SYNTHESIS AND STEREOCHEMISTRY OF NEW NAPHTHOXAZINE DERIVATIVES

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A. Introduction and aims

The Mannich reaction is one of the most frequently applied multicomponent reactions in organic chemistry. One of its special variants is the modified three-component Mannich reaction, in which the electron-rich aromatic compound is 1- or 2-naphthol. In this recent reaction, the character of the nitrogen sources used (ammonia or amine) greatly determines the reaction conditions and the method of isolation of the synthetized Mannich product. One hundred years ago, Mario Betti reported the straightforward synthesis of 1,3-diphenylnaphthoxazine, starting from 2-naphthol, benzaldehyde and methanolic ammonia. Acidic hydrolysis of the intermediate naphthoxazine led to 1-aminobenzyl-2-naphthol. This aminonaphthol became known in the literature as the Betti base, and the protocol as the Betti reaction. On the other hand, the use of non-racemic amines has opened up a new area of application of these enantiopure aminonaphthols as chiral catalysts in enantioselective transformations.

In the Institute of Pharmaceutical Chemistry, University of Szeged, quantitative investigations on the ring-chain tautomeric equilibria of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines, 2,4-diaryl-2,3-dihydro-1*H*-naphth[2,1-*e*][1,3]oxazines and 3-alky-l,1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines led to the first precise mathematical formulae with which to characterize the effects of aryl substituents situated other than between the heteroatoms. There appear to be no published examples of the study of such effects of an alkyl group at the same position of the naphthoxazine model system.

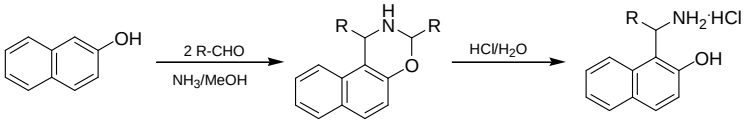
My PhD work focused on the syntheses of 1-naphthylaminomethyl-2-naphthol and 2-naphthylaminomethyl-1-naphthol derivatives and their transformation to different heterocyclic compounds through simple ring-closure reactions.

In the literature on the modified Mannich reaction, only a few examples can be found where benzaldehyde is replaced by some other aromatic aldehyde. We

therefore set out to prepare new primary aminonaphthols starting from 1- or 2-naphthol and 1- or 2-naphthaldehyde and to examine their transformations to heterocyclic compounds.

B. Results

1. 1-(1-Aminoalkyl)-2-naphthols **7-11** were synthetized by the classical Betti reaction: the condensation of 2-naphthol with aliphatic aldehydes in the presence of ammonia, followed by acidic hydrolysis. The overall yield was improved considerably when the solvent was evaporated off after the formation of the intermediate naphthoxazines **2-6** and the residue was directly hydrolysed with hydrochloric acid (*e.g.* for compound **7** the overall yield could be increased from 15% to 95%).

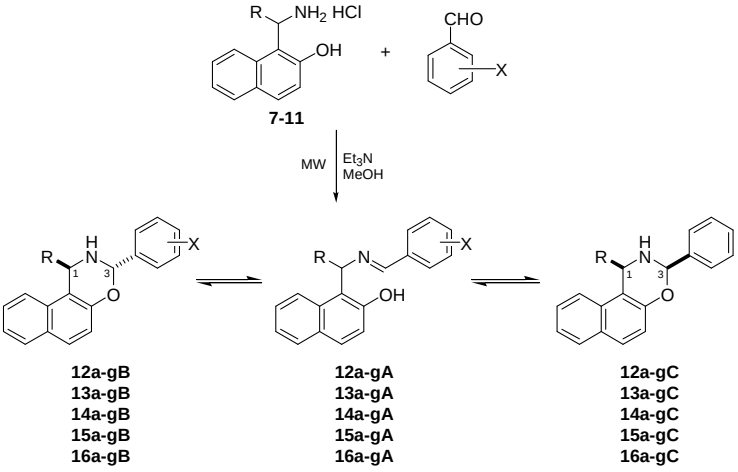


1 **2-6** **7-11**

2, 7: R = Me; **3, 8**: R = Et; **4**, **9**: R = Pr; **5, 10**: R = *i*Pr; **6**, **11**: R = *t*Bu

Scheme 1

2. By the classical condensation of **7-11** with an equivalent amount of aromatic aldehyde in the presence of abs. methanol and triethylamine, the desired products could not be prepared. By using microwave irradiation, 1-alkyl-3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**12-16**) could be isolated as crystalline products, which proved to be three-component (r*t*-o-r*c*) tautomeric mixtures in $CDCl_3$ at 300 K, involving C-3 epimeric naphthoxazines (**B** and **C**) and the open tautomer (**A**).



