Modification of conditions for the selective preparation of 2-amino-3-cyano-4-phenylpyridines

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Abstract

We herein describe the modification of the experimental conditions for the synthesis of certain 2-amino-4-aryl-3-cyanopyridines from benzaldehyde, malononitrile, ammonium acetate and aminoketones. The outcome of the reaction proved to be highly dependent on the experimental procedure, occasionally giving rise to metaphthalodinitriles. Mechanistical proposals are also reported, in order to explain the observed dependence on the procedure.

Keywords: Heterocycles, pyridines, medicinal chemistry, condensation, bicyclic compounds

Introduction

In the context of a current project developed in our laboratory for the synthesis of biologically active molecules, 2-amino-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitriles **I** (Figure 1) were selected for study as well as 2-aminopyridine- and 2-chloropyridine-3,5-dicarbonitriles.[1] Particular interest was focused on the highly functionalized molecules **1-3** (Figure 1).

R_1= H, alkyl, Ar, etc.
R_2= H, alkyl, Bn, etc.

**1** R= CH_2Ph
2 R= CH_2CCH
3 R= Boc
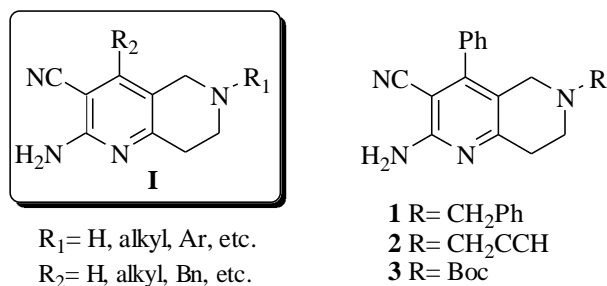
Figure 1. Target 2-amino-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitriles.

Literature searching shows that very few reports on the preparation of this type of heterocyclic ring system have been published. Among the few examples, 2-amino-6-methyl-4-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile **4** (Figure 2) has recently been included in a patent dealing with compounds altering the lifespan of eukaryotic organisms.[2] Regarding 2-amino-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile **5** and benzyl 2-amino-3-cyano-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate **6**, they have been used as intermediates in the synthesis of partially restricted linear, tricyclic 5-deaza antifolates.[3] Related *tert*-butyl 2-amino-4-phenyl-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate **7** has been described for the preparation of polysubstituted 2-aminopyrimidines.[4]
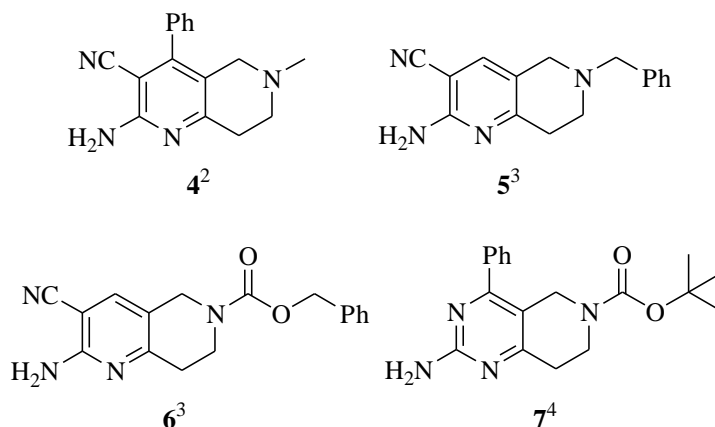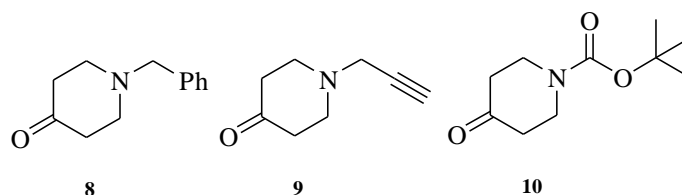

Figure 2. Examples of 2-amino-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitriles reported in the literature.

