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Synthesis and detailed conformational analysis of new naphthoxazino[2,3-*a*]benz[*c*]azepine and naphthoxazino[2,3-*a*]thieno[3,2-*c*]pyridine derivatives

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ABSTRACT

New naphth[1,3]oxazino-benzazepines and -thienopyridines were synthesized using a modified Mannich-type synthetic pathway by the reaction of 4,5-dihydro-3*H*-benz[*c*]azepine or 6,7-dihydrothieno[3,2-*c*]pyridine and different substituted aminonaphthols. Reaction conditions were optimized using microwave irradiation, with relatively short reaction times and a temperature of 80 °C. The formation of undesired naphthoxazine by-products made the separation/purification of the products challenging, therefore the reactions were repeated and systematically studied, starting from secondary and tertiary aminonaphthol derivatives, when the isolation of an *ortho*-quinonemethide structure occurred unexpectedly. Scope and limitations of its formation were also investigated. Conformational studies including ring inversion of a selection of the novel polyheterocycles were performed using NMR methods and supplementary DFT modelling.

1. Introduction

The Mannich reaction[1–3] is an important method to form new C–C bonds. This synthetic pathway is widely used in the formation of secondary and tertiary amine derivatives and it is a key step in the syntheses of numerous bioactive molecules and complex natural products.[4,5] In one of the special variations of the modified Mannich reaction (Fig. 1), 1- and 2-naphthols are applied as electron-rich aromatic compounds.[6,7]

The synthesis of new heterocycles is one of the most important areas of application of Mannich bases bearing two or more functional groups.[6,7] In previous papers, the synthesis and conformational studies of naphth[1,2-*e*][1,3]oxazino[3,4-*c*][1,3]benzoxazines,[8,9] naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolines,[10] naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones[11] and naphth[1,2-*e*][1,3]oxazino[4,3-*a*]isoquinoline derivatives[12] were published.

In our earlier studies, an unexpected reaction between 1-α-aminobenzyl-2-naphthol or 1-aminomethyl-2-naphthol and 6,7-dimethoxy-3,4-dihydroisoquinoline led to the formation of 9,10-dimethoxy-naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines under microwave (MW) irradiation.[13] In the latter syntheses, 1-aminomethyl-2-naphthol and substituted 1-aminobenzyl-2-naphthols were applied to prepare naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinoline derivatives. Mechanistically, aminonaphthols were proven to be the initiator of the intermediate for the [4+2] cycloaddition forming the desired pentacycles (Fig. 1). A detailed NMR spectroscopic and theoretical study on the dynamic behavior of these conformationally flexible heterocyclic ring systems confirmed an unexpected dynamic process between the *trans* and *cis* diastereomers.[14] Maycock et al. described an alternative synthesis of naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines *via* the copper-mediated intramolecular α-functionalization of tertiary amines through the oxidative activation of C–H bonds.[15]

Our major aim in this study was to extend this recent reaction, starting from 4,5-dihydro-3*H*-benz[*c*]azepine and 6,7-dihydrothieno[3,2-*c*]pyridine as cyclic imines and 1-aminobenzyl-2-naphthols and 2-aminomethyl-1-naphthols (Fig. 1).[16] In addition, we also studied the obtained conformationally flexible ring systems by means of NMR spectroscopy and complementary theoretical calculations carried out at the B3LYP/6-31 G(d) level of DFT.

In our first experiments, 4,5-dihydro-3*H*-benz[*c*]azepine (**1**) was reacted with aminonaphthol derivative **2a**. The precursor cyclic

