1,8-Naphthyridines II: synthesis of novel polyfunctionally substituted 1,8-naphthyridinones and their degradation to 6-aminopyridones

Ramadan A. Mekheimer*, Afaf M. Abdel Hameed, and Kamal U. Sadek

Department of Chemistry, Faculty of Science, El-Minia University, El Minia 61519, AR Egypt
E-mail: rmekh@yahoo.com

Abstract

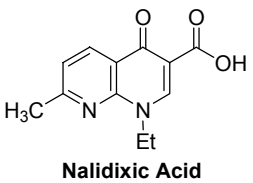
Reaction of 6-chloro-3-cyano-5-formyl-1,4-dimethyl-(1*H*)-pyridin-2-one (**1**) with [(ethoxy-carbonyl)methylene]triphenylphosphorane (**2**) afforded 5-ethoxycarbonylvinyl-2-pyridone derivative **3**. Azidation of **3** yielded 6-azido-2-pyridone derivative **4**, in excellent yield. Refluxing **4** with one equivalent of triphenylphosphine (aza-Wittig reaction) gave imino-phosphorane derivative **5**, and subsequent hydrolysis (Staudinger reaction) gave 6-amino-2-pyridone **6**. When aminopyridone **6** was refluxed in 1,2-dichlorobenzene it cyclised to the novel 1,8-naphthyridin-2-one **7**. Reaction of compound **1** with malononitrile in an ethanolic solution containing TEA afforded 6-chloropyridone derivative **18**, which reacted with sodium azide to furnish the corresponding azido compound **19.** Reduction of **19** with $Na_2S_2O_4$ did not give the corresponding aminopyridone **20** but rather the interesting 1,8-naphthyridin-2(1*H*)-ones **21**. Alternatively, compound **21** could also be obtained by refluxing aminopyridone **9** with malononitrile in an ethanolic solution containing TEA. On the other hand, reacting **9** with phenacylcyanide, under the same reaction conditions as used for the synthesis of **21**, did not afford the new 1,8-naphthyridine-2-one **22**, but rather 6-amino-3-cyano-1,4-dimethyl-(1*H*)-pyridine-2-one (**23**), *via* the thermal degradation of the intermediate **22**.

Keywords: 6-Aminopyridone, heterocyclic synthesis, 1,8-naphthyridine and ring degradation

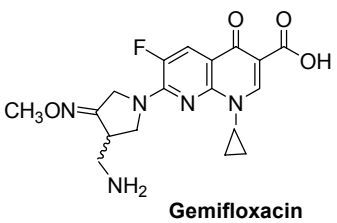
Introduction

1,8-Naphthyridine derivatives have attracted considerable attention because the 1,8-naphthyridine skeleton is present in many compounds that have been isolated from natural substances, with various biological activities. Nalidixic acid, for example, possesses strong antibacterial activity and used mainly for the treatment of urinary tract infections with gram negative pathogens [1]. In addition, Gemifloxacin is antimicrobial and antibacterial [2]. It is

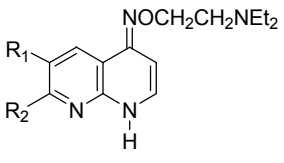
known that (*E*)- and (*Z*)-*O*-(diethylamino)ethyl oximes of 1,8-naphthyridine series (**A**) are potential drugs for local anesthesia [3], and 1-(2-fluorobenzyl)-3-(2-tolyl)-1,8-naphthyridin-2(1*H*)-one is used for the treatment of memory disorders, in particular, Alzheimer's disease [4]. 2-Amino-*N*-hydroxy-1,8-naphthyridine-3-carboxamidine possesses herbicidal properties and used for the selective control of weeds in barley, wheat, maize, sorghum and rice crops [5]. 1,8-Naphthyridine derivatives [6] also react with adenosine receptors of subtypes A_1 and A_{2A}. The important biological properties just descirbed stimulated studies on the synthesis of various functionalized (particularly, at positions 2,4 and 7) 1,8-naphthyridines, with the goal of designing new drugs for oral administration. Indeed, some 3-phenyl-1,8-naphthyridines which carry piperidyl, piperazinyl or morpholinyl groups or an *N*-diethanolamine side-chain in the 2-, 7- and 2,7- positions have been reported to show significant activity as inhibitors of human platelets aggregation induced by arachidonate and collagen [7]. In addition, 4-(*N*-methylenecyclo-alkylamino)-1,8-naphthyridine derivatives substituted in positions 2 and 7 are effective as antihypertensive agents [8]. 7-Amino-2-(4-carbethoxypiperazin-1-yl)-4-phenyl-1,8-naphthyridine has recently been synthesized and reported to have marked activity against mycobacterium tuberculosis [9]. A survey of the literature shows that the major synthetic approaches that are used to prepare various types of 1,8-naphthyridine system involves condensation of 2-aminopyridine derivatives with carbonyl compounds containing an activated methylene group [10-16] or with β-ketoesters [17]. Another general procedure for the preparation of 1,8-naphthyridine condensed ethanolic 2-amino-3-formylpyridines, in the presence piperidine base, with active methylene compounds, aldehydes, acyclic and cyclic ketones or diketones [18-24]. The most common method for the synthesis of 1,8-naphthyridine-4-ones begins with condensation of ethyl 2-chloronicotinoylacetates **I** with either triethylorthoformate/acetic anhydride, dimethylamine dimethylacetal, or an imino-chlorothioformate, followed by the reaction of intermediates **II** with amine to give the corresponding enamino ketoesters **III**. Subsequent intramolecular cyclization, under basic conditions, leads to 1,8-naphthyridone derivatives **IV** [25-31] (Chart 1). We have previously explored a new synthetic approach for the synthesis of polyfunctionally substituted 1,8-naphthyridin-2-one derivatives [32], and describe herein a new, efficient and convenient procedure for the synthesis of hitherto unreported polyfunctionally substituted 1,8-naphthyridin-2-one, 1,8-naphthyridin-2,7-dione. In addition, we report several new heterocyclic compounds, which are often difficult to obtain by other routes.



