

A Versatile Annulation Route to Primary-Amino-Substituted Naphthyridine Esters

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Abstract: A straightforward four-step synthesis of primary-amino-substituted naphthyridine esters from commercially available cyanopyridines was described. The route makes use of a condensation reaction between pyridinyl acetates with *N,N*-dimethylformamide dimethylacetal (DMF-DMA) to form *ortho*-cyano vinylogous carbamates. These intermediates can undergo facile cyclization with ammonium acetate in acetic acid to generate the corresponding naphthyridine esters in good synthetic yields. The synthesis of primary-amino-substituted 7-azaquinoxaline was also described.

Key words: naphthyridine, annulation, vinylogous carbamates, heterocycles, scaffold

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

As a part of a program that sought to utilize various regioisomeric primary-amino-substituted naphthyridine esters **4**, 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.^{5,6} 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.⁷

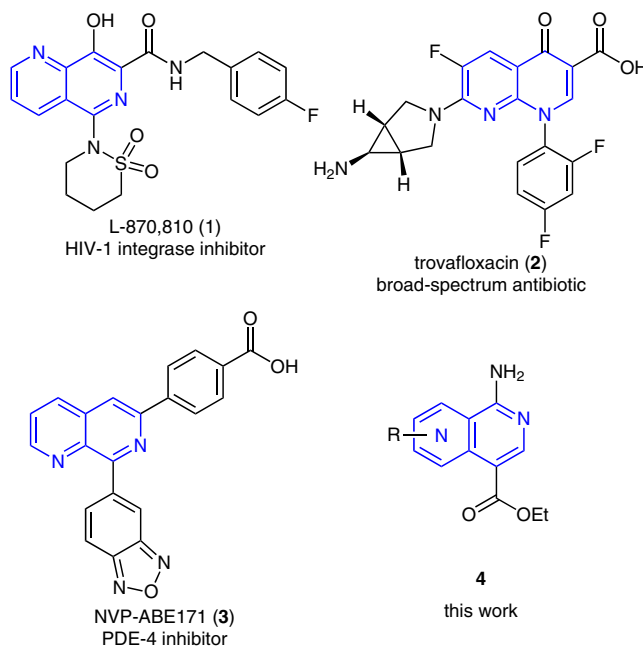
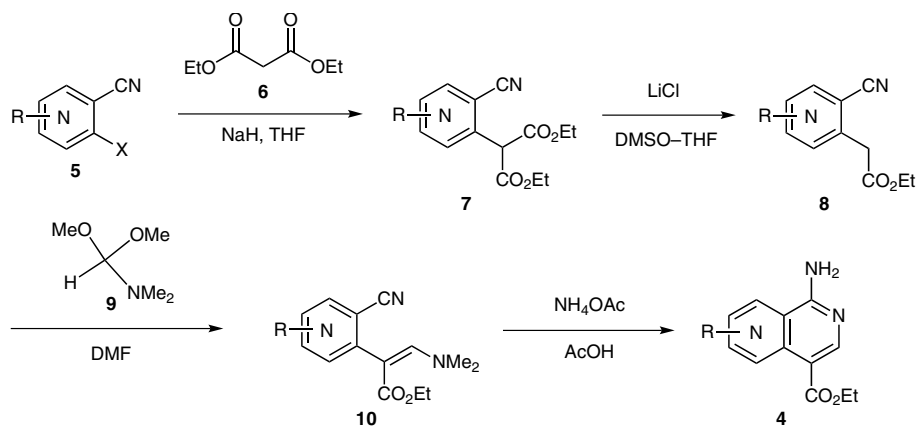


Figure 1 Examples of naphthyridine-containing compounds

In one example, S_NAr 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 **10a**. 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-