As a starting point, a protocol described for the synthesis of certain 2-amino-4-aryl-3-cyanopyridines was considered.[5] The attractiveness of this synthetic choice lies in the fact that it consists of a *one pot* procedure, involving the condensation of malononitrile with aromatic aldehydes and alkyl ketones in the presence of ammonium acetate. To the best of our knowledge, no *N*-substituted-4-piperidones have been tested under these conditions (Equation 1). Regarding our interest in obtaining 2-amino-4-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitriles, we decided to study the scope of the above mentioned method.

(**1**)
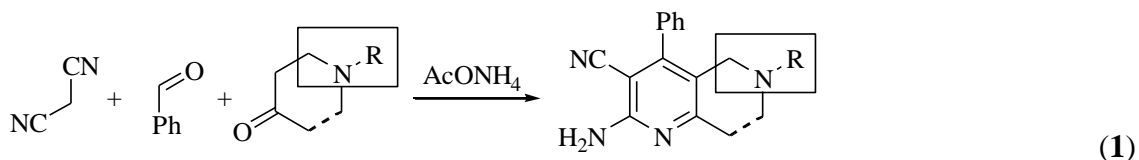
Results and Discussion

Figure 3 shows the piperidones **8**-**10** selected as the carbonyl partners. Whereas 1-benzylpiperidin-4-one **8** is commercially available, 1-(prop-2-ynyl)piperidin-4-one **9**[6] and *tert*-butyl 4-oxopiperidine-1-carboxylate **10**[7] were synthesized from piperidin-4-one **11** (see Supporting Information).

Figure 3. Selected ketones for the synthesis of 2-amino-4-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitriles.

A preliminary trial carried out under the experimental conditions reported for other aminoketones[5] gave rise to the desired 2-amino-6-benzyl-4-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile **1** (Figure 1) when mixing malononitrile, benzaldehyde, **8** and ammonium acetate, albeit in low chemical yield (21%).[8] With the aim of improving the yield, we decided to prepare 2-benzylidenemalononitrile **12** beforehand and add *in situ* piperidone **8**; the isolated precipitate was then further treated with an AcONH$_4$/ AcOH mixture.[9] Surprisingly, 6-amino-2-benzyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline-5,7-dicarbonitrile **13** (Scheme 1) and not compound **1** was obtained under these conditions. Although the ^{1}H-NMR spectra are very similar for both molecules, ^{13}C-NMR was conclusive; in the case of **13**, two signals at 115.6 and 115.2 ppm and two additional signals at 96.6 and 96.4 ppm account for two nitrile carbons atoms (CN) and two aromatic carbons bearing the nitrile groups (*C*-CN) respectively. The mass spectrum supported the proposed structure, showing a main peak at 365.2 (M+1). The formation of this product can be rationalized as shown in Scheme 1:[10] if ammonium acetate is not present but piperidone is, both formation of intermediate **II** and subsequent condensation with malononitrile take place; due to the reversibility of the initial benzaldehyde-malononitrile condensation, the presence of malononitrile would be guaranteed even though an excess of this reagent was not used.