Nalidixic Acid



Gemifloxacin



(A)

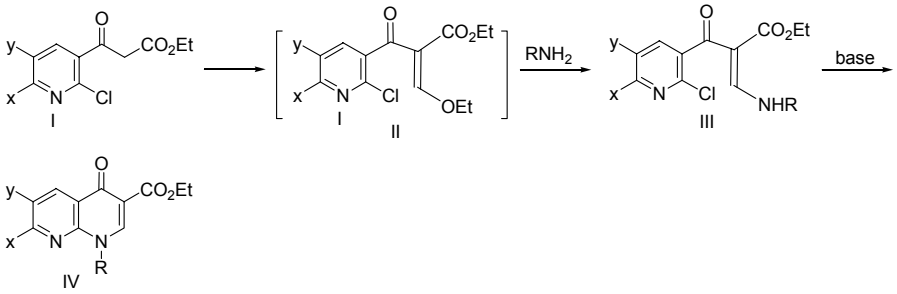
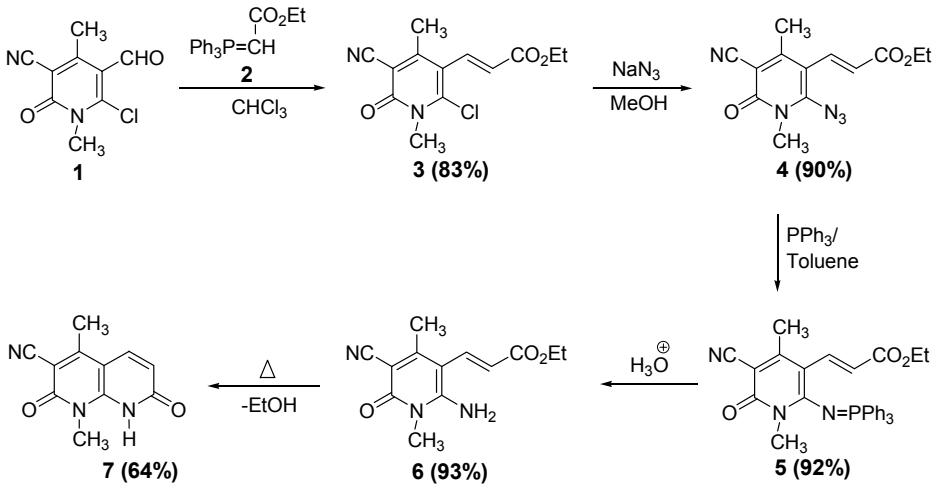


Chart 1

Results and Discussion

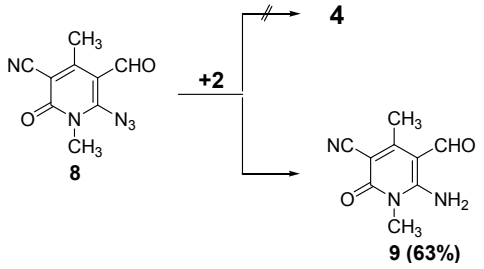
Our initial strategy targeted azidopyridone **4** and its conversion to the corresponding aminopyridone **6**, a putative synthon for the synthesis of 1,8-naphthyridin-2-ones **7**. The preparation of the aminopyridone **6** was accomplished via the classical Staudinger reaction [33]. Azidopyridone **4** was reduced to the corresponding aminopyridone **6** *via* formation of phosphazene intermediate **5**, as depicted in Scheme 1. 6-Chloro-3-cyano-5-ethoxycarbonyl-vinyl-1,4-dimethyl-(1*H*)- pyridine-2-one **3** was selected as our primary starting material for this series of reactions, and was readily obtained by treatment of 6- chloro-3-cyano-5-formyl-1,4-dimethyl-(1*H*)-pyridine-2–one (**1**) [32] with an equimolar amount of [(ethoxycarbonyl)-methylene]triphenylphosphorane (**2**) in chloroform at room temperature. Azidation of **3** with sodium azide in methanol at room temperature gave the corresponding azidopyridone **4**. Refluxing compound **4** with one equivalent of triphenylphosphine in dry toluene for 30 minutes yields 6-[(triphenylphosphoranylidene)amino]pyridone **5**, and subsequent acid hydrolysis of **5** with a mixture of acetic acid/water (5:1) provided the corresponding 6-aminopyridone derivative **6**, in excellent yield. Attempts to obtain 6-aminopyridone **6** by direct aminolysis of the chlorinated derivative **3** were unsuccessful, and only *E*-isomer was obtained for compounds **3**, **4**, **5** and **6**. In all cases, the ^{1}H NMR spectra include a characteristic AB system (≈ 7.02 and 7.61 ppm, with typical trans-coupling constant J = 16 Hz) due to the trans-configuration of vinylic protons in these compounds.