12a-gB
13a-gB
14a-gB
15a-gB
16a-gB

12a-gA
13a-gA
14a-gA
15a-gA
16a-gA

12a-gC
13a-gC
14a-gC
15a-gC
16a-gC

7, 12: R = Me; **8, 13**: R = Et; **9, 14**: R = Pr; **10, 15**: R = *i*Pr; **11, 16**: R = *t*Bu
a: X = *p*-NO_2; **b**: X = *m*-Cl; **c**: X = *p*-Br; **d**: X = *p*-Cl; **e**: X = H; ***f***: X = *p*-Me; **g**: X = *p*-OMe

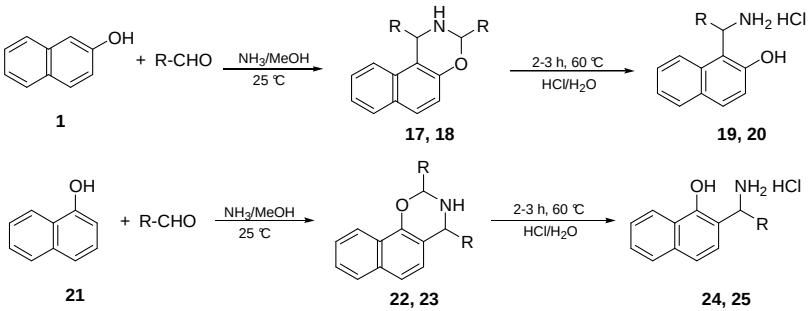
Scheme 2

3. The influence of the alkyl substituent at position 1 on the ring–chain tautomeric equilibria could be described by the Meyer parameter (V^a), and that of the aryl substituent at position 3 by the Hammett–Brown parameter (σ^+). To study the double substituent dependence in the tautomer equilibria, a Hansch-type equation was set up. The parameters of the equation were determined by using the SPSS statistical program. The results of multiple linear regression analysis showed that the equilibrium constants for both the *trans*–chain and *cis*–chain equilibria are influenced by V^a and σ^+. The slopes of the Meyer parameter V^a for the *trans* and *cis* forms displayed a significant difference, which was explained in terms of an alkyl substituent-controlled stereoelectronic effect (anomeric effect) in the *trans* ring form.

4. The anomeric effect was studied by means of quantumchemical calculations. The geometry optimization was carried out by using the Gaussian 03 program package, applying 6-31G* as the basis set. With the same basis in Natural Bond Orbital (NBO) analysis, the delocalization of the nitrogen and oxygen lone pairs was determined. Linear regression analysis of the calculated overlapping energy values adequately

supported that the relative stability difference between the two ring forms is a result of an alkyl substituent-induced quantitative conformational change in the naphthoxazine ring system. Analysis of the ^{13}C chemical shift changes induced by the substituents (SCS) for C-1 and C-3 revealed that, via the alkyl substituent-dependent small conformational changes, the substituent-dependent anomeric effect predominates in the preponderance of the *trans* over the *cis* isomer.

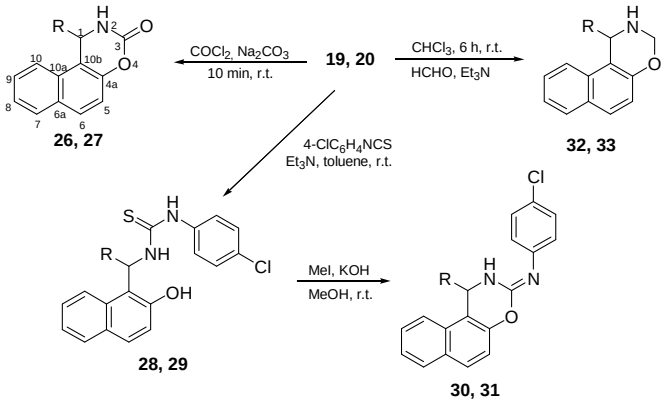
5. Four new aminomethylnaphthols, **19, 20, 24** and **25,** were synthetized in good yields by the condensation of 1- or 2-naphthol with 1- or 2-naphthaldehyde in the presence of ammonia, followed by acidic hydrolysis.