Continuing with our efforts to improve the yield of product **1**, an alternative stepwise protocol[5] was considered. Compound **12** was prepared and *isolated*; then, reaction with **8** and AcONH$_4$ in toluene was performed. By adding compound **8** and AcONH$_4$ at the same time, intermediate **II** formed upon reaction between **12** and **8** evolved to give rise compound **1**; moreover, a better yield of 46% was obtained when following this stepwise protocol.
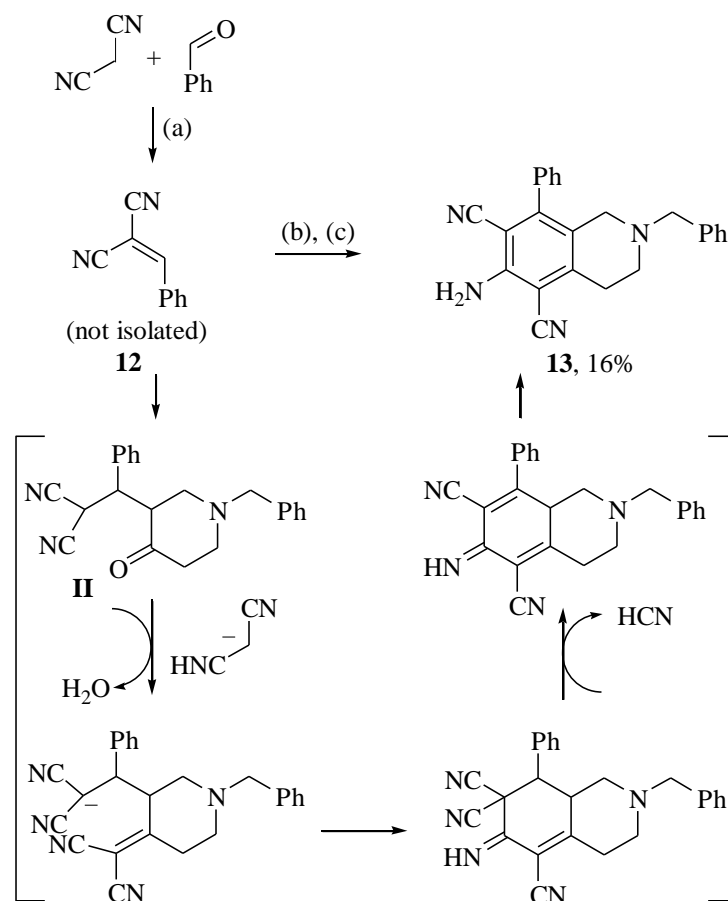
Scheme 1. Reaction conditions and mechanism of the formation of compound **13**: (a) piperidine (cat.), toluene, rt; (b) piperidone **8**; (c) AcONH$_4$/AcOH reflux.

Besides tetrahydronaphthyridine **1**, 2-benzylmalononitrile could be isolated from the crude mixture in 40% yield. This fact indicates that a side reaction is occuring, consisting of the reduction of starting 2-benzylidenemalononitrile. Thus, an additional trial to improve the yield of **1** was carried out by doubling the amount of this reagent (Scheme 2). In this way, the yield of isolated product **1** was increased up to 68%. Further experiments considering larger amounts of starting **12** were performed, although no significant improvement was achieved.

In a similar fashion, we applied this protocol to the reaction of piperidone **9** with 2 equivalents of 2-benzylidenemalononitrile in the presence of AcONH$_4$ and toluene as solvent. The formation of 2-amino-4-phenyl-6-(prop-2-ynyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile **2** was confirmed and the initial yield of 15% significantly increased to 45% (Scheme 2). On the contrary, derivative **3** (Figure 1) was not detected in the reaction with piperidone **10** even under these optimized conditions.
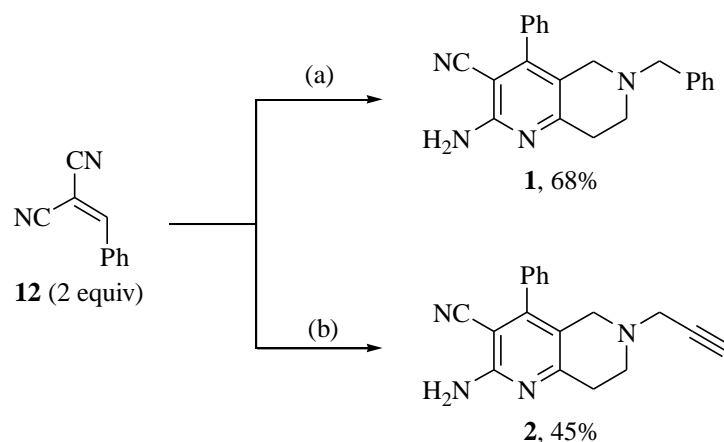
Scheme 2. Optimized method for the synthesis of compounds **1** and **2**. Conditions: (a) piperidone **8**, AcONH$_4$, toluene, reflux; (b) piperidone **9**, AcONH$_4$, toluene, reflux.