We investigated the intramolecular cyclization of aminopyridone **6**, with the hope of obtaining the interesting 1,8-naphthyridine-2,7-dione derivative **7**, first by in DMF, bromo-benzene and other high-boiling benzene derivatives. Compound **6** proved to be rather stable and partial decomposition occured with prolonged heating. No 1,8-naphthyridine-2,7-dione could be isolated from the decomposition products. The intramolecular cyclization of aminopyridone **6** was sluggish in boiling 1,2-dichlorobenzene, and a moderate yield of a new 3-cyano-1,4-dimethyl-(1*H*, 8*H*)-1,8-naphthyridine-2,7-dione **7**, was obtained after 20 hours. Longer reaction times (up to 60 hours) did not significantly improve the yield of **7**.



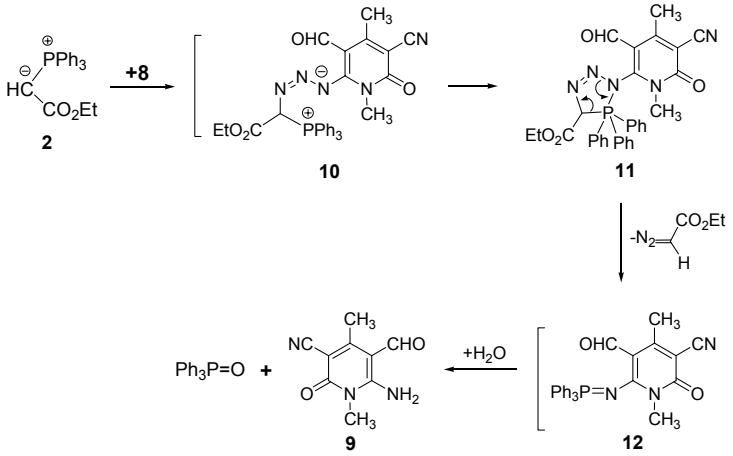
Scheme 1

In conjunction with this work, we believed that the desired synthon **4** might be obtained, in one step, by an alternate route that reacted azidopyridone **8** [32] with **2**. However, the reaction of compound **8** with **2** in $CHCl_3$, at room temperature for 2 hours, did not give azidopyridone **4**, but rather 6-amino-3-cyano-5-formyl-1,4-dimethyl-(1*H*)-pyridine-2-one (**9**), which was identical in all respects with an authentic sample previously prepared [32] (Scheme 2).



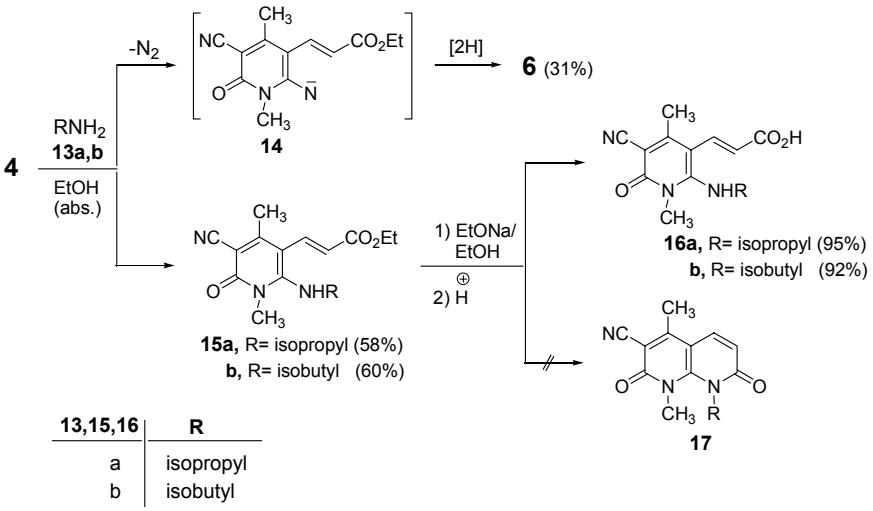
Scheme 2

Formation of **9** can be accounted for by reaction of **8** with **2** to give ring-opened intermediate **10**, followed by intramolecular cyclization to give intermediate **11**. Subsequent elimination of ethyldiazoacetate leads to the iminophosphorane intermediate **12**, which was hydrolysed by adventitious water to give the final product **9** along with triphenylphosphine oxide, as depicted in scheme 3.



