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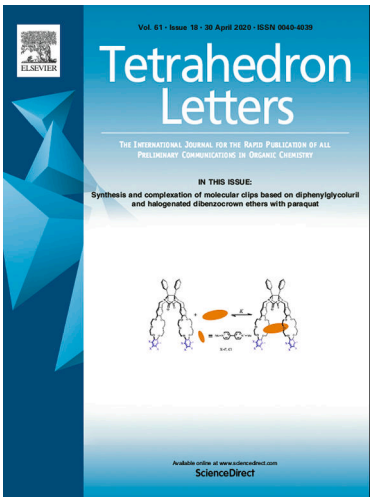

Synthetic Approaches to Tetrahydro-2,7- and -1,6-naphthyridines

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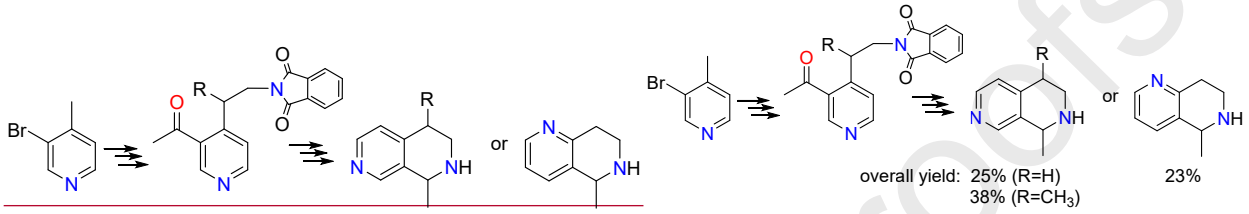

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Synthetic Approaches to Tetrahydro-2,7- and -1,6-naphthyridines

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ABSTRACT

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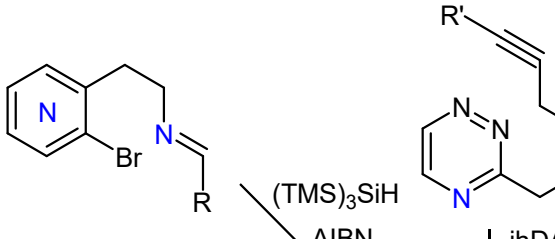
Three new tetrahydronaphthyridines were prepared starting from readily available 3-bromopicolines. The key step of the proposed strategy consists of reduction of the imine ~~that was~~ prepared by intramolecular reaction of the acyl and amine groups. The amine group was introduced *via* deprotonation of the methyl group in bromopicoline, its reaction with dimethylcarbonate, reduction to the corresponding alcohol and Mitsunobu reaction with phthalamide. The acyl group was placed at the bromine position *via* the Stille cross-coupling reaction of tributyl(1-ethoxyvinyl)stannane followed by hydrolysis. The proposed chemical sequence allowed the multigram preparation of tetrahydro-2,7- and 1,6-naphthyridines.

1. Introduction

Partially saturated bicyclic heterocycles are utilized ~~successfully~~ in drug discovery because ~~as~~ they are structurally more complex molecules~~.~~[1] and allow the study of increased ~~They allow studying more~~ diverse chemical space. Moreover, ~~the~~ compounds with a~~the~~ greater fraction of sp^3 centers also tend to be less toxic.[2] Various regioisomeric tetrahydronaphthyridines are the requisite bicyclic saturated heterocycles, but ~~they are hardly accessible. There are a~~ few reliable synthetic approaches have been reported~~to tetrahydronaphthyridines~~ (Scheme 1).

Diverse tetrahydronaphthyridines were prepared *via* a formal Pictet–Spengler reaction of electron-poor pyridines of type **A**.[3] The key step of the method is radical addition to imines using different radical sources and reaction conditions. The method gives the best results for 1,7-tetrahydronaphthyridines since 2-pyridyl radicals are more stable compared to the 3- and 4 – pyridyl radicals. Nevertheless, other isomers such as 1,6- and 2,7-tetrahydronaphthyridines were also prepared, albeit in lower yields. Predictably, better results were achieved with aromatic and heterocyclic aldehydes because alkylimines are less stable. Various 1,5-, 1,6- and 1,8-tetrahydronaphthyridines were prepared *via* an inverse-electron demand hetero-Diels–Alder (ihDA)/retro-Diels–Alder (rDA) sequence in which 1,2,4-triazines **B** acted as electron deficient 4π-components. This sequence gives access to diversely substituted tetrahydronaphthyridines, but it requires less accessible starting materials.[4–8] 2,6-__and 2,7-Tetrahydronaphthyridines were synthesized starting from the appropriately substituted bromoformylpyridines **C**. Addition of arylmagnesium bromide to the aldehydes and Heck coupling of the arylbromides with *N*-vinylphthalimide gave alcohols. Hydrogenation of the double bonds followed by oxidation of the alcohols to ketones gave compounds **C1**. Cleavage of the phthalimides with hydrazine afforded transient primary amines, which subsequently cyclized to ketimines. The ketimines were then reduced with sodium borohydride to give the target tetrahydronaphthyridines.[9] A total asymmetric synthesis of the tetrahydronaphthyridine alkaloid (-)-normalindine was accomplished *via* the addition of a laterally metalated 4-methyl-3-cyanopyridine **D** to a sulfinimine as the key step.[10] A route to 5,6,7,8-tetrahydro-1,6-naphthyridines and related heterocycles was developed using microwave-promoted, Co-catalyzed [2+2+2] cyclizations of compounds **E**. Both intra- and intermolecular approaches were shown to work well.[11] 1,6-Naphthyridinium salts **F** were used to prepare various substituted tetrahydronaphthyridines *via* reduction.[12,13] This approach was used for synthesis of blockers of canonical transient receptor potential channels.[14] A series of tetrahydro-1,6-naphthyridine derivatives were recently described as potential anticancer agents. The key step was the cyclization of compounds of type **G**.[15] Although, the above-mentioned methods allow the synthesis of various terahydronaphthyridine derivatives, it is clear that the search for new convenient methods is a worthwhile task.