Scheme 1 General synthetic route for the preparation of naphthyridine isomers

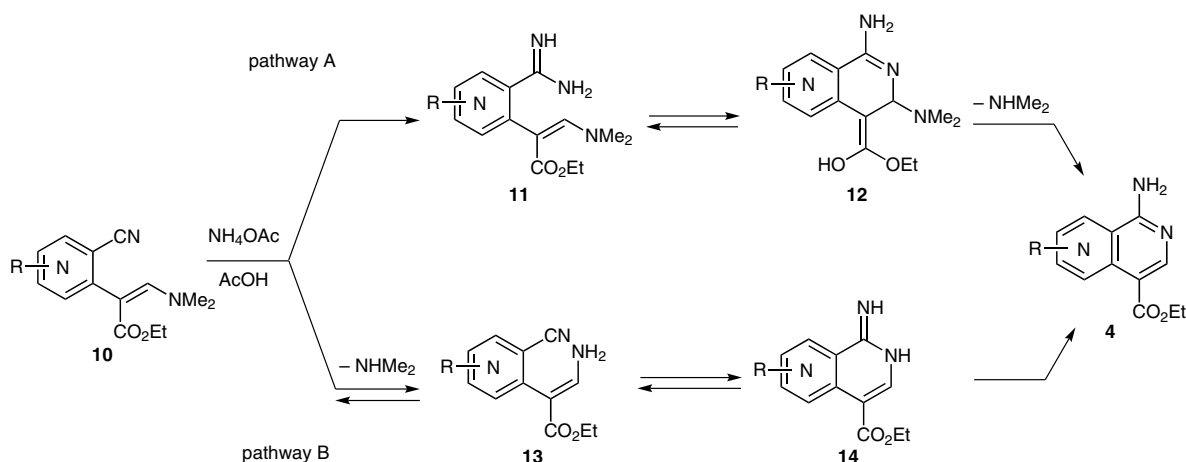
Table 1 Reaction Screening for Effective Cyclization Conditions

Entry	Conditions	Results
1	NH ₃ , H ₂ O–EtOH (10:1), reflux	<5% desired product + complex mixture of undesired products
2	NH ₄ Cl, HCl, EtOH, reflux	0% product; extensive nitrile hydrolysis to amide
3	NH ₄ OAc, AcOH (1:5), 80–100 °C	60–70% yield of 4a

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-azaquinoxaline, 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

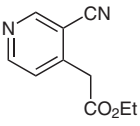
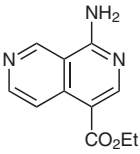
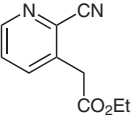
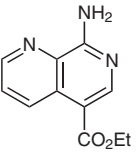
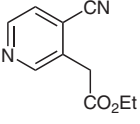
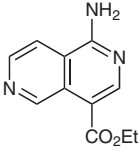
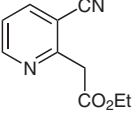
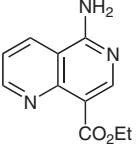
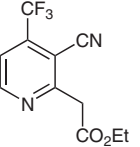
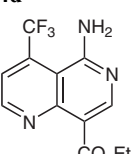
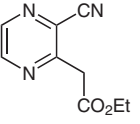
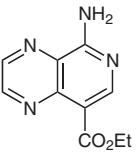
5). Unfortunately, an electron-rich methoxy-substituted precursor could not be prepared as the S_NAr reaction proved unsuccessful.

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-



Scheme 2 Proposed reaction mechanisms for cyclization leading to naphthyridine ester **4**

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

Entry	Substrate	Product	Yield (%) ^a
1	 8a	 4a	43
2	 8b	 4b	41
3	 8c	 4c	23
4	 8d	 4d	48
5	 8e	 4e	16
6	 8f	 4f	33

^a Final two steps.

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.,⁷ 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.

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) in THF (5 mL) dropwise at 0 °C under N₂ atmosphere. After the reaction mixture was stirred at 0 °C for 10 min, compound **5a** (500 mg, 3.61 mmol) in THF (5 mL) was added. The reaction mixture was heated at reflux for 4 h under N₂ and was quenched with aq NH₄Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine (2 × 10 mL), dried over Na₂SO₄, and concentrated to give **7a** as a crude product, which was used for the next step without further purification.

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 resulting 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 over Na₂SO₄, and concentrated. The residue was purified by column chromatography (PE–EtOAc = 8:1) to give **8a** as white solid (300 mg, 43% over two steps). ¹H NMR (400 MHz, DMSO-*d*₆): 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)-3-(dimethylamino)acrylate (**10a**)

A solution of compound **8a** (100 mg, 0.526 mmol) and DMF–DMA (157 mg, 1.31 mol) in DMF (5 mL) was heated at 80 °C overnight. The mixture was evaporated to dryness and carried on to the next step without further purification.

Ethyl 1-Amino-2,7-naphthyridine-4-carboxylate (**4a**)

A mixture of crude compound **10a** from the previous step (150 mg) and NH₄OAc (1.0 g, 13.15 mmol) in AcOH (5 mL) was heated at 80–100 °C overnight. The mixture was cooled to ambient temperature and poured into ice water. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was concentrated to give the crude product, which was purified by preparative TLC (PE–EtOAc = 1:1) to give the desired product **4a** (50 mg, 43% over two steps). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.19 (s, 1 H), 8.87 (s, 1 H), 8.75 (d, *J* = 6.0 Hz, 1 H), 8.68 (d, *J* = 6.0 Hz, 1 H), 5.78 (br, 2 H), 4.35 (q, 2 H), 1.37 (m, *J* = 6.8 Hz, 1 H), 1.20 (t, 3 H).

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