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Scope and limitations of the Minisci reaction for the synthesis of aza-heterocycles

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ABSTRACT

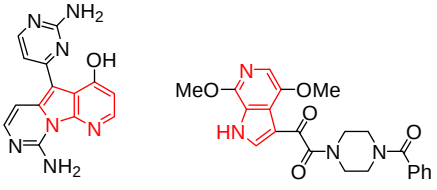
Attempts to prepare several classes of aza-heterocycles by application of the Minisci radical cyclisation reaction are described. Competing β-scission, hydrolytic cleavage and lactonisation reactions were found to be major hurdles to adopting this strategy for the synthesis of such targets.

Aza-heterocycles represent important scaffolds in drug discovery platforms, including the azaindole nucleus which has shown great potential as a structural subunit and as an indole biostere in the search for biologically relevant molecules (Fig. 1). Although significantly less predominant than their indole counterparts, several natural products that contain this substructure have also been isolated, including the variolin family, some of which have been found to exhibit anti-cancer and anti-viral properties.[1] It is not surprising that numerous methods have been described for their synthesis, from classical condensation reactions to transition metal-mediated routes, all of which have been extensively reviewed.[2]

In addition to these methods, a common strategy to form aza-heterocycles involves the use of radical cyclisation as the key step. Most of these transformations occur via 4-, 5- or 6-*exo-trig*/*dig* modes from a carbon or nitrogen radical onto an alkene or alkyne acceptor.[3] An alternative approach would be by the direct addition of a carbon-centred radical to a pyridine nucleus (Fig. 2).

Such a radical could be generated from a carboxylic acid, making use of the elegant work of Minisci et al., who demonstrated that carbon-centred radicals could be formed through the silver-catalysed decomposition of carboxylic acids, and that the radical formed would add in an intermolecular fashion to a protonated pyridine at the 2- and 4-position.[4] Use of an acid and oxidant, such as ammonium persulfate, increases the efficiency of the reaction through activation of the pyridine as an electron acceptor, in addition to ensuring efficient re-oxidation of the aromatic moiety and silver salts.[5] An advantage of this strategy would be the ability to couple readily available and structurally diverse bromopyridines and β-amino acids, ultimately allowing access to substituted azaindoles.

For this strategy, formation of the key carboxylate precursor **1** was initially envisioned using an organometallic-mediated coupling reaction. However, despite numerous attempts at conducting Ullman-type couplings using conditions reported by Ma and Xia (10 mol % CuI, K_2CO_3 in DMF) for the coupling of bromobenzenes with amino acids,[6] the reaction of β-alanine with 3-bromopyridine did not afford anything other than non-quantitative return of starting material. An alternative approach using 3-aminopyridine as a nucleophile, and methyl acrylate as a Michael acceptor proceeded reasonably well under solvent-free conditions in 41% yield (Scheme 1). Lewis acid catalysis [$Yb(OTf)_3$, $Bi(OTf)_2$, $Zn(OTf)_2$] in CH_3CN afforded much lower yields (<10%). The subsequent hydrolysis step proceeded smoothly, but it was not possible to obtain the carboxylic acid (pK_a 4.8) due to the similar pK_a values of the acid (propanoic acid, pK_a 4.9) and the conjugate acid of the pyridine



Variolin B *BMS-488043*

Figure 1. Representative azaindoles.

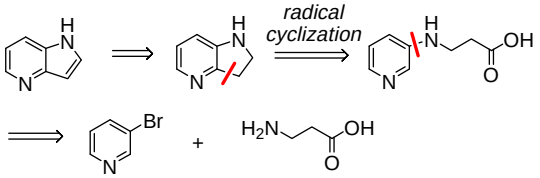


Figure 2. Retrosynthetic strategy.

