Chemoselective Cyclization of Aminonicotinic Acid Derivatives to 1,8-Naphthyridin-2-ones via a Potential Intramolecular Azadiene-Ketene Electrocyclization Reaction

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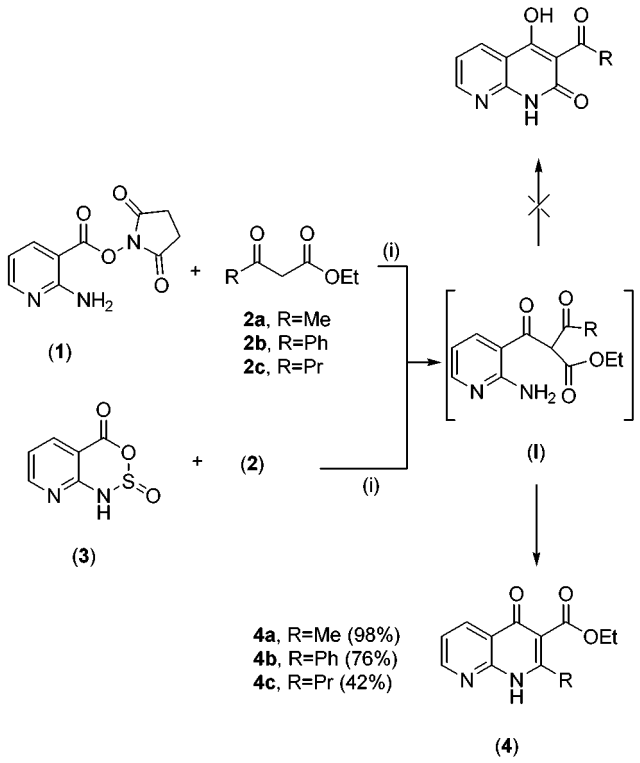
1,8-Naphthyridinones are useful synthetic products that were found to possess a variety of biological properties. Two classes of compounds, 1,8-naphthyridin-2-ones and 1,8-naphthyridin-4-ones, have mainly attracted the focus of the scientific community due to their unique antibacterial,[1] antiinflammatory,[2] antiallergic, and antisecretory activities.[3]

3-Substituted 1,8-naphthyridin-2-ones have been prepared by treating substituted 2-aminonicotinic acid with ethyl malonyl chloride[4] or by reaction of 2-aminopyridines with malonic esters.[5] Similarly, the preparation of 2,3-disubstituted 1,8-naphthyridin-4-ones was achieved by cyclization of the appropriate substituted aminopyridine derivatives.[6]

One of the most common methods is that proposed by Coppola, which involves reaction of aza-isatoic anhydride with anions of β-keto esters.[7] Although his method appears to be general for the preparation of both 1,8-naphthyridin-2-ones and 1,8-naphthyridin-4-ones, it presents disadvantages, such as the use of severe reaction conditions and the formation of unequal amounts of both products due to the intramolecular nucleophilic attack of the aromatic amine on both the ester and ketone carbonyl groups.[7]

In the course of our research on the synthesis of heterocyclic systems comprising a β-dicarbonyl moiety,[8] we required a facile route to substituted 1,8-naphthyridinones. To achieve the synthesis of 1,8-naphthyridin-4-ones, we have modified Coppola's methodology by making use of two new acylating agents, the *N*-succinimide ester of aminonicotinic acid (**1**) and azathio isatoic anhydride (**3**). Both are excellent activating systems of the carboxylic acid moiety and susceptible to nucleophilic attack by β-keto esters (**2**) under smooth reaction conditions (Scheme 1).

Scheme 1[a]



[a] Key: (i) *t*-BuOK, THF.

Unexpectedly, the reaction of these activated systems with nucleophiles does not give mixture of products in contrast to Coppola's method.

Thus, reaction of activated derivatives of aminonicotinic acid with 2 equiv of the appropriate β-ketoester under basic solution of *t*-BuOK in THF gives only 2-alkyl-3-alkoxycarbonyl 1,8-naphthyridin-4-one derivatives (**4**) in good yields (Scheme 1).

Extending this method, we considered a versatile way of preparing chemoselectively 1,8-naphthyridin-2-one derivatives. The idea was to modify intermediate C-acylation compound (**I**) in order to activate ester carbonyl moiety.

Thus, insertion of an electron-withdrawing group in the amino functionality could give the desired activation of ester group via a potential formation of a ketene intermediate (**II**) (Figure 1).

Preparation of pyrido [2,3-*d*][3,1] oxazin-4-ones (**5**) gives activation on the carboxylic acid moiety and the desired protection for amino functionality. Reaction of **5** with anions of β-keto esters yields 1,8-naphthyridin-2-ones (**6**) in a one-step route (Scheme 2). The protocol used requires the reaction of **5** with 2 equiv of the anion of the appropriate β-ketoester, generated with potassium *tert*-butoxide. After acidification with 10% hydrochloric acid, products of type **6** were obtained as pure solids.

