Tetrahedron xxx (2015) 1–6

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Selective *N*-alkylation of isoquinolines, benzazepines and thienopyridines with aromatic aldehydes and naphthols

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ARTICLE INFO

Article history:
Received 22 December 2014
Received in revised form 6 February 2015
Accepted 3 March 2015
Available online xxx

Dedicated to the memory of Professor A. R. Katritzky

Keywords:
Mannich reaction
Aminonaphthol
Tetrahydroisoquinoline
N-alkylation
α-Functionalization

ABSTRACT

The reactions of 1- or 2-naphthol, benzaldehyde or substituted benzaldehydes with tetrahydroisoquinoline, tetrahydrobenzo[*d*]azepine, tetrahydrobenzo[*c*]azepine or tetrahydrothieno[3,2-*c*]pyridine under solvent-free conditions, allowed a series of tertiary aminonaphthols to be prepared. The reactions were accelerated by the use of microwave irradiation, and the yields were also improved. As an exception, the aminoalkylation of 2-naphthol with 1,2,3,4-tetrahydroisoquinoline in the presence of benzaldehyde led to the parallel *N*-alkylation and redox α-arylation of the tetrahydroisoquinoline in a ratio of 4:1. The reaction of 1-naphthol with 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine led to the formation of the *N*-alkylated compound as a single product, illustrating that the reaction route depends on the structures of the cyclic amine and the naphthol.

1. Introduction

The Mannich reaction[1] 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.[2] In the past decade, modified three-component Mannich reactions (mMRs), based on the aminoalkylation of 2- or 1-naphthol as electron-rich aromatic compounds, have become of considerable importance for the formation of aminonaphthols under mild experimental conditions.[3,4] The compounds obtained in this way depend on the starting nitrogen source: the use of primary or secondary amines leads to secondary or tertiary aminonaphthols,[5–10] while when ammonia is used, primary aminonaphthols are obtained.[11–15]

In view of the two or more functional groups in the aminonaphthols, one of the most important areas of application is the synthesis of new heterocycles,[3,4] while enantioenriched aminonaphthol derivatives have been successfully applied in enantioselective transformations.[3,4] 1-((2-Hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-ol derivatives were earlier designed and synthetized as novel selective ostrogen receptor modulators,[16,17] while 1-[(6-halo- or 4-methylbenzo[*d*]thiazol-2-ylamino)phenylmethyl]naphthalen-2-ol derivatives and 5-[(6-halo- or 4-methylbenzo[*d*]thiazol-2-ylamino) phenylmethyl]quinolin-6-ol derivatives were found to exert repellent, insecticidal and larvicidal activity against the mosquito *Anopheles arabiensis*.[18]

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.[19–21] When pyrrolidine was aminoalkylated with electron-rich aromatic compounds in the presence of aromatic aldehydes, the two possible main products, i.e. α-arylated or *N*-alkylated, could be isolated only if the aldehyde component was added extremely slow to the reaction mixture containing acid as catalyst. It was also demonstrated that 2-naphthol can be sufficiently acidic to promote the required tautomerization.[20] This process, starting from 1,2,3,4-tetrahydroisoquinoline as substrate, can theoretically lead to the formation of the regioisomeric tertiary aminonaphthols (***A*** or ***B***) according to Scheme 1, where HNu is an electron-rich aromatic compound such as 2- or 1-naphthol. Our present primary aim was to investigate the application of 1,2,3,4-tetrahydroisoquinoline and analogous secondary amines such as 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine in mMRs. A further aim was a systematic investigation of the α-arylation/

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http://dx.doi.org/10.1016/j.tet.2015.03.011
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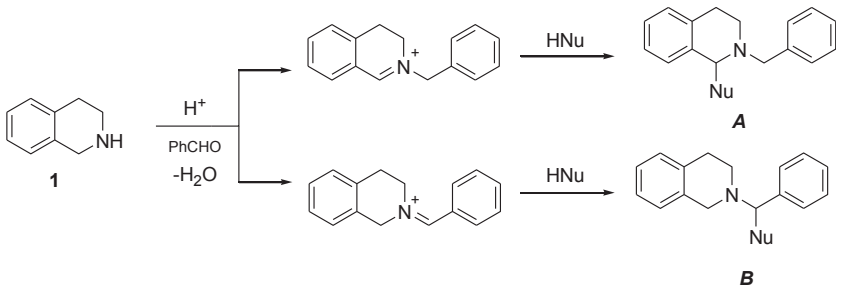


Scheme 1. Reaction pathway for the formation of the possible α-arylated (***A***) and *N*-alkylated (***B***) products starting from tetrahydroisoquinoline (**1**) (HNu=nucleophile).

