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The Bohlmann–Rahtz route to functionalised pyridine scaffolds and their use in library synthesis

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Abstract—The Bohlmann–Rahtz reaction has been used to prepare 2,3,6-trisubstituted pyridines suitable for use in library synthesis. The synthesis of piperidine substituted nicotinic acid derivative **9** has been optimised and carried out on a large scale to give ca. 500 g of scaffold which was used in the generation of the pyridine library **11**.

The wide ranging biological activity associated with many pyridine derivatives, both naturally occurring and synthetic, ensures that the synthesis of this important ring system remains a topic of current interest.[1,2] In addition, simple low molecular weight heterocyclic molecules make ideal scaffolds on which to base the high throughput synthesis of libraries of drug-like compounds. Recent examples include the use of 1,2,5-thiadiazolidin-3-one-1,1-dioxide and pyrimidine scaffolds in the synthesis of serine proteinase and kinase inhibitors respectively,[3,4] and the use of simple pyridine scaffolds to generate libraries of inhibitors of HIV-1 protease and Factor Xa.[5,6] In a programme designed to develop new heterocyclic scaffolds for library synthesis, the trisubstituted pyridines **1** (Fig. 1) containing three points of potential diversity seemed particularly attractive.

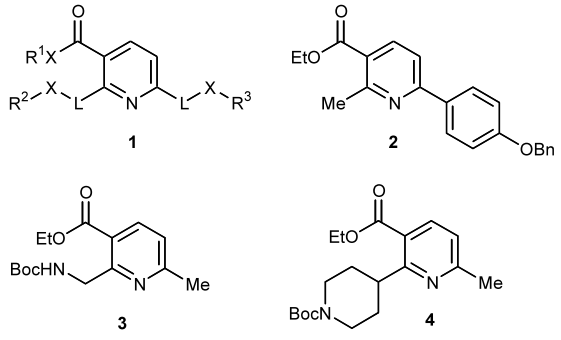

Figure 1. R^1, R^2, R^3 points of diversity; X = O, NH; L = linker.

Although many synthetic routes to pyridines already exist, the synthesis of 2,3,6-trisubstituted derivatives first reported by Bohlmann and Rahtz in 1957 is particularly versatile,[7] although surprisingly it has been little used. We have applied it to the synthesis of the pyridine core of the promothiocin antibiotics,[8,9] and Baldwin and co-workers have used similar chemistry in the synthesis of novel heterocyclic substituted α-aminoacids.[10,11] Most recently Bagley and co-workers have modified the original reaction conditions and applied them to the synthesis of various pyridine based heterocyclic systems.[12–17] We now report the application of the Bohlmann–Rahtz reaction to the synthesis of the 2,3,6-trisubstituted pyridines, and their subsequent use in the generation of libraries based on the general structure **1**.

Three initial targets **2**–**4** containing just two points of diversity and different types of linker L were chosen to exemplify the methodology, although only one (the piperidine derivative **4**) was used in library generation (q.v.). The pyridines were successfully obtained on a small scale (0.5–1.0 mmol) by reacting the corresponding enamine **5** with the alkynone **6** (5 equiv.) under the

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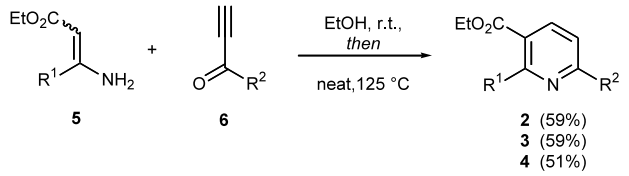
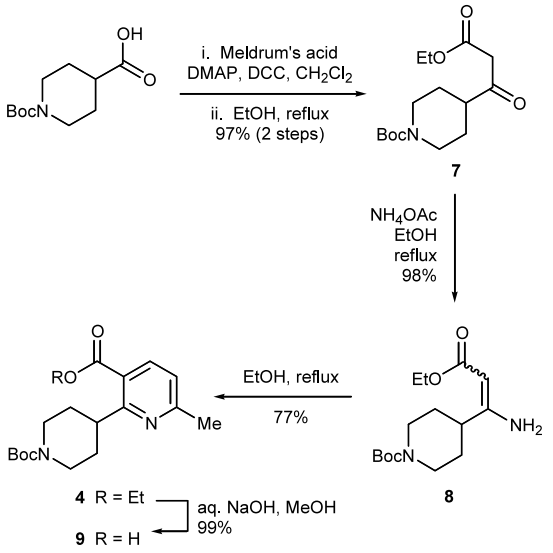


Scheme 1.



