Ph.D. Thesis

Syntheses and transformations of carbamatoalkynaphthols prepared via modified Mannich reactions

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A. INTRODUCTION AND AIMS

The Mannich reaction is one of the most frequently applied multicomponent reaction in organic chemistry. One of its special variants is the modified three-component Mannich reaction (mMR), in which the electron-rich aromatic compounds are 1- or 2-naphthol.

Since one of the most important areas of application of aminonaphthols prepared via mMRs is the synthesis of new heterocycles, my Ph.D. work focused on the synthesis of novel trifunctional aminonaphthol derivatives. I therefore set out to prepare hydroxynaphthyl-substituted glycines as new α-amino acid derivatives by starting from 1- or 2-naphthol. As the newly prepared aminononaphthol derivatives contain one chiral centre, the separation of their enantiomers was a further aim.

In order to extend the series of naphthoxazino-fused heterocyclic ring systems (naphth[1,2-e][1,3]oxazino[1,3]benzoxazines and naphth[1,2-e][1,3]oxazinoisoquinolines) during my Ph.D. work, the syntheses of naphth[1,2-e][1,3]oxazino[3,4-c]quinazoline and the ring-anellation analogue naphth[1,2-e][1,3]oxazino[3,2-c]quinazoline derivatives were planned. Another goal was the conformational analysis of the newly prepared naphth[1,2-e][1,3]oxazinoquinazolines by means of NMR spectroscopy and accompanying molecular modelling.
B. RESULTS AND DISCUSSION

1. Hydroxynaphthyl-substituted glycine derivatives 2a and 5a were successfully prepared from 2- or 1-naphthol, glyoxylic acid and benzyl carbamate in MeOH via a mMR in the presence of p-TSA, followed by removal of the protecting group. Acidic hydrolysis of 2a and 5a resulted in the expected α-amino acids 3 and 6. The optimized reaction conditions were extended by starting from EtOH. Benzyloxycarbonyl-protected ethyl esters 1b and 4b were isolated in lower yields as compared with those of methyl esters 1a and 4a (Scheme 1).

Reagents, conditions and yields: (i) p-TSA, MeOH, reflux, 26 h, 69%; (ii) p-TSA, EtOH, reflux, 94 h, 34%; (iii) Pd/C, H2, MeOH, r.t., 1 h, HCl–EtOH, 75%; (iv) Pd/C, H2, EtOH, r.t., 1.5 h, HCl–EtOH, 72%; (v) R = Me, 5% aq. HCl, reflux, 2 h, 82%; (vi) MeOH, reflux, 36 h, 53%; (vii) EtOH, reflux, 97 h, 27%; (viii) Pd/C, H2, MeOH, r.t., 1 h, HCl–EtOH, 84%; (ix) Pd/C, H2, EtOH, r.t., 1.5 h, HCl–EtOH, 69%; (x) R = Me, 10% aq. HCl, reflux, 4 h, 88%.

Scheme 1

2. The enantiomers of 2a and 5a were successfully separated on analytical and semi-preparative HPLC columns (Fig. 1). Their absolute configurations were determined by CD analysis supported by TDDFT CD calculations, which revealed that the absolute configuration of the second-eluting enantiomer of 2a was S and of the first-eluting enantiomer of 5a was S.
3. A new, highly functionalized aminonaphthol derivative, 1-(amino(2-aminophenyl) methyl)-2-naphthol (9), was synthetized through two synthetic pathways. The reaction of 2-naphthol, 2-nitrobenzaldehyde and tert-butyl carbamate led to the formation of nitro derivative 7. After the removal of the protecting group and reduction of the NO₂ group, the desired trifunctional aminonaphthol derivative 9 was obtained. The reaction pathway was simplified when tert-butyl carbamate was replaced by benzyl carbamate (Scheme 2).

**Scheme 2**

**Reagents, conditions and yields:** (i) 80 °C, 47 h, 53%; (ii) 99% TFA, r.t., 10 min, 10% Na₂CO₃, 90%; (iii) Pd/C, H₂, MeOH, r.t., 1.5 h, 68%; (iv) 80 °C, 32 h, 76%; (v) Pd/C, H₂, MeOH, r.t., 2 h, 69%.
The aminonaphthol derivative (9) thus obtained was converted in a ring closure reaction with formaldehyde to 10,11-dihydro-8H,15bH-naphth[1,2-e][1,3]oxazino[3,4-c]quinazoline (11). The ring closure reaction of the starting diamine with phosgene and/or benzaldehyde led to the formation of new naphthoxazinoquinazolinone derivatives (12, 14 and 15; Scheme 3).

Reagents, conditions and yields: (i) 2 equiv. 30%aq. CH₂O, CHCl₃, r.t., 1.5 h, 40%; (ii) 0.5 equiv. (COCl)₂, 5 equiv. Na₂CO₃, toluene, r.t., 45 h, 40%; (iii) 1.1 equiv. PhCHO, MeOH, r.t., 24 h, 88%; (iv) 4 equiv. (COCl)₂, 10 equiv. Na₂CO₃, toluene, r.t., 6.5 h, 31%; (v) 4 equiv. (COCl)₂, 10 equiv. Na₂CO₃, toluene, r.t., 8.5 h, 67%.