Scheme 3

In order to construct new derivatives of the interesting 1,8-naphthyridines of type **17**, that are alkylated at the heterocyclic nitrogens, we attempted reaction of the azidopyridone **4** with alkylamines. Refluxing compound **4** with an excess of alkylamines **13a,b** in absolute EtOH for 3 hours, gave in each case two products, 6-aminopyridone **6** (minor product) and new 6-alkylamino-3-cyano-5-ethoxycarbonylvinyl-1,4-dimethyl-(1*H*)-pyridine-2-one **15** (major product), which were readily separated by preparative silica gel TLC (PLC). The structures of the major components **15a,b**, which formed *via* the nucleophilic substitution of the azido group at pyridinic C-6 in **4** with amino group, were substantiated on the basis of IR, ^{1}H NMR and mass spectroscopy. The IR spectra showed no azide absorption at 2140 cm^{-1}, but the absorption band at 3400 cm^{-1} was assigned as an NH function. The ^{1}H NMR spectra of **15a,b** revealed the presence of signals for NH and alkyl protons at C-6 in addition to signals of other groups. Furthermore, their structures were supported by correct mass spectra, which were compatible with assigned structures (see Experimental). Analytical data are in accordance with the proposed structures for compounds **15a,b**. The mechanism of the formation of **6** from the reaction of **4** with alkylamines **13a,b** is assumed to proceed *via* the formation of nitrene intermediate **14**, which then abstracts hydrogen under these reaction conditions to give compound **6** (Scheme 4).

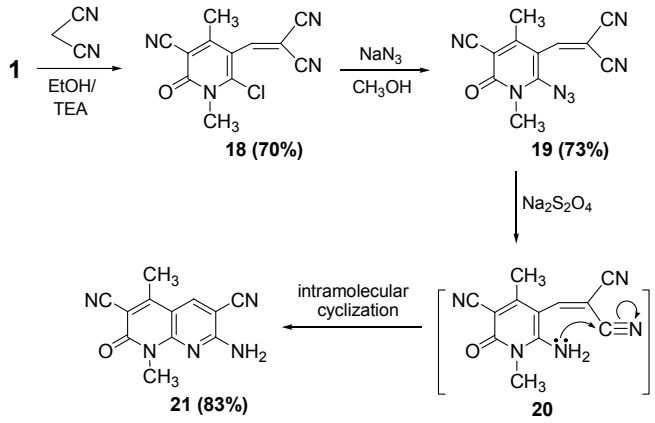


Scheme 4

Attention was next turned to the cyclization of 6-alkylaminopyridone **15** to 1,8-naphthyridine-2,7-dione **17**, which failed when **15** was heated in different solvent of higher boiling points. Variation of solvent, temperature and reaction time gave no polyfunctionally substituted 1,8-naphthyridin-2,7-dione **17**. When we examined the reaction of **15a,b** with non-nucleophilic bases, such as NaH and t-BuOK, varying solvent and time, the starting materials were recovered and no cyclization was observed. However, refluxing **15a,b** with sodium ethoxide for 3 h gave the corresponding acids **16a,b**.

Our interest in developing synthetic approaches with a view to synthesize new derivatives of the interesting 1,8-naphthyridine-2-one of type **21**, the azidopyridone **19**, in which the 5-position is substituted with methylenemalononitrile group, was thus investigated as a good starting material for this purpose. Treatment of compound **1** with an equimolecular amount of malononitrile in ethanol, in the presence of triethylamine at room temperature for 2 hours afforded the 6-chloropyridone **18**. Reaction of compound **18** with sodium azide in MeOH at room temperature for 2 hours gave the corresponding 6-azidopyridone **19.** Reduction of the azide moiety in **19** with $Na_2S_2O_4$ gave aminopyridone **20**, which cyclised spontaneously to afford the hitherto unknown 7-amino-3,6-dicyano-1,4- dimethyl- naphthy- ridine-2-one (**21**) (Scheme 5). The structure of **21** was substantiated by its elemental analysis and spectral data. The IR spectrum revealed the presence of the amino function (NH_2) at 3322 and 3231 cm^{-1}. Furthermore, the ^1H NMR gave strong evidence for the formation of compound **21**. The data confirmed the absence of the methine proton (-CH=C) at C-5 in azidopyridone **19**, the presence of two singlets at δ 8.53 ppm and 7.82 ppm attributable to the amino group at C-7 and the H-5 proton, respectively, in addition of signals due to two methyl groups in their expected positions. Moreover, structure **21** was supported by correct mass spectrum, which was compatible with assigned structure (see Experimental). To obtain unequivocal evidence for the structure,

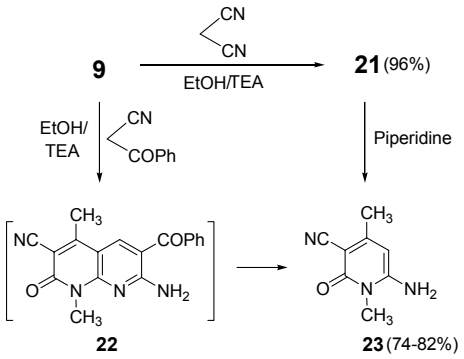
compound **21** was alternatively synthesized by refluxing the 6-amino-pyridone **9** with malononitrile in ethanol (Scheme 6).