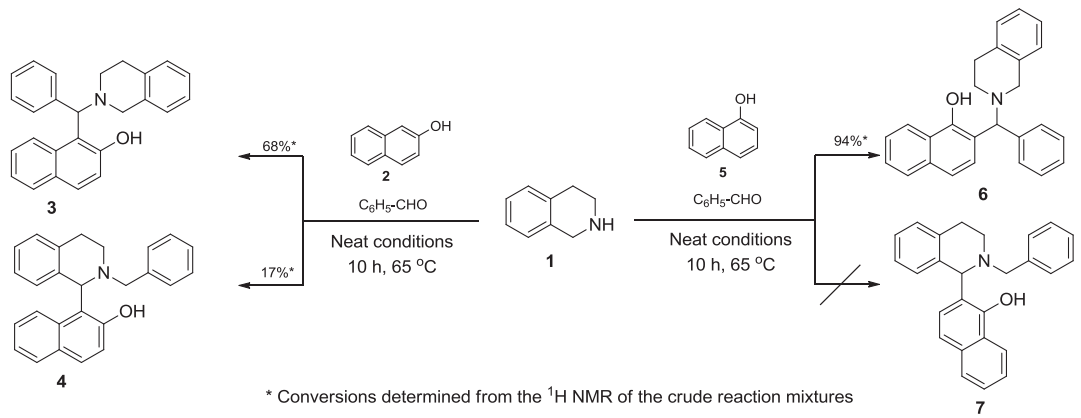
N-alkylation process starting from tetrahydroisoquinoline, tetrahydrobenzazepine or tetrahydrothieno[3,2-*c*]pyridine by using 2- or 1-naphthol as nucleophile in the presence of benzaldehyde.

2. Results and discussion

First, 1,2,3,4-tetrahydroisoquinoline (**1**), 2-naphthol (**2**) and benzaldehyde were reacted under neat conditions at 65 °C. After a reaction time of 4 h, the desired 1-[(3,4-dihydro-1*H*-isoquinolin-2-yl)phenylmethyl]naphthalen-2-ol (**3**, Scheme 2) was isolated by crystallization with MeOH. Since the yield of the reaction was only 28%, the reaction was repeated under microwave (MW) irradiation at 65 °C. After a relatively long reaction time (1.5 h), the ^{1}H NMR spectra of the crude reaction mixture did not reveal the formation of **3**. The synthesis of **3** was earlier performed[22] by refluxing **2**, 1,2,3,4-tetrahydroisoquinoline (**1**) and benzaldehyde in ethanol for 12 h, **3** being isolated as a 'yellow gummy solid' in a yield of 78%.[22] However when we attempted to repeat this under the same reaction conditions, the ^{1}H NMR spectra of the crude product indicated that, the desired product **3** was formed in only trace amounts.

product formed, **3**:**4**, was found to be constant (4:1) throughout reaction (Scheme 2).

To extend this mMR, 1-naphthol (**5**) was reacted with 1,2,3,4-tetrahydroisoquinoline (**1**) in the presence of benzaldehyde, when the possible products obtained by α-arylation/*N*-alkylation of **1** were **6** and **7** (Scheme 2). For a systematic study of this reaction, the *N*-alkylated product 2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-1-ol (**7**) was synthetized from 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-1-ol[23] and benzyl bromide. 1-Naphthol (**5**), 1,2,3,4-tetrahydroisoquinoline (**1**) and benzaldehyde were reacted under neat conditions, by heating at 65 °C, or under MW irradiation at the same temperature. The presence of the possible products (**6** and **7**) was followed by NMR spectroscopy, with a comparison of the relative intensities of the characteristic singlets of **6** and **7** in the crude product. Interestingly, in contrast with our expectations, the signals of the crude product indicated only the formation of **6** when classical heating was applied at 65 °C (Scheme 2). This tendency seemed to be independent of the reaction conditions (classical or MW heating): even after relatively short reaction times (1.5 h on classical heating; 0.5 h on MW) both conditions, led to the formation of **6** in excellent yields.



Scheme 2. Reaction of **1** with 2- or 1-naphthol in the presence of benzaldehyde.

In the above experiments, the possibility of formation of the α-arylated product **4** was not taken into account. For a systematic investigation of this reaction, **4** was synthetized from 1-(1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-2-ol[23] and benzyl bromide on the basis of the literature process.[24] 2-Naphthol (**2**), 1,2,3,4-tetrahydroisoquinoline (**1**) and benzaldehyde were reacted under neat conditions at 65 °C. The formation of the possible products (**3** and **4**) and the conversion of the reaction were followed by ^{1}H NMR spectroscopy at different reaction times up to 10 h. The ratio of the

The series of 2-substituted 1-naphthol analogs was extended by using different 4-substituted benzaldehydes such as 4-methoxybenzaldehyde or 4-chlorobenzaldehyde leading to, **8a** and **8b** (Scheme 3), while 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**9**) was tested as substrate with 1-naphthol and benzaldehyde or 4-substituted benzaldehydes, leading to **10a**–**c** (Scheme 3).

To test the scope and limitations of the reaction, 1-naphthol was reacted with other secondary cyclic amines, such as 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (**11**), 2,3,4,5-tetrahydro-1*H*-benzo

Please cite this article in press as: Sas, J.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.03.011