17, 19, 22, 24: R = 2-naphthyl
18, 20, 23, 25: R = 1-naphthyl

Scheme 3

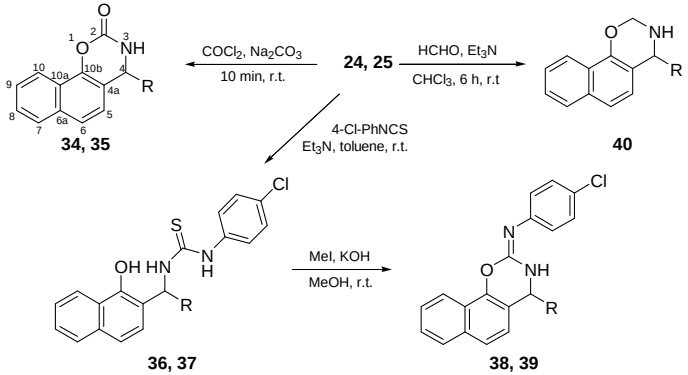
6. In the first stage of the transformations of **19, 20, 24** and **25** to heterocyclic derivatives, an sp^2 carbon (C-3 or C-2) was inserted between the hydroxy and amino groups. The condensations of **19, 20, 24** and **25** with phosgene or 4-chlorophenyl isothiocyanate in two steps led to the desired naphthoxazine derivatives in good yields (40-86%).



26, 28, 30, 32: R = 2-naphthyl
27, 29, 31, 33: R = 1-naphthyl

Scheme 4

7. The reactions of aminonaphthols **19, 20** and **24, 25** with paraformaldehyde under mild conditions (at room temperature for 6 h) gave the corresponding 3- and 2-unsubstituted naphthoxazines **32, 33** and **40** in yields of 37-49% (Schemes 4 and 5).

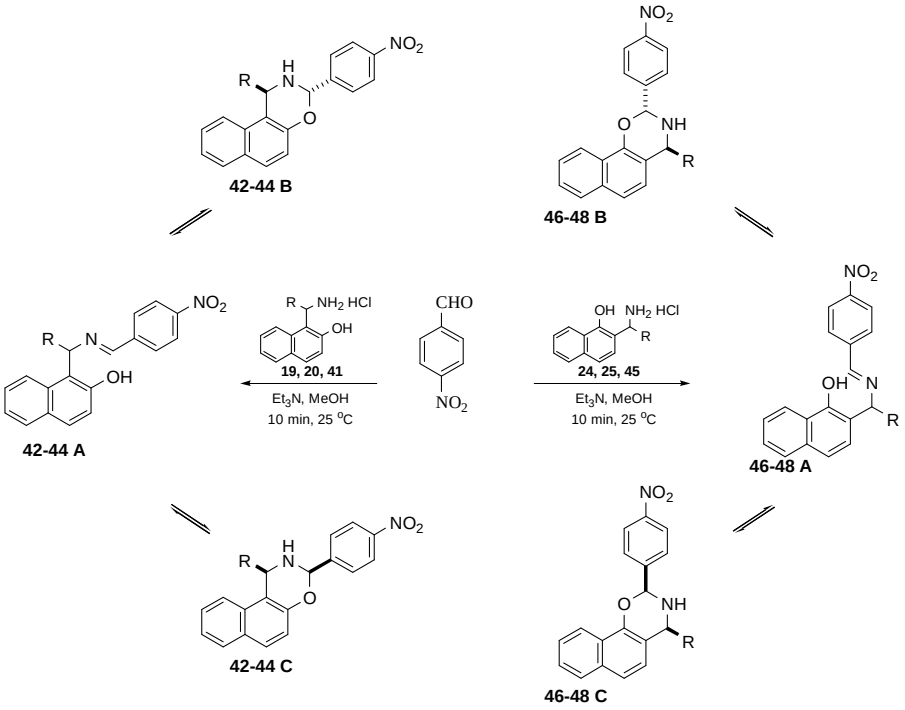


34, 36, 38: R = 2-naphthyl
35, 37, 39, 40: R = 1-naphthyl

Scheme 5

The ring closures of **19, 20, 41** and **24, 25, 45** with 4-nitrobenzaldehyde were accomplished under mild conditions. The products **42-44** and **46-48** were separated from the reaction mixture in good yields (78-84%, Scheme 6). Compounds **42-44** and

46-48 in solution can participate in three-component ring-chain tautomeric equilibria involving the C-3 (**42-44**) or C-2 (**46-48**) epimeric naphthoxazines (**B** and **C**) and the open tautomer (**A**). The tautomeric behaviour (the tautomeric ratios) of **42-44** and **46-48** was found to depend on the steric hindrance of the aromatic rings at position 1 or 4 and by the connecting position of the naphthyl rings at the same positions.