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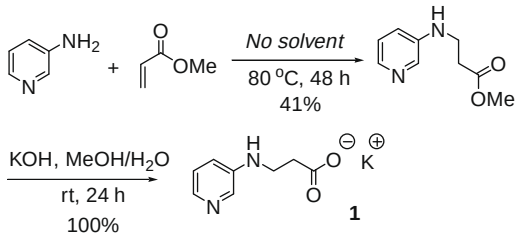


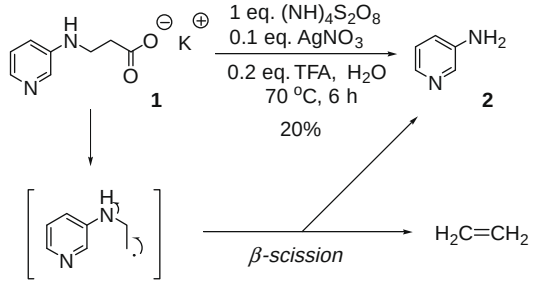
Scheme 1. Synthesis of key carboxylate intermediate **1**.

(3-aminopyridine, pK_a 6.0) moieties. The carboxylate **1** was isolated directly by removal of solvent in quantitative yield.

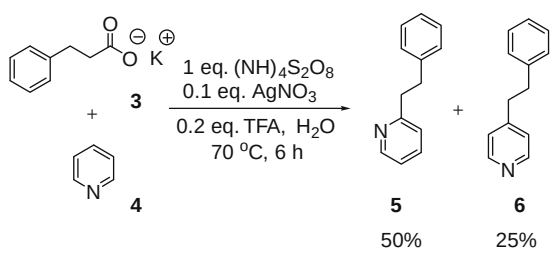
The Minisci reaction was performed on carboxylate **1** by application of optimised literature conditions,[7] and upon work-up, the only product isolated in low yield was 3-aminopyridine **2** (Scheme 2).

A degradation pathway to account for this observation can be envisioned where the radical generated undergoes irreversible β-scission, which upon work-up would yield 3-aminopyridine and ethene. The low yield of the 3-aminopyridine can be accounted for by the poor mass return resulting from the water solubility of both this compound and the starting material **1**. This hypothesis was supported by attaching a bromine water trap to the outlet of the reaction condenser, which decolourised as the reaction proceeded and ethene gas was generated. A control reaction involving intermolecular Minisci reaction of potassium 3-phenylpropionate **3** and pyridine **4** led to the coupled products **5** and **6** in yields of 50% and 25%, respectively, with no decolouration of the bromine water (Scheme 3).

Heating the potassium salt **1** at reflux in the presence of TFA and H_2O without a radical initiator for 6 h at 70 °C, followed by quenching with KOH, returned starting material **1** in quantitative yield, ruling out hydrolytic cleavage. Thus, although the key radical was formed, β-scission competes at a faster rate than the desired cyclisation. It is therefore unlikely that aza-heterocycles could be formed by this strategy if the radical is in the β-position relative to a good leaving group, in this case 3-aminopyridine. In order to circumvent β-scission, a homologue was considered, thus allowing



Scheme 2. Attempted Minisci cyclisation.



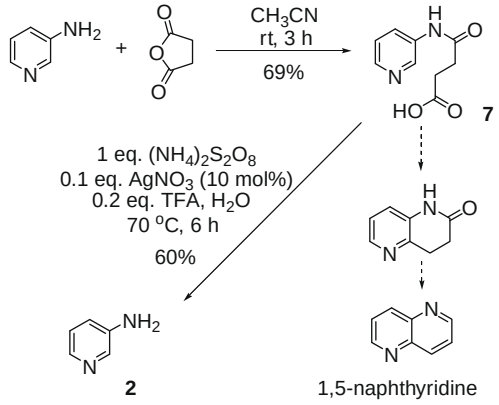
Scheme 3. Control intermolecular Minisci reaction.

access to 1,5-naphthyridines (Scheme 4), perhaps the least studied of the naphthyridine family, but still having an important role in medicinal chemistry applications.[8]