Scheme 5

In order to extend the scope of this reaction, 6-aminopyridone **9** was reacted with phenacylcyanide, with the hope of obtaining the interesting 1,8-naphthyridine derivative **22**. However, surprisingly, 6-amino-3-cyano-1,4-dimethyl-(1*H*)-pyridine-2-one (**23**) was unexpectedly obtained as the only identifiable product, identical in all respects with the structure reported in the literature [32]. The formation of **23** can be explained by the degradation of 1,8-naphthyridine-2-ones intermediate **22**. On the other hand, the formation of **21** from compound **9** and malononitrile under basic conditions implies that 1,8-naphthyridine-2-one **21** is more stable than **22** under these reaction conditions.

This observation prompted us to investigate the stability of **21** under various conditions. Compound **21** was unreactive in refluxing solvents such as bromobenzene, 1,2-dichlorobenzene or other high-boiling benzene derivatives for extended periods. However, refluxing **21** in piperidine for 30 minutes yielded 6-aminopyridone **23** as the sole product (Scheme 6). On the basis of these results, it may be concluded that the use of piperidine, as a basic reagent, facilitates the opening of the pyridine ring in **21**. The proposed mechanism for the conversion of 1,8-naphthyridine-2-one **21** to 6-aminopyridone **23** may resemble the mechanism described previously [32].



Scheme 6

Conclusions

This second-generation of our annulation strategy shows that the azidopyridone derivatives were converted to the corresponding aminopyridones in excellent yields. These amino compounds are useful precursors in the preparation of novel 1,8-naphthyridine-2-one and 1,8-naphthyridine-2,7-dione derivatives. The intramolecular cyclization of these ortho-substituted aminopyridone derivatives appears to be an unequivocal method for the synthesis of 1,8-naphthyridine derivatives, it is an efficient and convenient experimental procedure which requires only readily available starting materials. This synthetic approach, for the synthesis of polyfunctionally substituted 1,8-naphthyridine, may be useful in view of the pharmacological interest in this compound class. The novel cleavage of 1,8-naphthyridine ring systems to the corresponding aminopyridones has been described.

Experimental Section

General Procedures. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 plates, 0.25 mm thick with F-254 indicator. Visualization was accomplished by UV light. Solvents for extraction and chromatography were reagent grade and used as received. ^{1}H NMR spectra were recorded with Bruker AM 400 spectrometer at 400 MHz with DMSO-d_6 and $CDCl_3$ as solvents and TMS as an internal standards; Chemical shifts (δ) are reported in ppm. Mass spectra were measured on a Gc/Ms-QP1000EX (EI, 70 eV) mass spectrometer. IR spectra were recorded with a Schimadzu 470 spectrophotometer in KBr disks. Microanalyses were performed by the microanalytical Data Unit at Cairo University.

6-Chloro-3-cyano-5-ethoxycarbonylvinyl-1,4-dimethyl-(1*H*)-pyridine-2-one (3). A mixture of **1** (1 g, 4.75 mmol) and **2** (1.65 g, 4.75 mmol) in $CHCl_3$ (15 ml) was stirred for 2 h at room temperature. The resulting solid product was collected by filtration, washed with MeOH, dried and recrystallized from EtOH to afford compound **3** as colorless crystals 1.10 g, 83 % yield, mp 223-224˚C, IR (KBr pellet): 2990 (aliph. CH), 2220 (CN), 1700 (CO, ester), 1660 (CO) cm^{-1}; MS (EI): m/z 282 (M^+, 5), 280 (M^+, 6), 235 (12), 208 (83), 207 (100), 192 (3), 179 (4), 144 (7), 129 (5), 114 (2), 88 (3), 73 (2), 54 (2); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.61 (d, 1H, J =16 Hz, CH), 7.14 (d, 1H, J = 16 Hz, CH), 4.19 (q, 2H, J = 7 Hz, CH_2), 3.65 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 1.24 (t, 3H, J = 7 Hz, CH_3); Calcd. for $C_{13}H_{13}ClN_2O_3$ (280.74); C, 55.61; H, 4.67; Cl, 12.64; N, 9.97; Found: C, 55.49; H, 4.46; Cl, 12.73; N, 9.85.

6-Azido-3-cyano-5-ethoxycarbonylvinyl-1,4-dimethyl-(1*H*)-pyridine-2-one (4). Sodium azide (0.052 g, 0.80 mmol) was added to a solution of **3** (0.180 g, 0.64 mmol) in MeOH (5 ml) and the mixture was stirred for 2 h at room temperature (25˚C). Then the reaction mixture was poured into H_2O and the precipitated solid product was filtered, washed well with H_2O, dried and recrystallized from MeOH to afford compound **4** as yellow crystals 0.165 g, 90 % yield, mp 141-142˚C (decomp.), IR (KBr pellet): 2900 (aliph. CH), 2220 (CN), 2140 (N_3), 1700 (CO, ester), 1645 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.59 (d, 1H, J = 16 Hz, CH), 7.11 (d, 1H, J = 16 Hz, CH), 4.19 (q, 2H, J = 7 Hz, CH_2), 3.45 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 1.21 (t, 3H, J = 7 Hz, CH_3); Calcd. for $C_{13}H_{13}N_5O_3$ (287.26): C, 54.35; H, 4.56; N, 24.38; Found: C, 54.24; H, 4.82; N, 24.57.