Scheme 3

4. Products 13a-g obtained via the condensation of 9 with substituted benzaldehydes can potentially furnish five-component tautomeric mixtures in CD₂Cl₂ at 300 K. We succeeded in detecting three of the five components: one epimeric quinazoline (B) and two epimeric naphthoxazines (D and E, Scheme 4). The influence of aryl substituents on the tautomeric composition could be described in terms of the Hammett-Brown parameter (σ⁺). It can be concluded that electron-donating substituents increase the proportion of the quinazoline form (B), while electron-withdrawing substituents prefer the naphthoxazine forms (D and E, Table 1).
Reagents, conditions and yields: (i) \( p-\text{NO}_2\)-PhCHO, MeOH, r.t., 24 h, 13a: 77%; (ii) \( m-\text{Cl}\)-PhCHO, MeOH, r.t., 24 h, 13b: 52%; (iii) \( p-\text{Cl}\)-PhCHO, MeOH, r.t., 24 h, 13c: 63%; (iv) PhCHO, MeOH, r.t., 24 h, 13d: 88%; (v) \( p-\text{Me}\)-PhCHO, MeOH, r.t., 24 h, 13e: 66%; (vi) \( p-\text{OMe}\)-PhCHO, MeOH, r.t., 24 h, 13f: 90%; (vii) \( p-\text{NMe}_2\)-PhCHO, MeOH, r.t., 24 h, 13g: 57%.

Scheme 4

<table>
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<th>( X )</th>
<th>( \sigma^+ )</th>
<th>A (%)</th>
<th>B (%)</th>
<th>C (%)</th>
<th>D (%)</th>
<th>E (%)</th>
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<tr>
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<td>-</td>
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<td>-</td>
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<tr>
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<td>88.6</td>
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5. The syntheses of naph[1,2-e][1,3]oxazino[3,2-c]quinazolin-13-one derivatives (18a and 18c) were achieved by the solvent-free heating of benzyloxycarbonyl-protected intermediates (17a and 17c) with MeONa. Compounds 17a and 17c were synthetized by the reactions of substituted aminonaphthol derivatives (16a and 16c) with benzyl N-(2-formylphenyl)carbamate. This synthetic pathway was extended to the preparation of naphthoxazinoquinazolinones containing different aryl substituents at position 15 (p-Cl-Ph: 18b, p-OMe-Ph: 18d, 1-Nph: 18e, and 2-Nph: 18f). During the reaction of 17b-f with MeONa, the formation of two diastereomers is possible; the diastereomeric ratio was therefore checked by NMR spectroscopy on the crude product. The NOE measurements on purified 18b-f indirectly proved the trans arrangement of H-15 and H-7a (Scheme 5).

\[
\begin{align*}
R & = \text{H;} \quad \text{p-Cl-Ph: b; Ph: c; p-OMe-Ph: d; 1-Nph: e; 2-Nph: f} \\
\end{align*}
\]

Reagents, conditions and yields: (i) Et₃N, EtOH, r.t., 2-4 days; (ii) MeONa, 174 °C, 10 min, 18a: 70%; (iii) MeONa, 179 °C, 20 min, 18b: 61%; (iv) MeONa, 152 °C, 30 min, 18c: 54%; (v) MeONa, 154 °C, 40 min, 18d: 60%; (vi) MeONa, 203 °C, 15 min, 18e: 74%; (vii) MeONa, 165 °C, 20 min, 18f: 51%.

Scheme 5

6. In solution at 300 K, 17a-f can furnish three-component tautomeric mixtures containing diastereomeric ring forms (B and C) besides the chain form (A). When the NMR spectra of 17a-f were recorded in DMSO, the spectra of 17b-d,f revealed the presence of a new
tautomeric chain form ($A^2$) besides the trans ring form $B$ and the chain form $A^1$. The reason for the formation of $A^2$ may be the possibility of conjugation of substituent R (aryl) with the C=N double bond, which is supported by the lack of $A^2$ in 17a and 17e. In 17a there is no aromatic ring, while for 17e the hindered rotation of the 1-naphyl ring restricts the conjugation. The amount of $A^2$ increases, while those of $B$ and $A^1$ decrease as the duration of standing in DMSO becomes longer.

7. Compounds 11, 14 and 18a-f were studied in all the configurations at the DFT level of theory with respect to the preferred conformers and conformational equilibria. The experimental NMR parameters obtained were in general agreement with the theoretical findings. The conformational study of phenyl-10,11-dihydro-8H,15bH-naphth[1,2-e][1,3]oxazino[3,4-c]quinazolin-10-one (14) revealed that the oxazine ring proved to prefer an envelope, and the quinazolone ring a twisted boat conformation; while in naphth[1,2-e][1,3]oxazino[3,2-c]quinazolin-13-ones (18a-f) the oxazine ring prefers a twisted chair conformation and the quinazolone ring is almost planar (Fig. 2).