The reaction is probably based on the formation of an azadiene−ketene intermediate (**IV**), which is cyclized by an intramolecular electrocyclization reaction. The determinative factor in the formation of **IV** appears to be the

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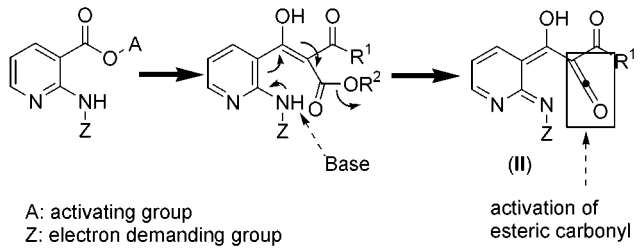
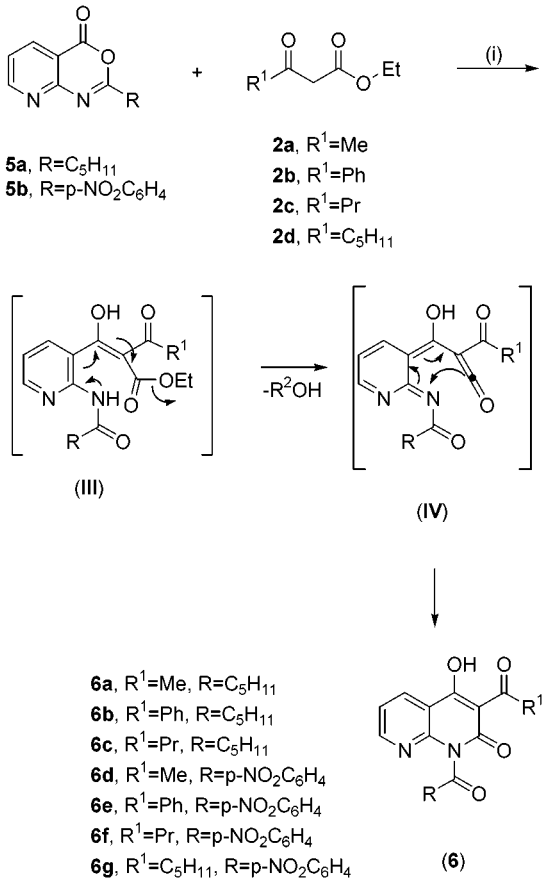


Figure 1.

Scheme 2[a]



[a] Key: (i) method A: *t*-BuOK, THF; method B: *t*-BuOK, *t*-BuOH.

substituent bonded on the nitrogen. Powerful electron-withdrawing groups lead spontaneously to the formation of **IV**. 2-Pentylpyrido[2,3-*d*]oxazin-4-one (**5a**) gives smaller yields in contrast to 2-(4-nitrophenyl)pyrido[2,3-*d*][3,1]-oxazin-4-one (**5b**), which is in accordance with the hypothetical mechanism (Table 1).

In conclusion, we are reporting a synthetic route for the preparation of 1,8-naphthyridin-4-ones based on the reaction of two new acylating agents with β-ketoesters under smooth reaction conditions. The proposed methodology leads to the formation of pure 1,8-naphthyridin-4-ones without byproducts formed through the alternate nucleophilic attack of aromatic amine to the esteric carbonyl moiety. In our attempt to synthesize 1,8-naphthyridin-2-ones, we have designed and applied a new method involving a potential intramolecular electrocyclization reaction of an azadiene-ketene intermediate. By this methodology, the chemoselective preparation of 1,8-naphthyridin-2-ones is feasible in high yields.

Table 1. 1,8-Naphthyridin-2-ones Obtained with the Proposed Methodology

starting material	product	method	reaction time (h)	yield (%)
5a	**6a**	A	2	7
5a	**6a**	A	24	62
5a	**6b**	A	2	8
5a	**6b**	A	24	50
5a	**6c**	A	2	10
5a	**6c**	A	24	53
5b	**6d**	A	2	99
5b	**6d**	B	2	75
5b	**6e**	A	2	98
5b	**6e**	B	2	76
5b	**6f**	A	2	85
5b	**6f**	B	2	80
5b	**6g**	A	2	80

Further research on the elucidation of the reaction mechanism providing chemoselectively 1,8-naphthyridin-2-ones is currently carried out in order to confirm the existence of azadiene-ketene intermediate.

Experimental Section

General Methods. All the commercially available starting materials were used without further purification. The β-keto esters used were either purchased from Fluka or prepared by a literature procedure.[9] Commercially available THF was dried prior to use by refluxing over sodium. Melting points are uncorrected. Chemical shifts are quoted in ppm and *J* values in Hz (t = triplet, dd = doublet of doublets, m = multiplet, br = broad).