3-Cyano-5-ethoxycarbonylvinyl-1,4-dimethyl-6-[(triphenylphosphoranylidene)amino]-(1*H*)-pyridine-2-one (5). A mixture of **4** (0.1 g, 0.34 mmol) and triphenylphosphine (0.09 g, 0.34 mmol) in dry toluene was heated under reflux for 30 min. After concentration and cooling to room temperature, the resulting solid product was filtered off, washed with a small amount of toluene, dried and recrystallized from toluene to give compound **5** as yellow crystals 0.167 g, 92% yield, mp 228-230˚C, IR (KBr pellet): 3050 (arom. H), 2900 (aliph. CH), 2220 (CN), 1700 (CO, ester), 1650 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.55-7.76 (m, 15H, Ar-H + vinylic H), 7.04 (d, 1H, J = 16 Hz, CH), 4.12 (q, 2H, J = 7 Hz, CH_2), 3.47 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 1.21 (t, 3H, J = 7 Hz, CH_3); Calcd. for $C_{31}H_{28}N_3O_3P$ (521.54): C, 71.39; H, 5.41; N, 8.06; Found: C, 71.12; H, 5.52; N, 7.96.

6-Amino-3-cyano-5-ethoxycarbonylvinyl-1,4-dimethyl-(1*H*)-pyridine-2-one (6) and 6-alkylamino-3-cyano-5-ethoxycarbonylvinyl-1,4-dimethyl-(1*H*)-pyridine-2-ones 15a,b.

Route (A) for compound 6. Triphenylphosphoranylideneaminopyridone **5** (0.3 g, 0.58 mmol), AcOH (5 ml) and H_2O (1 ml) refluxed for 6 h. After concentration and cooling to room temperature, the resulting solid product was collected by filtration, washed well with MeOH to remove Ph_3PO, dried and recrystallized from EtOH to give compound **6**.

Route (B) for compounds 6 and 15a,b. Alkyl amine (2.08 mmol) was added to a solution of compound **4** (0.3 g, 1.04 mmol) in absolute EtOH (5 ml) and the mixture was refluxed for 3 h. After concentration and cooling to room temperature, the resulting solid product was chromatographed on a preparative TLC using (toluene:acetone, 10:3) as eluent to give two

zones. Extraction with acetone followed by recrystallized from EtOH gave compounds **6** and **15a,b**.

6-Amino-3-cyano-5-ethoxycarbonylvinyl-1,4-dimethyl-(1*H*)-pyridine-2-one (6). Yellow crystals, yield: [0.140 g, 93% (route A) and 0.085 g, 31% (route B, in case of isopropylamine); 0.075g, 27% (route B, in case of isobutylamine)], mp 302-303˚C, IR (KBr pellet): 3400, 3350 (NH_2), 2900 (aliph. CH), 2220 (CN), 1670 (CO, ester), 1650 (CO) cm^{-1}; MS (EI): m/z 261 (M^+, 9), 232 (3), 216 (13), 189 (89), 188 (100), 173 (14) , 158 (3), 104 (2), 76 (3); ^{1}H NMR (DMSO-d_6 , 400MHz): δ 7.88 (br s, 2H, NH_2), 7.56 (d, 1H, *J* = 16 Hz, CH), 6.94 (d, 1H, *J* = 16 Hz, CH), 4.11 (q, 2H, *J* = 7 Hz, CH_2), 3.35 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 1.21 (t, 3H, *J* = 7 Hz, CH_3); Calcd. for $C_{13}H_{15}N_3O_3$ (261.27): C, 59.76; H, 5.79; N, 16.08; Found: C, 59.54; H, 5.91; N, 15.97.

3-Cyano-5-ethoxycarbonylvinyl-6-*iso*-propylamino-1,4-dimethyl-(1*H*)-pyridine-2-one (15a). Yellow crystals 0.185 g, 58% yield; mp 183-184˚C, IR (KBr pellet): 3350 (NH), 2980 (aliph. CH), 2200 (CN), 1680 (CO, ester), 1660 (CO) cm^{-1}; MS (EI): m/z 303 (M^+, 16), 288 (3), 258 (9), 231 (60), 230 (66), 217 (9), 189 (84), 188 (100), 173 (14), 158 (6), 143 (4), 102 (4), 58 (2); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.67 (d, 1H, *J* = 16 Hz, CH), 7.39 (d, 1H, *J* = 5Hz, NH), 7.12 (d, 1H, *J* = 16 Hz, CH), 4.38 (m, 1H, N-CH), 4.21 (q, 2H, *J* = 7 Hz, CH_2), 3.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 1.35 (d, 6H, *J* = 6 Hz, $2CH_3$), 1.30 (t, 3H, *J* = 7 Hz, CH_3); Calcd. for $C_{16}H_{21}N_3O_3$ (303.35): C, 63.35; H, 6.98; N, 13.85. Found: C, 63.21; H, 7.13; N, 13.68.