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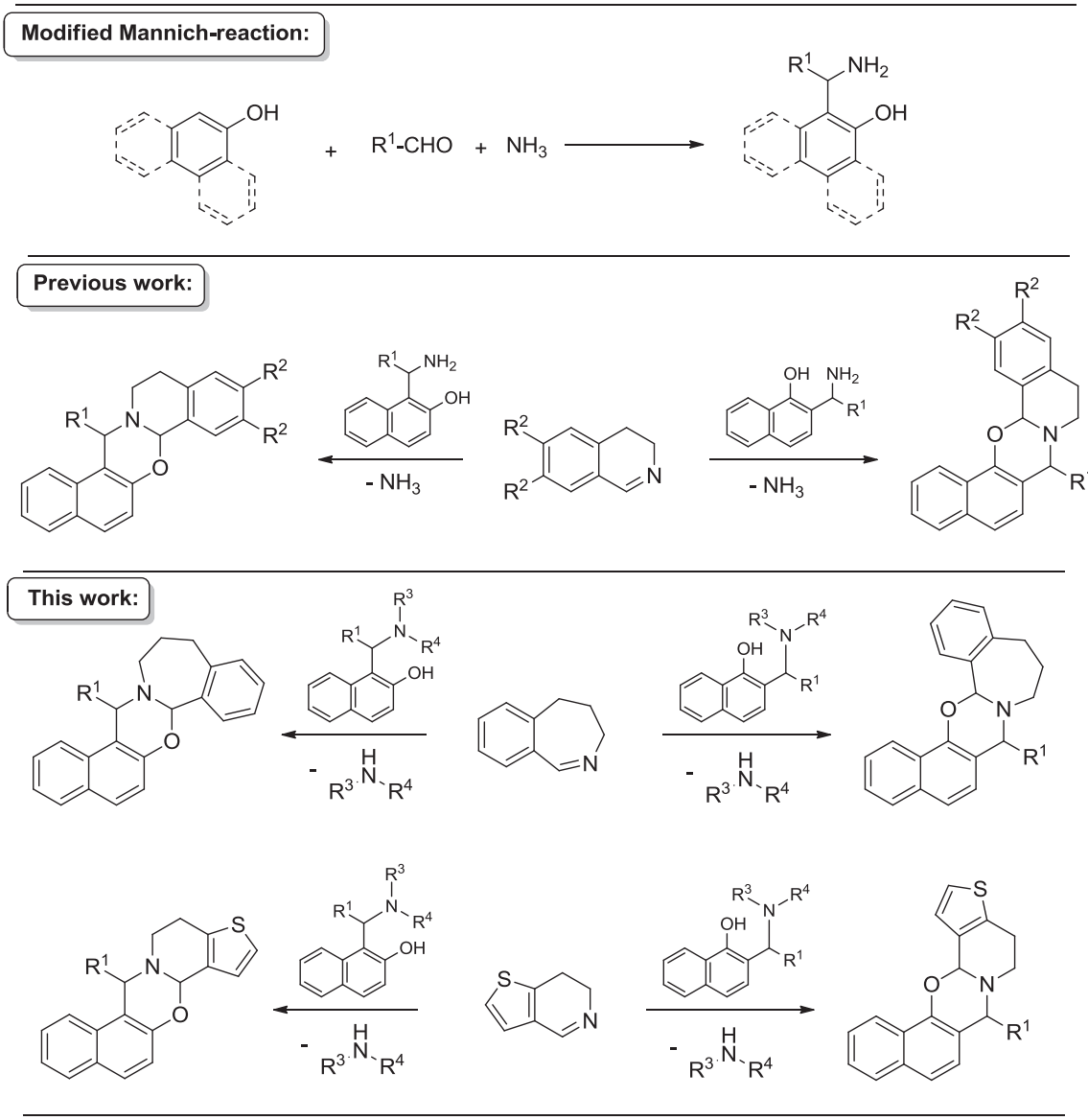

Fig. 1. Summary of modified Mannich reaction and present work.

imine **1** was synthesized using literature methods in four steps starting from α-tetralone.[17,18] The reaction between **1** and **2a** was performed in 1,4-dioxane under microwave irradiation at 80 °C. Crystallization of the product in MeOH resulted in formation of **3a** in a good yield (Table 1).

The reaction of **1** and primary aminonaphthol **2b**, gave undesired compound **4b**. It was presumed to be a side product[19] formed by the reaction of **2b** and benzaldehyde (the decomposition product of **2b**). *Trans*-**4b** and its acyclic imine form were detected by TLC and by NMR spectroscopy using the characteristic H-3 chemical shift at 5.64 ppm and at 8.77 ppm. Purification by column chromatography gave new pentacycle **3b** identified as the *trans* diastereomer **3bA** (Scheme 1) by the NOE interaction between H-7a and the *ortho* H-2′6′ protons of the phenyl group attached to position 16. These conditions were then applied to the reactions starting from **2c** and **2d**. In these two cases, the NMR spectra recorded for the crude products indicated the presence of the desired pentacycles **3c** and **3d** contaminated by naphthoxazines **4c** and **4d**, respectively. The protocol based on column chromatography proved to be successful in the separation of **3c** and **4c**, but failed for the mixture of **3d** and **4d**. Since further attempts (*e.g.* recrystallization) were found to be inefficient to separate the desired naphthoxazine, the development of a new synthetic strategy was needed to isolate **3d** in pure form.

To examine the possibility of the extension of the reaction, 2-aminobenzyl-1-naphthols (**5b-d**) were also applied as reactants in the annulation reactions. Related results and conditions are summarized in Table 1. By-products **7b-d**[20,21] were also detected but the separation process with **7b-d** was successful and new derivatives **6b-d** were isolated in pure form (Scheme 1).

Next, 6,7-dihydrothieno[3,2-*c*]pyridine (**8**) was chosen as a new representative cyclic imine. Its synthesis was achieved *via* a Bischler-Napieralski cyclization starting from 2-thiophen-2-yl-ethylamine.[22] Through the reaction of **8** and **2a**, the formation of the desired unsubstituted naphthoxazine **9a** was obtained in good yield (74%, Table 2).

When the synthesis started from aminoarylnaphthols (**2b-d** or **5b-d**; Scheme 2) the results of the separation process of the pentacycles **9b-d** or **10b-d** from the naphthoxazines **4b-d** or **7b-**