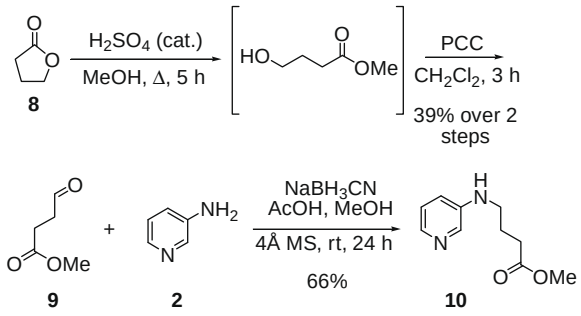
Amide **7** was prepared in good yield (69%) by condensation of 3-aminopyridine and succinic anhydride, and using this substrate under the optimised Minisci reactions yielded 3-aminopyridine **2** in 60% yield. Two control experiments, the first using TFA and water, and second omitting the TFA from the Minisci conditions, led to the formation of 3-aminopyridine **2**, and in the latter case also returned succinic acid. Thus, although a radical-mediated cleavage cannot be ruled out, it is highly likely in this case that the Achilles heel of this strategy is the labile nature of this particular amide bond. To remove the problematic amide functionality, a number of reducing agents were applied to the key substrate **7**, with H_2/PtO_2 returning starting material, whilst $LiAlH_4$, $LiBH_4$ and Red-Al at different temperatures and in various solvents yielded none of the desired product. Related transformations have been described in the literature, although not for pyridine-containing substrates.[9]

A new route was devised that avoided the problems of the amide functionality. Methanolysis of γ-butyrolactone **8** under acidic conditions, followed by immediate oxidation of the crude reaction mixture with PCC afforded, after distillation, the aldehyde **9** in 39% yield (Scheme 5).

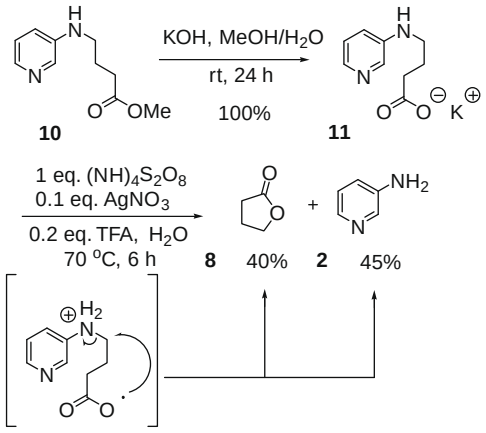
Reductive amination of aldehyde **9** with 3-aminopyridine **2** using $NaBH_3CN$ in glacial acetic acid in the presence of activated molecular sieves gave the reduced product **10** in 66% yield. Hydrolysis was performed as previously using KOH in MeOH/H_2O, providing the potassium salt **11** in quantitative yield. This was subjected to the standard Minisci conditions (Scheme 6), but the expected cyclised product was not seen, the ^{1}H NMR spectrum of the crude reaction mixture revealing a nearly equal mixture of 3-aminopyridine **2** and γ-butyrolactone **8**.



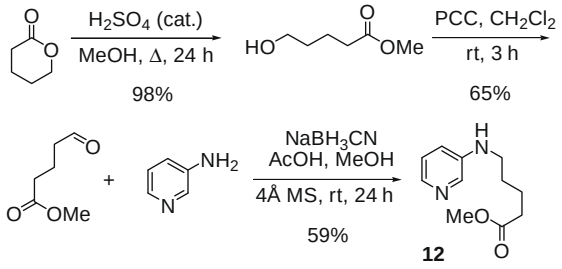
Scheme 4. Attempted synthesis of 1,5-naphthyridine.



Scheme 5. Synthesis of a 1,5-naphthyridine intermediate.



Scheme 6. Attempted Minisci cyclisation.