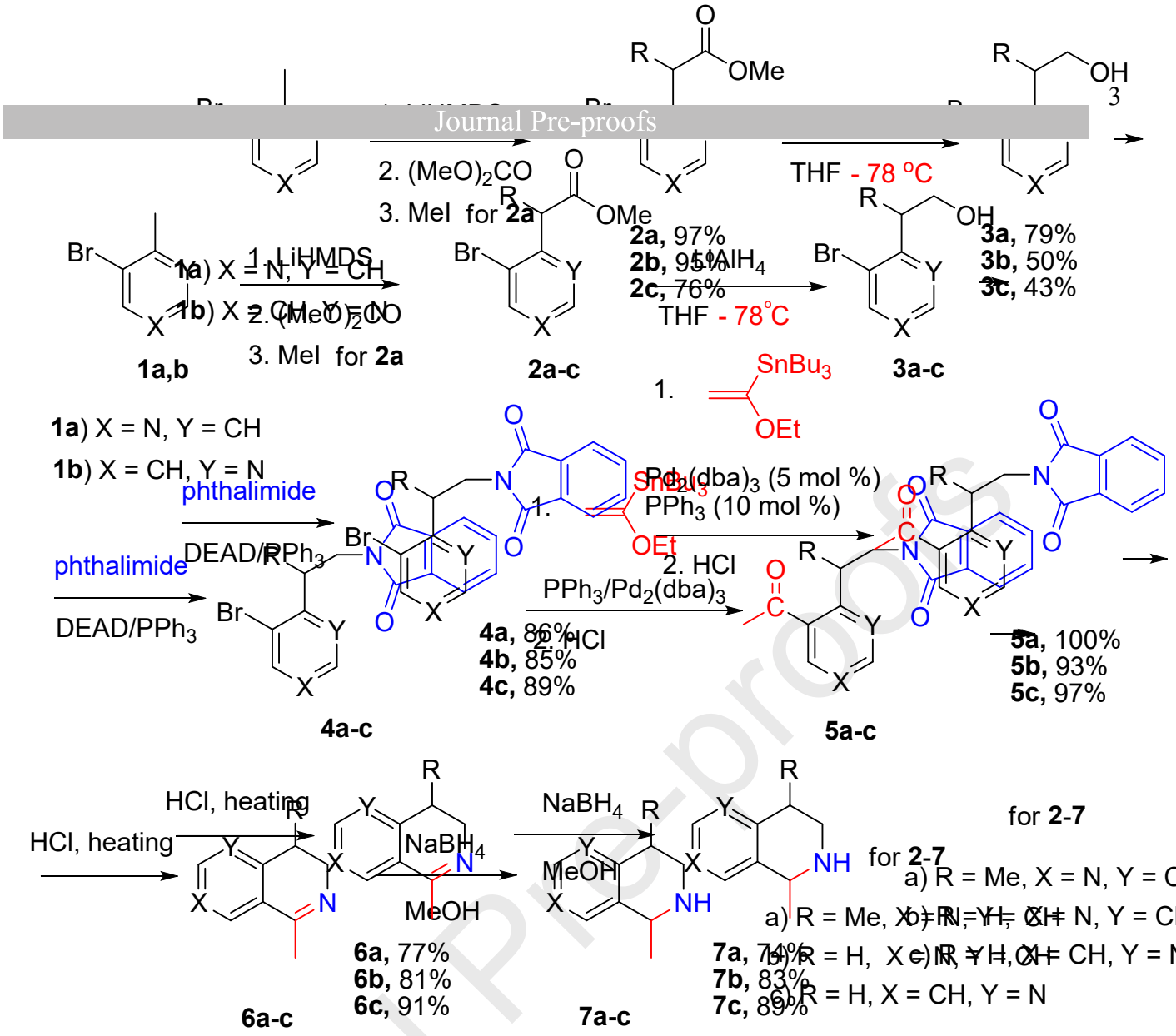


Our strategy for the synthesis of tetrahydronaphthyridines was determined by two factors: the use of readily available starting materials and the possibility to scale up the procedures. We started from available 3-bromopicolines. Thus, 3-bromo-4-methylpyridine **1a** was deprotonated with 2.1 equivalents of lithium bis(trimethylsilyl)amide followed by the addition of dimethyl carbonate to give compound **2b** in high yield (Scheme 2). ~~The~~ Ceompound **2b** was prepared previously, and we slightly modified the procedure.[16] Compound **2a** was prepared analogously, but after the addition of dimethyl carbonate ~~followed alkylation with~~ methyl iodide was added, and ~~then~~ the reaction mixture was quenched with aqueous ammonium chloride. In both cases, the yields were almost quantitative. In the case of isomeric 3-bromo-2-methylpyridine **1b**, the yield was slightly lower – (75%). The reduction of compounds **2a-c** was carried out with lithium aluminum hydride in THF at -78 °C to give **3a-c** in 43-78~~–~~% yield~~s~~ (Scheme 2). It is important to maintain a low temperature during the ~~course of the~~ reduction of the ester group and while quenching the reaction mixture. Column chromatography was used to purify compounds **3a-c**. Compound **3c** was previously prepared by the reduction of ethyl 2-(3-bromopyridin-2-yl)acetate with DIBAL-H in 80% yield. ~~Its spectral characteristics~~ Our spectroscopic data were identical to those previously reported.[3]

The Mitsunobu reaction was selected to transform the hydroxyl group into an amine group. Phthalimides bearing a highly acidic NH are known to readily take part in *N*-alkylation.[17] In our case, the reaction proceeded in high yield (85-89%). Introduction of an acyl group was carried out by the Pd-catalyzed cross-coupling reaction of bromopyridines **4a-c** with 1-(ethoxyvinyl)tri(*n*-butyl)stannane in near quantitative yield.[18]

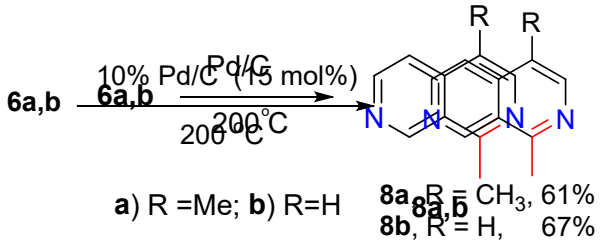
