The naphthyridine scaffold has found some utility as a template in medicinally active compounds. It has been shown to be a rigid replacement for diketo acids, comprising the central architecture of antiviral drug L-870,810 (1) and the antibiotic trovafloxacin (2) (Figure 1). In addition, it can serve as a suitable core for phosphodiesterase-4 inhibitors such as NVP-ABE171 (3) as well as several known kinase inhibitors.

As a part of a program that sought to utilize various regioisomeric primary-amino-substituted naphthyridine esters, we required a facile route for the preparation of such compounds. Previously, this type of heterocycle had been prepared in lengthy and low-yielding chemical routes. We sought instead to develop a more concise and general strategy for preparing various naphthyridine isomers in a controlled fashion. Herein we report one such approach that proved to be useful for the construction of several primary-amino-substituted naphthyridine esters (Scheme 1). The key transformation in this approach is the annulation of 2-cyano-substituted vinylogous carbamates 10 with ammonium acetate under mildly acidic conditions. The method described makes use of readily available halogenated azine heterocycles (pyridines or pyrazine) bearing an ortho-substituted nitrile group 5. These can be transformed into the bicyclic ring makeup of the naphthyridines in a few iterative steps. Pirnat et al. have previously reported a similar approach, although their method was only demonstrated to work for 2,7-naphthyridin-1-ones.

In one example, SNAr reaction of 3-cyano-4-fluoropyridine (5a) with the sodium salt of diethyl malonate was used to generate 7a (Scheme 1). Krapcho decarboxylation of 7a provided the pyridinyl acetate 8a. Condensation with DMF-DMA then generates the cyclization precursor 4a. With 10a in hand, three screening conditions were attempted to effect the transformation to the naphthyridine ester 4a (Table 1). We observed that subjecting the substrate 10a to an ammonia solution in water–ethanol (10:1) resulted only in a minimal amount of the naphthyridine product 4a being generated (Table 1, entry 1). Next, we found that using ammonium chloride and hydrochloric acid, a strong acid, resulted predominantly in undesired nitrile-group hydrolysis (Table 1, entry 2). Finally, employing ammonium acetate and a milder acid (acetic acid) at slightly elevated temperatures yielded 60–70% of the desired product 4a (Table 1, entry 3).

Encouraged by the latter result, the substrate scope was then examined (Table 2). A variety of commercially available regioisomeric halogenated pyridines were employed in the two-step conversion into the precursor pyridinyl acetates 8b–e. As exemplified by 8f, this methodology was also applicable to the synthesis of pyrazine-derived ana-
logues. As with the screening substrate 10a, the conditions for the annulation step using ammonium acetate in hot acetic acid were applied to each of the vinylogous carbamate substrates in the final step of the transformation. All substrates were converted in reasonable isolated yields to the respective naphthyridines (or 7-azaquinoline, Table 2, entry 6) from the corresponding acetate intermediate. Even the electron-poor substrate bearing a trifluoromethyl group was successful in generating the naphthyridine in 16% yield over two steps (Table 2, entry 5). Unfortunately, an electron-rich methoxy-substituted precursor could not be prepared as the S_{N}Ar reaction proved unsuccessful.

Two plausible reaction mechanisms for the annulation step are shown in Scheme 2. Under the acidic reaction conditions employed, ammonium acetate can add to the nitrile to form an incipient amidine 11. This compound can then undergo facile conjugate cyclization to generate the corresponding naphthyridine heterocycle 12. Finally, extrusion of dimethylamine proceeds to furnish the de-
sired product 4 (pathway A). Alternatively, early expulsion of dimethylamine can lead to 13, which upon rapid cyclization onto the pendant nitrile provides 14. This intermediate can then tautomerize to generate the desired product 4 (pathway B). We speculate that pathway B is more feasible because formation of the amidine 11 in pathway A is an energetically disfavored process. Moreover, in the work reported by Pirnat et al., they failed to observe any amidines among the various intermediates that were isolated.

In summary, a unified approach to the preparation of primary-amino-substituted naphthyridines as well as a 7-azaquinoxaline was described. By making use of easily accessible 2-halocyanopyridines, these various naphthyridines were derived in a four-step sequence that provides the desired products in synthetically useful yields. As a demonstration of the broader utility of this method, we were able to prepare an entire set of regioisomeric primary amino naphthyridine esters. Further application of this method in a more complex setting such as the synthesis of active pharmaceuticals is currently under way.

Table 2 Isolated Yields for Two-Step Annulation from Pyridinyl Acetate to Naphthyridines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)a</th>
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<tr>
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</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="" /></td>
<td><img src="image12" alt="" /></td>
<td>43</td>
</tr>
</tbody>
</table>

* Final two steps.

Diethyl 2-(3-Cyanopyridin-4-yl)malonate (7a)
To a stirred solution of NaH (289 mg, 7.22 mmol, 60%) in THF (5 mL) was added diethyl malonate (1.16 g, 7.22 mmol) and LiCl (459 mg, 10.82 mmol), and the resulting mixture was stirred at 100 °C overnight. After the reaction mixture was cooled to r.t., it was treated with EtOAc (3 × 20 mL), washed with brine (2 × 10 mL), dried over Na2SO4, and concentrated. The residue was purified by column chromatography (PE–EtOAc = 8:1) to give 7a as white solid (300 mg, 43% over two steps). 1H NMR (400 MHz, DMSO-d6): δ = 8.82 (s, 1 H), 8.70 (d, J = 6.4 Hz, 1 H), 7.37 (d, J = 6.4 Hz, 1 H), 4.19 (q, 2 H), 1.24 (t, 3 H).

Ethyl 2-(3-Cyanopyridin-4-yl)acetate (8a)
To a solution of crude compound 7a (1.0 g, 3.61 mmol) in DMSO (30 mL) were added H2O (1 mL) and LiCl (459 mg, 10.82 mmol), and the mixture was stirred at 100 °C overnight. After the reaction mixture was cooled to r.t., it was extracted with EtOAc (3 × 20 mL), washed with brine (10 × 2 mL), dried with Na2SO4, and concentrated. The residue was purified by column chromatography (PE–EtOAc = 6:4) to give 8a as a crude product, which was used for the next step without further purification.

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References