6-*iso*-Butylamino-3-cyano-5-ethoxycarbonylvinyl-1,4-dimethyl-(1*H*)-pyridine-2-one (15b). Yellow crystals 0.20 g, 60% yield; mp 198-200˚C, IR (KBr pellet): 3400 (NH), 2950 (aliph. CH), 2200 (CN), 1680 (CO, ester), 1640 (CO) cm^{-1}; MS (EI): m/z 317 (M^+, 17), 272 (8), 246 (15), 245 (64), 244 (100), 188 (47), 174 (9), 144 (5), 103 (3), 57 (10); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.59 (d, 1H, *J* = 16 Hz, CH); 7.48 (t, 1H, *J* = 5 Hz, NH), 6.98 (d, 1H, *J* = 16 Hz, CH), 4.12 (q, 2H, *J* = 7 Hz, CH_2), 3.47 (t, 2H, *J* = 6 Hz, CH_2), 3.31 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.00 (m, 1H, CH), 1.23 (t, 3H, *J* = 7 Hz, CH_3), 0.91 (d, 6H, *J* =7 Hz, $2CH_3$); Calcd. for $C_{17}H_{23}N_3O_3$ (317.37): C, 64.33; H, 7.30; N, 13.24; Found: C, 64.18; H, 7.48; N, 13.06.

3-Cyano-1,4-dimethyl-(1*H*, 8*H*)-1,8-naphthyridine-2,7-dione (7). A solution of aminopyridone 6 (0.5g, 1.91 mmol) in 1,2-dichlorobenzene was heated under reflux for 20 h (TLC control). After concentration and cooling to room temperature, the resulting solid product was chromatographed on a preparative TLC using (toluene:acetone, 10:3) as eluent. Extraction with acetone followed by recrystallization from DMF gave compounds **7** as brownish crystals 0.265 g, 64% yield, mp 280-282˚C, IR (KBr pellet): 3350 (NH), 2900 (aliph. CH), 2220 (CN), 1645 (CO) cm^{-1}; MS (EI): m/z 215 (M^+, 2), 200 (2), 188 (100), 173 (79), 158 (5), 144 (26), 118 (12), 69 (7); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.70 (s, 1H, NH), 8.08 (d, 1H, *J* = 16 Hz, H-5), 6.23 (d, 1H, *J* = 16 Hz, H-6), 3.39 (s, 3H, CH_3), 2.39 (s, 3H, CH_3); Calcd. for $C_{11}H_9N_3O_2$ (215.20): C, 61.39; H, 4.21; N, 19.53; Found: C, 61.21; H, 4.43; N, 19.34.

6-Amino-3-cyano-5-formyl-1,4-dimethyl-(1*H*)-pyridine-2-one (9). A mixture of **8** (0.250 g, 1.15 mmol) and **2** (0.401 g, 1.15 mmol) in $CHCl_3$ (15 ml) was stirred for 2 h at room temperature. The resulting solid product was collected by filtration, washed with a small amount

of MeOH, dried and recrystallized from DMF to give compound **9** as colorless crystals 0.138 g, 63% yield; mp 311-313˚C (decomp.) [Lit. [32]: 98% yield, mp 312-314˚C (decomp.)].

General procedure for 3-(6-Alkylamino-3-cyano-1,4-dimethyl-2-oxo-1(2*H*)-pyridine-5-yl)-acrylic acids 16a,b. Compounds **15a,b** (0.66 mmol) was dissolved in solution of NaOEt/EtOH, prepared from Na (46 mg) and anhyd. EtOH (10 ml). The mixture was refluxed for 3 h, during which solid product separated out. After cooling to room temperature and acidification with conc. HCl, the resulting solid product was filtered off, washed well with H_2O, dried and recrystallized from EtOH to give **16a,b**.

3-(3-Cyano-1,4-dimethyl-2-oxo-6-*iso*-propylamino-1(*2H*)-pyridine-5-yl)-acrylic acid (16a). Colorless crystals 0.172 g, 95% yield, mp 229-230˚C, IR (KBr pellet): 3328 (NH), 2982, 2932 (aliph. CH), 2200 (CN), 1680 (CO, acid) 1640 (CO) cm^{-1}; MS (EI): m/z 275 (M^+, 12), 242 (1), 230 (25), 188 (100), 174 (17), 160 (9), 146 (10), 104 (9), 71 (1), 58 (4); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.0 (br s, 1H, OH), 7.56 (d, 1H, J = 16 Hz, CH), 6.93 (d, 1H, J = 16 Hz, CH), 6.82 (d, 1H, J = 5 Hz, NH), 4.46 (m, 1H, N-CH), 3.35 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 1.32 (d, 6H, J = 7 Hz, $2CH_3$); Calcd. for $C_{14}H_{17}N_3O_3$ (275.30): C, 61.08; H, 6.22; N, 15.26; Found: C, 60.92; H, 6.35; N, 15.37.