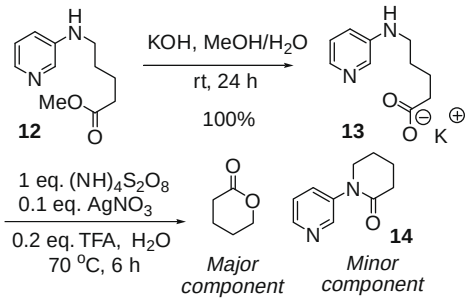
Scheme 7. Preparation of a 1,6-naphthyridine intermediate.

Several possibilities exist for the formation of the lactone. Ring closure may occur by an ionic *5-exo-tet* mechanism before the carboxyl radical is formed, or by an analogous radical mechanism, which is presumably faster than the rate of any decarboxylation process. When the potassium salt was heated at 70 °C in the presence of TFA and H_2O for the same length of time followed by basic work-up (KOH), the ^{1}H NMR spectrum of the crude reaction product revealed mainly starting material as well as a small amount (~20%) of potassium 4-hydroxybutyrate resulting from hydrolytic cleavage of the substrate. This indicates that although an ionic cyclisation occurs under the reaction conditions, the radical-based pathway occurs at a significantly faster rate.

Since the problem with this reaction was the fast five-membered ring closure, formation of a six-membered ring would be expected to be slower, and hence may allow for the decarboxylation-Minisci step to occur before any competing ring closure. The synthesis of the Minisci precursor **12** for this new system was analogous to that of substrate **10** and was easily accessed in moderate to good yields (Scheme 7).

With the ester **12** in hand, hydrolysis to the carboxylate **13** was carried out in KOH in MeOH/H_2O in quantitative yield (Scheme 8).

Reaction of carboxylate **13** under the standard Minisci conditions led to a complex mixture, predominantly containing δ-valerolactone. Repeated column chromatography resulted in a fraction with a pyridine-containing component that was tentatively assigned as the lactam **14** by analogy with the ^{1}H NMR spectrum of *N*-acetyl 3-aminopyridine. Attempts to prepare lactam **14**



Scheme 8. Attempted Minisci cyclisation of a 1,6-naphthyridine precursor.

by an independent route failed. However, it is clear that the predominant pathway in this reaction is likely to once again be a radical-mediated cyclisation.

Through the attempts made towards the synthesis of azaindoles, 1,5-naphthyridines and the homologue towards a 6,7-fused system, it has become clear that a route based on the Minisci reaction is not feasible for any of these systems. Though disappointing, key points about the nature of the mechanism have been investigated and elucidated in one case. Importantly, although the 3-aminopyridine moiety provides a useful scaffold, it creates significant problems arising from its ability to act as a leaving group, leading to β-scission or by facilitating competing ionic or radical pathways (5-*exo-tet* vs Minisci reaction). Additionally, the study demonstrates that for the synthesis of fused aza-heterocycles using the Minisci reaction, it is essential that the second ring system comprises a carbon atom at the benzylic position.

Acknowledgements

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7. Extensive optimisation reactions were performed on the intermolecular Minisci reaction depicted in Scheme 3. Critical to success was to use fresh supplies of ammonium persulfate, the shelf-life of which is only guaranteed for one year. Additionally, the potassium salt of 3-phenylpropionic acid **3** was employed in an identical manner as the more commonly used carboxylic acid. This was more useful in our approach due to the problems associated with isolating a homogenous sample of the carboxylic acid because of the similar pK_a values of the pyridine and carboxylic acid functional groups.
8. For example, see: Gellibert, F.; Woolven, J.; Fouchet, M.-H.; Mathews, N.; Goodland, H.; Lovegrove, V.; Laroze, A.; Nguyen, V.-L.; Sautet, S.; Wang, R.; Janson, C.; Smith, W.; Krysa, G.; Boullay, V.; de Gouville, A.-C.; Huet, S.; Hartley, D. *J. Med. Chem.* **2004**, *47*, 4494–4506.
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