So far, the experiments described just involved *N*-substituted 4-piperidones, and consequently, the regioselectivity of the reaction was not an issue. We then decided to study the outcome of the reaction when using methylalkylketones such as β-aminoketone **14** (Scheme 3). The latter was readily synthesized by a Michael-type reaction of but-3-en-2-one and *N*-methylpropargylamine in almost quantitative chemical yield (Scheme 3). Under the improved experimental conditions above described for **1** and **2**, the reaction gave rise to a complex mixture, from which only compound **15** could be isolated, in poor yield (14%).[11] The structure of this product was confirmed on the basis of its analytical and spectroscopic data as well as by X-ray diffraction analysis (Figure 4).[12] Surprisingly, 2-butanone reacts with 2-benzylidenemalonitrile to give exclusively 2-amino-5,6-dimethyl-4-phenylnicotinonitrile in 65% yield.[5] Thus, the aminated fragment seems to be playing a role; steric effects might justify the observed result.
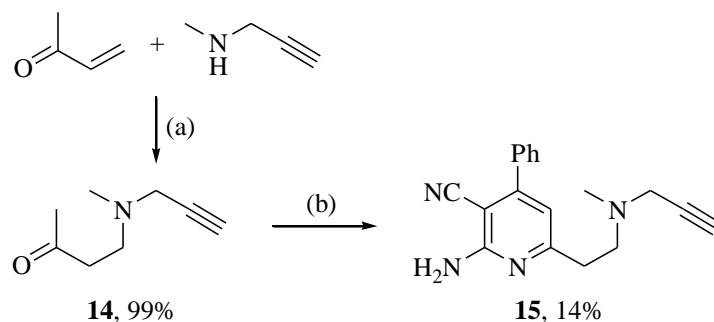

Scheme 3. Preparation of β-aminoketone **14** and transformation into the unexpected 2-amino-3-cyanopyridine **15**. Conditions: (a) toluene, reflux; (b) reagent **12**, AcONH$_4$, toluene, reflux.
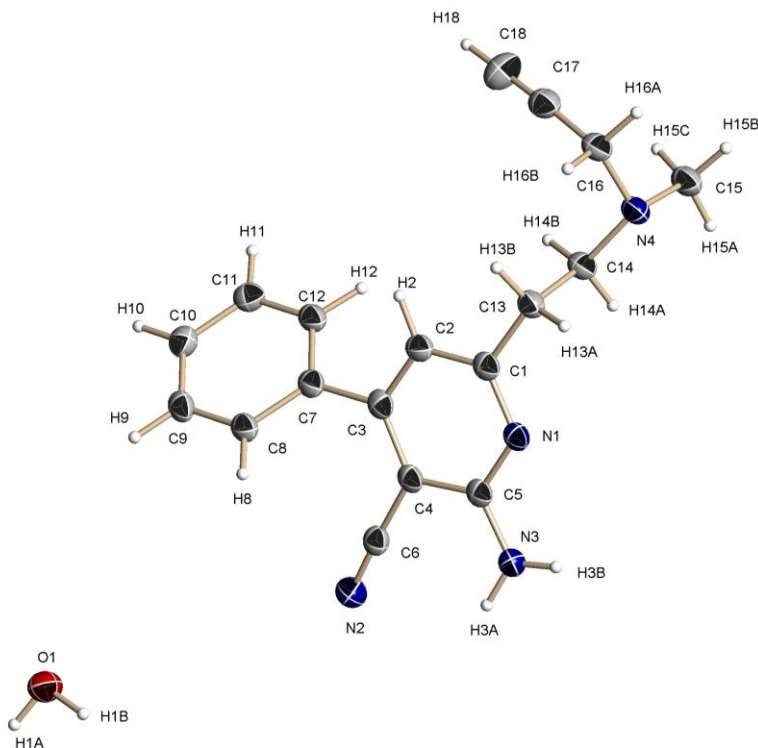
Figure 4. X-ray diffraction analysis of compound **15**.