![Fig. 2. Global minimum-energy structures of 14 and 18c](image)

8. The anisotropic effect of the 15-aryl ring on H-1 was calculated for 18b-f: the excellent agreement of the computational and experimental results proved the stereochemistry of the naphth[1,2-e][1,3]oxazino[3,2-c]quinazolin-13-one derivatives (18b-f) deduced from the theoretical calculations. Fig. 3 illustrates the ring current effects of the phenyl ring in 18c and the 1-naphthyl ring in 18e on H-1.
9. The reactions of 1-(amino(2-aminophenyl)methyl)-2-naphthol (9) and 1-(amino(2-hydroxyphenyl)methyl)-2-naphthol (20) with glutardialdehyde resulted in the formation of piperidine-fused quinazolinonaphthoxazine 19 and benoxazinonaphthoxazine 21, respectively, both in diastereopure form. The NOESY measurements on 19 and 21 revealed the following relative arrangements of H-7a–H-15b–H-10a:

\[ H - 7a \leftrightarrow_{\text{trans}} H - 15b ; H - 10a \leftrightarrow_{\text{cis}} H - 15b ; H - 7a \leftrightarrow_{\text{trans}} H - 10a . \]

Scheme 6

The experimental results were supported by theoretical calculations at the DFT level of theory. These calculations and the H,H coupling pattern of the protons in the flexible part of the piperidine ring moiety highlighted that the configuration with a twisted chair conformation is preferred for both 19 and 21 (Fig. 4).
C. METHODS

The reactions were accomplished on the milligrams or gram scale. The derivatives prepared were purified by recrystallization or column chromatography. The new derivatives were characterized by their physical constants (melting point), mass-spectrometric measurements and elemental analysis. The $^1$H, $^{13}$C, H-COSY, gs-HMQC, gs-1D-HMQC, gs-HMBC and NOESY spectra were recorded in DMSO or in CD$_2$Cl$_2$ solution, in 5 mm tubes, at r.t., on a Bruker Avance DRX400 spectrometer at 400.13 ($^1$H) and 100.61 ($^{13}$C) MHz and on a Bruker Avance III spectrometer at 600.13 ($^1$H) and 150.61 ($^{13}$C) MHz. The enantiomers of hydroxynaphthyl-substituted glycine derivatives were separated by chiral HPLC technique. The \textit{ab initio} calculation were carried out at the B3LYP/6-31G** level of theory with the Gaussian 09 program package.
D. PUBLICATIONS

I. Renáta Csütörtöki, István Szatmári, Attila Mándi, Tibor Kurtán, Ferenc Fülöp
Synthesis of hydroxynaphthyl-substituted α-amino acid derivatives via a modified Mannich reaction
*Synlett* 2011, 1940-1946.  
*IF:* 2.447

II. Renáta Csütörtöki, István Szatmári, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Synthesis and conformational analysis of new napth[1,2-e][1,3]oxazino[3,4-c]quinazoline derivatives
*IF:* 3.011

III. Renáta Csütörtöki, István Szatmári, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Syntheses and conformational analyses of new napth[1,2-e][1,3]oxazino[3,2-c]quinazolin-13-ones
*IF:* 3.011

IV. Renáta Csütörtöki, István Szatmári, Matthias Heydenreich, Andreas Koch, Ines Starke, Ferenc Fülöp, Erich Kleinpeter
Novel piperidine-fused benzoxazino- and quinazolinonaphthoxazines – synthesis and conformational study
*IF:* 3.011

V. Renáta Csütörtöki, István Szatmári, Ferenc Fülöp
Syntheses of amido-, carbamido- and carbamatoalkynaphthols
E. Conference Lectures

VI. Csütörtöki Renáta
Módosított Mannich-reakció alkalmazása új funkcionalizált aminonaftol-származékok szintézisére

VII. Csütörtöki Renáta
Módosított Mannich-reakció alkalmazása α-aminosav-származékok szintézisére

VIII. István Szatmári, Renáta Csütörtöki, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Synthesis and conformational analysis of new naphth[1,2-e][1,3]oxazino[3,4-c]quinazoline derivatives

IX. Ines Starke, Renáta Csütörtöki, Andreas Koch, Erich Kleinpeter, István Szatmári, Ferenc Fülöp
Mass spectrometric behaviour of new naphth[1,2-e][1,3]oxazino[3,2-c]quinazolin-13-ones

X. Renáta Csütörtöki, István Szatmári, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Synthesis and conformational analysis of naphth[1,2-e][1,3]oxazino[3,2-c]quinazolin-13-ones

XI. Csütörtöki Renáta, Szatmári István, Fülöp Ferenc
Naftoxazinnal kondenzált kinazolin-származékok szintézise és konformáció-analizise