***N*-Succinimide Ester of Aminonicotinic Acid (1).** To a solution of 2-aminonicotinic acid (7.2 mmol, 1.00 g) and *N*-hydroxysuccinimide (0.014 mol, 1.67 g) in THF (70 mL) was added DCC (7.2 mmol, 1.49 g), and the mixture was stirred for 24 h at room temperature. The mixture was filtered, and the filtrate was evaporated in vacuo to give the title compound (0.80, 47%). Mp: 167−169 °C. Anal. Calcd for $C_{10}H_9O_4N_3$: C, 51.06; H, 3.86; N, 17.87. Found: C, 51.04; H, 3.84; N, 17.83. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.85 (4H, s), 6.71 (1H, dd, J = 4, 8), 8.18 (1H, dd, J = 2, 8), 8.35 (1H, dd, J = 2, 4). ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.7, 162.0, 160.1, 156.8, 139.9, 112.5, 99.0, 25.5.

Azathioisatoic Anhydride (3). In a dispersion of 2-aminonicotinic acid (0.011 mol, 1.52 g) in carbon tetrachloride was added thionyl chloride (0.22 mol, 2.61 g), and the mixture was stirred for 2 h under reflux. The mixture was cooled and evaporated under vacuo to give the title compound (1.66 g, 82%). Mp: 192−194 °C. Anal. Calcd for $C_6H_4O_2N_2S$: C, 42.86; H, 2.38; N, 16.67; S, 19.04. Found: C, 42.80; H, 2.39; N, 18.91. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.97 (1H, dd J = 6, 8), 8.28 (1H, dd J = 2, 7), 8.55 (1H, dd J = 2, 7). ^{13}C NMR (75 MHz, DMSO-d_6): δ 112.1, 124.6, 141.6, 147.6, 153.8, 165.8.

General Procedure for the Preparation of Pyrido[2,3-*d*][3,1]oxazin-4-ones (5a,b). A solution of 2-aminonicotinic acid (0.011 mol) in pyridine (20 mL) was cooled at 0 °C, and the appropriate acid chloride (0.011 mol) was added dropwise over a period of 15 min. The reaction mixture was stirred at room temperature for 1.5 h. The protected aminonicotinic acid was cyclized either with DCC or with other dehydrating reagents.

2-Pentylpyrido[2,3-*d*][3,1]oxazin-4-one (5a). A mixture of 2-aminonicotinic acid (0.011 mol, 1.52 g), pyridine−benzene (1:1, 40 mL), and caproyl chloride (0.011 mol, 1.51 g) was stirred for 1.5 h at room temperature. The mixture was quenched with water, and the organic layer was separated and evaporated in vacuo. The residue was dried, and its solution in dichloromethane was stirred with an equivalent amount of DCC. The mixture was stirred for 24 h at room temperature and filtered. The filtrate was evaporated in vacuo to give the title compound (1.61 g, 67%). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.08; H, 6.49; N, 12.80. ^{1}H NMR (300 MHz,

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$CDCl_3$): δ 0.90 (3H, t, $J = 8$), 1.37 (4H, m), 1.87 (2H, qt, $J = 8$), 2.76 (2H, t, $J = 8$), 7.47 (1H, dd, $J = 3, 7$), 8.50 (1H, dd, $J = 2, 5$), 8.96 (1H, dd, $J = 2, 5$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 167.7, 151.2, 145.2, 144.7, 118.6, 117.3, 38.1, 31.0, 24.5, 22.1, 13.6.

2-(4-Nitrophenyl)pyrido[2,3-*d*][3,1]oxazin-4-one (5b). A mixture of 2-aminonicotinic acid (0.011 mol, 1.52 g), pyridine (20 mL), and 4-nitrobenzoyl chloride (0.011 mol, 2.04 g) was stirred for 1.5 h at room temperature. Benzoyl chloride (0.011 mol,1.54 g) was then added to the mixture and stirring continued at room temperature for 1 h. The mixture was quenched with water, filtered, and washed with water to give the title compound (1.90 g, 64%). Mp: 235−237 °C. Anal. Calcd for $C_{13}H_7O_4N_3$: C, 58.00; H, 2.62; N, 15.61. Found: C, 57.99; H, 2.62; N, 15.63. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (1H, dd, $J = 3, 7$), 8.40−8.60 (4H, m), 8.61 (1H, dd, $J = 2, 5$), 9.08 (1H, dd, $J = 2, 5$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 158.0, 157.3, 150.9, 138.2, 135.1, 130.1, 129.1, 124.6, 124.1, 113.2.

General Procedure for the Preparation of 1,8-Naphthyridin-4-ones (4a−c) and 1,8-Naphthyridin-2-ones (6a−g). To a solution of potassium *tert*-butoxide (4.5 mmol) in anhydrous THF (25 mL) (method A) or in anhydrous *t*-BuOH (method B) was added dropwise the appropriate β-keto ester **2** (4.5 mmol), and after the mixture was stirred at room temperature for 30 min a clear solution resulted. The activated derivative of aminonicotinic acid (**1**, **3**, or **5**) (2.2 mmol) was added at once in the solution, and the mixture was stirred for 2 h (or 24 h for **4a−c** or **6a−c**) and then quenched with water (10 mL). The mixture was concentrated in a rotary evaporator, and the aquatic residue was washed with ether (5 mL). The aqueous solution was acidified with 10% hydrochloric acid under cooling in an ice−water bath to obtain the product in a solid form.

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