3-(6-*iso*-Butylamino-3-cyano-1,4-dimethyl-2-oxo-1(2*H*)-pyridine-5-yl)-acrylic acid (16b). Yellow crystals 0.175 g, 92% yield, mp 224-226˚C, IR (KBr pellet): 3330 (NH), 2900 (aliph. CH), 2200 (CN), 1710 (CO, acid), 1655 (CO) cm^{-1}; MS (EI): m/z 289 (M^+, 13), 245 (57), 244 (73), 188 (100), 174 (17), 133 (4), 104 (14), 57 (13); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.02 (br s, 1H, OH), 7.54 (d, 1H, J = 16 Hz, CH), 7.42 (br s ,1H, NH), 6.89 (d, 1H, J =16 Hz, CH), 3.59 (t, 2H, J = 7 Hz, CH_2), 3.37 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 1.90 (m, 1H, CH), 0.89 (d, 6H, J = 7 Hz, $2CH_3$); Calcd. for $C_{15}H_{19}N_3O_3$ (289.32): C, 62.27; H, 6.62; N, 14.52; Found: C, 62.12; H, 6.73; N, 14.34.

[(2-chloro-5-cyano-1,4-dimethyl-6-oxo-1,6-dihydropyridin-3-yl)methylene]malononitrile (18). Triethylamine (0.20 g, 2 mmol) was added to a solution of compound **1** (0.210 g, 1mmol), and malononitrile (0.083 g, 1.25 mmol) in absolute EtOH (5 ml). Stirring was maintained at room temperature (25˚C) for 2 h. The resulting solid product was collected by filtration, dried and recrystallized from EtOH to afford compound **18** as yellow crystals 0.180 g, 70% yield, mp 161-162˚C, IR (KBr pellet): 2990 (aliph. CH), 2220 (CN), 1640 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.62 (s, 1H, methine H), 3.42 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), Calcd. for $C_{12}H_7ClN_4O$ (258.70): C, 55.71; H, 2.73; Cl, 13.72; N, 21.65; Found: C, 55.68; H, 2.85; Cl, 13.82; N, 21.54.

2-(6-Azido-3-cyano-1,4-dimethyl-2-oxo-1(2*H*)-pyridine-5-yl-methylene)-malononitrile (19). To a solution of **18** (0.20 g, 0.77 mmol) in MeOH (10 ml), sodium azide (0.063 g, 0.97 mmol) was added and the mixture was stirred for 2 h at room temperature (25˚C). Then the reaction mixture was poured into H_2O and the precipitated solid product was filtered, washed well with H_2O and dried to afford compound **19** as yellow crystals 0.150 g, 73% yield, mp 171-172˚C (decomp.), IR (KBr pellet): 2900 (aliph. CH), 2220 (CN), 2140 (N_3), 1640 (CO) cm^{-1}; Because

of the poor stability of this compound, satisfactory ^{1}H NMR, MS and elemental analysis could not be obtained and it was used without delay in the next reaction.

7-Amino-3,6-dicyano-1,4-dimethyl-(1*H*)-1,8-naphthyridine-2-one (21)

Route A. Sodium dithionite (0.40 g, 2.30 mmol) was added portionwise to a stirred solution of **19** (0.20 g, 0.75 mmol) in MeOH (15 ml)-water (5 ml) mixture. Stirring was maintained at room temperature (25˚C) for 3 h. The reaction mixture was poured into water. The precipitated solid product was collected by filtration, washed well with water and dried to give compound **21**.

Route B. Triethylamine (0.211g, 2.09 mmol) was added to a solution of **9** (0.20 g, 1.05 mmol) and malononitrile (0.086 g, 1.31 mmol) in absolute EtOH (10 ml). The reaction mixture was refluxed for 15 min. After concentration and cooling, the resulting solid product was collected by filtration, dried and recrystallized from EtOH to give compound **21** as yellow crystals yield [0.150 g, 83% (route A) and 0.240 g, 96% (route B)]; mp 240-242˚C, IR (KBr pellet): 3322, 3231 (NH_2), 2925 (aliph. CH), 2220 (CN), 1645 (CO) cm^{-1}; MS (EI): m/z 239 (M^+, 100), 212 (99), 186 (56), 171 (47), 100 (25), 57 (67); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.53 (br s, 2H, NH_2). 7.82 (s, 1H, H-5), 3.35 (s, 3H, CH_3), 2.43 (s, 3H, CH_3); Calcd. for $C_{12}H_9N_5O$ (239.22): C, 60.25; H, 3.79; N, 29.27; Found: C, 60.34; H, 3.91; N, 29.04.

6-Amino-3-cyano-1,4-dimethyl-(1*H*)-pyridine-2-one (23)

Route A. Triethylamine (0.211 g, 2.09 mmol) was added to a solution of **9** (0.20 g, 1.046 mmol) and phenacylcyanide (0.191g, 1.31 mmol) in absolute EtOH (10 ml). The reaction mixture was refluxed for 3 h. After concentration and cooling, the resulting solid product was filtered and dried to give compound **23**.

Route B. A solution of compound **21** (0.20 g, 0.84 mmol) in piperidine (5 ml) was heated under reflux for 30 min. After cooling and concentration, the resulting product was filtered, dried and recrystallized from MeOH to give compound **23** as colorless crystals, yield: [0.140 g, 82% (route A); 0.10 g, 74% (route B)]; mp 285-286˚C (decomp.) [Lit. [32] 64% yield, mp 286-287˚C (decomp.)].

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