As the observed regioselectivity in the previous example was not the one leading to nicotinic derivatives, we tried to control the regioselectivity by increasing the acidity of the required proton atoms in the carbonylic reagent. 1,3-dicarbonylic compound **16**[13] (Figure 5) was then prepared and tested under the above mentioned optimized conditions. The reaction turned out to give a high degree of decomposition and no defined products could be detected. At this point, we decided to follow an alternative synthetic method to prepare 6-amino-5-cyano-2-methyl-4-phenyl-*N*-(prop-2-ynyl)nicotinamide **17** as shown in scheme 4. According to this, *tert*-butyl acetoacetate was chosen as the 1,3-dicarbonylic compound.[14] Under the optimized conditions previously described, expected *tert*-butyl 6-amino-5-cyano-2-methyl-4-phenylpyridine-3-carboxylate **18** was isolated in 41% yield. Removal of the *tert*-butyl group and subsequent amide formation with *N*-propargylamine and EDCI/HOBt provided us with the required nicotinamide in 29% yield (from starting **18**).


16
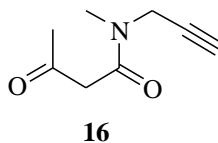
Figure 5
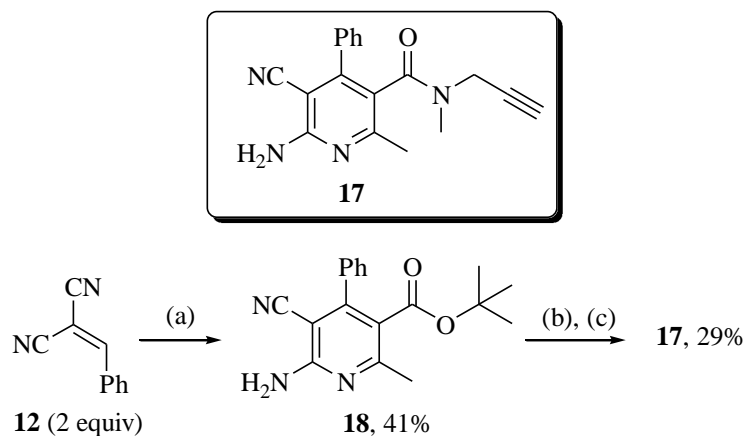
Scheme 4. Alternative way to prepare nicotinamide **17**. Conditions: (a) *tert*-butyl acetoacetate, AcONH₄, toluene, reflux; (b) i) TFA, CH₂Cl₂, rt, 7 days ii) NaOH 2N; c) EDCI, DIPEA, HOBt, *N*-methylpropargylamine, CH₂Cl₂, 0 ºC to rt, 12h.

For comparison, a trial of preparation of compound **18** in a *one-pot* fashion was carried out by mixing malononitrile, benzaldehyde, *tert*-butyl acetoacetate and ammonium acetate in methanol. Decomposition was observed in this case too and just a 4% of compound **19** (Figure 6) could be isolated. On the other hand, an attempt of obtaining compound **18** from the pyrane precursor **20** (Figure 6)[9,14] gave rise to pyridine **21** (Figure 6), which implied a decarboxylation process taking place. These facts showed again that slight variations of the protocol afforded quite different compounds.
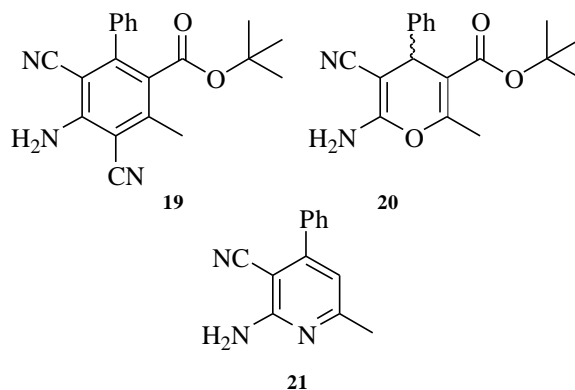
Figure 6