Scheme 2.

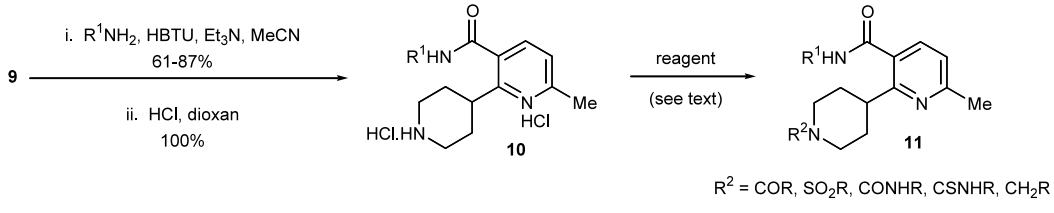
original Bohlmann–Rahtz conditions in ethanol at room temperature, followed by heating neat to a higher temperature (Scheme 1).

The synthesis of the pyridine **4** was then optimised for use on a large scale (Scheme 2). Thus *N*-Boc-isonipecotic acid was converted into the β-ketoester **7** by coupling to Meldrum's acid followed by ethanolysis[18] in excellent yield. Reaction with ammonium acetate in ethanol gave the enamine **8** in high yield and purity. In order to reduce the number of equivalents of alkynone needed, we, like others,[12–17] have modified the conditions for the Bohlmann–Rahtz reaction, and found that the enamine **8** reacted with butynone in boiling ethanol to give the pyridine **4** in 77% yield. Finally hydrolysis of the ester **4** gave the acid **9** for use in library synthesis. Using the modified conditions described in Scheme 2, the whole sequence has been carried out on a large scale to give ca. 500 g of the pyridine scaffold **9**.

Adopting a product-based, reagent-biased library design approach and utilising both ChemSpace™ and ChemCore™,[19] a diverse selection of drug-like products were computationally selected for use as a general screening library. Reagent biasing was applied to the virtual library by implementing filters from a knowledge base maintained in ChemCore™, removing reagents containing competing functionality and chemical substructures classified as undesirable in drug-like molecules. Following reagent filtering, the virtual library was filtered to include products with physical property criteria in the spirit of 'drug-like' molecules as described by Lipinski.[20] In particular products were constrained to have a molecular weight below 550 and a $C\log P \leq 6.0$. Finally, to reduce the virtual library to a size that was practical for synthesis, a selection algorithm utilising both Unity 2D fingerprints and Topomers was applied to the virtual library.[21–23]

Following from this design process, the acid **9** was coupled to a range of amines[24] to provide 14 protected intermediates in 61–87% yield on a 100 mmol scale. Subsequent treatment with HCl in dioxan removed the *tert*-butoxycarbonyl protecting group for further coupling reactions. Coupling of the deprotected intermediates **10** with various active species was performed on a 0.22 mmol scale and all products were analysed (after aqueous work-up but no further purification) by LC-MS at 254 nm. The scope of the library was firstly exemplified by reaction of **10** (R^1 = benzyl) with two carboxylic acids [two amides, 93 and 95% purity], two acid chlorides [two amides, 85 and 98% purity], two sulfonyl chlorides [two sulfonamides, 95 and 97% purity], two isocyanates [two ureas, 85 and 98% purity], two isothiocyanates [two thioureas, both 91% purity], and two aldehydes under reductive amination conditions [two tertiary amines, 83 and 94% purity] to give 12 example library compounds **11** (Scheme 3). A larger library was then constructed with all 14 R^1 intermediates **10** reacted with 148 carboxylic acids [2072 amides, 1140 compounds were ≥70% purity] and 11 isothiocyanates [154 thioureas, 86 compounds were ≥70% purity].

In summary, we have developed an efficient large scale synthesis of the pyridine scaffold **9** containing two points of diversity and demonstrated its use in library synthesis.



Scheme 3.

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