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

Jinhua Chen, a Zijin Xu, a Tao Wang, a Joseph P. Lyssikatos, b Chudi O. Ndubaku* b

a Wuxi AppTec, 288 Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai 200131, P. R. of China
b Discovery Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA
Fax +1(650)7424943; E-mail: chudin@gene.com
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Abstract: A straightforward four-step synthesis of primary-amino-substituted naphthyridine esters from commercially available cyano-pyridines 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 diketo 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

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-
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$_2$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-
In the work reported by Pirnat et al., they failed to observe any amidines among the various intermediates that were isolated. We speculate that pathway B is more feasible because formation of the amidine intermediate can then tautomerize to generate the desired cyclization onto the pendant nitrile provides a final two steps. This is in contrast to pathway A, which upon rapid cyclization of dimethylamine can lead to the desired product as a crude product, which was used for the next step without further purification.

**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). 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. The crude product was purified by preparative TLC (PE–EtOAc = 8:1) to give 7a as a 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 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). 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 = 6.4 Hz) to give 8a as white solid (300 mg, 43% over two steps).

**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 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 (2 × 10 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- d6): 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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**References**