Next, the reaction mixture was treated with hydrochloric acid to transform the ethoxyvinyl group into an acyl group. Under these conditions, the phthalimide group remained intact. Cleavage of the phthalimide protecting group required overnight heating under acidic conditions. Cyclisation took place upon basification. Compound **6a** has been described in the literature.[19] ~~T~~However, the compound was characterized only as its hydrochloric salt using ~~with~~its melting point, and no spectroscopic~~spectral~~ data were provided.

The final stage of the synthesis was the reduction of dihydronaphthyridines **6** into tetrahydronaphthyridines **7**. Compounds **6a-c** were reduced with sodium borohydride in methanol in high yields. Compound **7a** was prepared as a mixture of cis:trans isomers in a 1.7:1 ratio which was purified by gradient column chromatography. The last collected fraction contained compound **7a** in 80% *de* excess. Its structure was established by 2D NMR experiments (see ESI).



Scheme 2. Synthesis of 2,7- and 1,6-naphthyridines **7a-c**.

Tetrahydronaphthyridine **7c** was previously prepared from 6-benzyl-1,6-naphthyridin-6-ium bromide.[12] It should be noted that this~~its~~ method requires expensive 1,6-naphthyridine as a starting material.



Scheme 3. Catalytic dehydrogenation of tetrahydronaphthyridines **6a,b**.

We have also shown that tetrahydronaphthyridine **6a**,**b** can be converted into naphthyridines **8a**,**b** by catalytic dehydrogenation at 200 °C in~~at~~ mesitylene for 3 h (Scheme 3). Naphthyridine **8b** was previously prepared from the corresponding chloronaphthyridine *via* cross-coupling with MeMgCl using catalytic $CoCl_2$. The spectroscopic and physical data were identical to those reported in the literature.[20]

Conclusion. A convenient and general approach to tetrahydro-2,7- and 1,6-naphthyridines has been developed. They were prepared on a multigram scale from readily available starting materials - 3-bromopicolines.

References and notes

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Declaration of interests

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Supplementary Material

Supplementary materials can be found online at:

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Tetrahydro-2,7- and -1,6-naphthyridines multigram synthesis
- Stille cross-coupling reaction of bromopicolines
- From bromopicolines to 2,7-naphthyridines