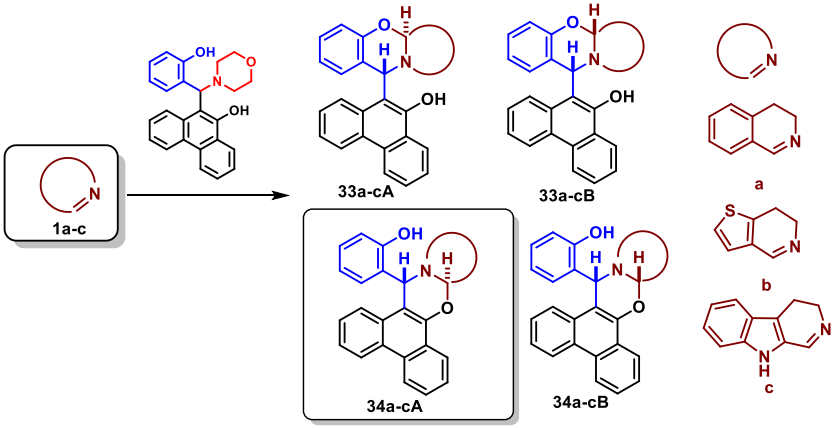
6. The relative stabilities of *o*-QMs/*aza*-*o*-QM were examined by calculating their relative energies. The obtained results (**20b** is more stable than **20a**) supported completely the experimental findings, that naphthoxazines are formed during the cycloaddition reactions when aminodiole **19** was the starting compound. When aminodiol **25** was applied as precursor, the regioselectivity of the reaction was found to be driven by the higher nucleophilicity of the amino group compared with that of the hydroxyl group. During the synthesis and/or transformation of functionalyzed aminonaphthols, unexpected heterocycles (benzo[*a*]xanthen-12-one and benz[*a*]acridine) were obtained. Their formation was explained through formed *o*-QMs and/or *aza*-*o*-QM intermediates and the processes can be recommended as useful synthetic methods for synthesis of benzo[*a*]xanthen-12-ones and benz[*a*]acridines, respectively.

7. The synthesis of functionalised aminophenanthrol **32** could only be achieved by using salicylic aldehyde in the presence of pyrrolidine. Applying morpholine in this modified Mannich reaction led to the formation of 14-morpholinyl-dibenzo[*a*,*c*]xanthene (**30**, Scheme 9).



Scheme 9

Phenanthrol-based bifunctional Mannich product was further tested in [4+2] cycloaddition by using 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine or 3,4-dihydro-*β*-carboline as dienophiles. In all cases the regio- and diastereoselectivity of the reactions were also proved and the detailed NMR analysis adequately supported that the isolated products are the *trans* phenanthroxazines (**34a-34cA**, Scheme 10).



Scheme 10

C. PUBLICATIONS

I. István Szatmári, **Khadija Belasri**, Matthias Heydenreich, Andreas Koch, Erich Kleinpeter and Ferenc Fülöp
Ortho-Quinone Methide Driven Synthesis of New O,N- or N,N-Heterocycles
ChemistryOpen **2019**, *8*, 961-971. DOI: 10.1002/open.201900150 **IF: 2.205**

II. **Khadija Belasri**, Ferenc Fülöp and István Szatmári
Solvent-Free C-3 Coupling of Azaindoles with Cyclic Imines
Molecules **2019**, *24*, 3578. DOI: 10.3390/molecules24193578 **IF: 3.060**

III. **Khadija Belasri**, Matthias Heydenreich, Andreas Koch, Erich Kleinpeter, Ferenc Fülöp and István Szatmári
Solvent-Free C-3 Coupling of Azaindoles with Cyclic Imines
Molecules **2020**, under publication **IF: 3.060**

D. CONFERENCE LECTURES

I. Khadija Belasri, Ferenc Fülöp and István Szatmári:
Ortho-quinonemethid driven synthesis of new O,N- or N,N-heterocycles
A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány előadóülése,
May 15, 2018.

II. Khadija Belasri, István Szatmári, Matthias Heydenreich, Andreas Koch, Erich Kleinpeter and Ferenc Fülöp.
Ortho-quinonemethid driven Synthesis of new O,N- or N,N-heterocycles.
SCT Young Researchers, Paris, France,
February 19-21, 2019.

III. Khadija Belasri, Ferenc Fülöp and István Szatmári:
Catalyst-free coupling of azaindoles with cyclic imines
MTA Alkaloid- és Flavonoidkémiai munkabizottság ülése,
April 11-12, 2019.

IV. Khadija Belasri, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp and István Szatmári:
Synthesis and transformations of functionalyzed aminonaphthol derivatives
Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése Balatonszemes,
June 3-5, 2019.

V. István Szatmári, Khadija Belasri and Ferenc Fülöp.
Catalyst-free coupling of azaindoles with cyclic imines.
20th Tetrahedron Symposium, Bangkok, Thailand,
June 18-21, 2019.

VI. Khadija Belasri, Leila Topal, Ferenc Fülöp and István Szatmári
C-10 substitution of 9-phenanthrol
18th Blue Danube Symposium on Heterocyclic Chemistry, Ljubljana,
September 18-21, 2019.