R = 2-naphthyl: **19**, **42**, **24**, **46**; 1-naphthyl: **25**, **47**, **20**, **43**; Ph: **45**, **48**, **41**, **44**

Scheme 6

8. Conformational analysis revealed that the conformation of the oxazine ring moiety depends on the hybridization of the carbon at position 3 or 2. The compounds containing an sp^3 carbon preferred a twisted-chair conformation, whereas the insertion of an sp^2 carbon led to a nearly flat naphthoxazine ring moiety.

C. Publications

Papers related to the thesis

I. Diána Tóth, István Szatmári, Ferenc Fülöp
Substituent Effects in the Ring-Chain Tautomerism of 1-Alkyl-3-arylnaphth-[1,2-*e*][1,3]oxazines
Eur. J. Org. Chem. **2006**, 4664-4669. i.f.: 2.426

II. István Szatmári, Diána Tóth, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Study of the Substituent-influenced Anomeric Effect in the Ring-Chain Tautomerism of 1-Alkyl-3-aryl-naphth[1,2-*e*][1,3]oxazines
Eur.J. Org. Chem. **2006**, 4670-4675. i.f.: 2.426

III. Diána Tóth, István Szatmári, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Synthesis and Conformational Analysis of Naphthoxazine Derivatives
J. Mol. Struct. **2009,** *929*, 58-66. i.f.: 1.486

Other publications

IV. Attila Papp, Diána Tóth, Árpád Molnár
Suzuki-Miyaura Coupling on Heterogeneous Palladium Catalysts
React. Kinet. Catal. Lett. **2006**, *87*, 335-342.i. i.f.: 0.514

V. Anita Sztojkov-Ivanov, Diána Tóth, István Szatmári, Ferenc Fülöp, Antal Péter
High-performance Liquid Chromatographic Enantioseparation of 1-(Aminoalkyl)-2-naphthol Analogs on Polysaccharide-based Chiral Stationary Phases
Chirality **2007,** 374-379. i.f.: 1.976

VI. Nóra Gyémánt, Helga Engi, Zsuzsanna Schelz, István Szatmári, Diána Tóth, Ferenc Fülöp, József Molnár, PAM de Witte
In Vitro and In Vivo Multidrug Resistance Reversal Activity by a Betti-base Derivative of Tylosin
Brit. J. Cancer **2010**, *103*, 178-185. i.f.: 4.846

D. Conference lectures

VII. Diána Tóth, István Szatmári, Ferenc Fülöp: Substituent Effect in the Ring-Chain Tautomerism of 1-Alkyl-3-aryl-naphth[1,2-*e*][1,3]oxazines
1st BBBB Conference on Pharmaceutical Sciences
September 26-28, 2005, Siófok, Abstr.: P-52

VIII. Diána Tóth, István Szatmári, Ferenc Fülöp: Substituent Effect in the Ring-Chain Tautomerism of 1-Alkyl-3-aryl-naphth[1,2-*e*][1,3]oxazines
13th FECHEM Conference on Heterocycles in Bioorganic Chemistry
May 28-31, 2006, Sopron, Abstr.: PO-39

IX. Tóth Diána: Szubsztituenshatás vizsgálata 1-alkil-3-aril-naft[1,2-*e*][1,3]oxazinok gyűrű-lánc tautomériájában
A Szegedi Ifjú Kémikusokért Alapítvány Előadóülése
January 17, 2006, Szeged

X. Szatmári István, Tóth Diána, Gyémánt Nóra, Molnár József, Peter de Witte, Fülöp Ferenc: Betti-reakció alkalmazása új, MDR aktív vegyületek szintézisére
Gyógyszerkémia és Gyógyszertechnológiai Szimpózium 2006
September 18-19, 2006, Eger, Abstr.: p. 4.

XI. Tóth Diána: Szubsztituens-indukált anomer hatás tanulmányozása az 1-alkil-3-aril-naft[1,2-e][1,3]oxazinok gyűrű-lánc tautomériájában
XXIX. Kémiai Előadói Napok
October 31, 2006, Szeged, Abstr.: p. 79.