Conclusions

To sum up, this is the first time that a simple method based on four components is used for the preparation of 2-amino-3-cyano-4-phenylnicotinic compounds. The previously described

synthesis of 2-amino-4-aryl-3-cyanopyridines inspired us to prepare the required tetrahydro-1,6-naphthyridines **1** and **2**. A slight modification of the protocol afforded tetrahydroisoquinoline **13** instead of the required **1**. Mechanistical explanations for the high dependence on the followed procedure in the preparation of nicotinic compounds from four components have been provided. Moreover, unexpected regiochemistry was observed when employing β-aminoketone **14**. In order to obtain the desired regiochemistry, *tert*-butyl acetoacetate was used as the carbonylic reagent and intermediate **18** was succesfully prepared. Finally, subsequent modification of the latter afforded nicotinamide **17**.

Experimental Section

General. Unless otherwise stated, all reagents were purchased from commercial sources (Aldrich, Fluka) and used without further purification. Anhydrous toluene was obtained by passing the solvent through an activated alumina column on a PureSolv™ solvent purification system (Innovative Technologies, Inc., MA). Flash column chromatography was carried out using silica gel C60 (230 mesh) as the stationary phase. Analytical thin layer chromatography was performed on 0.25 mm thick precoated silica gel plates (60F$_{254}$). Compounds were visualized under UV light at 254 nm or either staining with a 1% ninhydrin in EtOH solution or with cerium molybdate. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature in CDCl$_3$ or d$_6$-DMSO, at 300, 400 or 500 MHz and at 75, 100 or 125 MHz, respectively, using solvent peaks (7.26 (*H*), 77.2 (*C*) ppm) as internal reference. The assignment of chemical shifts is based on standard NMR experiments (^{1}H, ^{13}C-DEPT, ^{1}H,^{1}H-COSY, gHSQC, gHMBC). Melting points were determined on a microscope type apparatus and are uncorrected. Mass spectra (EI, ES) were carried out by the mass spectrometry services at CQO (CSIC, Spain), as well as elemental analysis.

2-Amino-6-benzyl-4-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile (**1**). AcONH$_4$ (116 mg, 1.5 mmol), dry toluene (3 mL), benzylidenemalononitrile (308 mg, 2 mmol) and *N*-benzyl-piperidin-4-one **8** (189 mg, 1 mmol) were mixed and heated under reflux for 4h in a Dean-Stark system. Solvents were then removed *in vacuum* and the resulting residue purified by flash column chromatography (30% ethyl acetate in hexane, then 40% and finally 50%) yielding the titled compound (231 mg, 68%) as a colorless solid.
Mp 193-195 ºC. IR (KBr): 3457, 3342, 3221, 2937, 2819, 2764, 2220, 1627, 1564, 1496, 1456, 1430, 1365, 1247 cm^{-1}.^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.42-7.34 (m, 3H, ArH), 7.25-7.12 (m, 7H, ArH), 5.19 (br s, 2H, NH$_2$), 3.47 (s, 2H, NC*H$_2$*CCH), 3.23 (s, 2H, CCC*H$_2$*N), 2.81 (t, *J* = 6.0 Hz, 2H, C*H$_2$*CH$_2$N), 2.62 (t, *J* = 6.0 Hz, 2H, CH$_2$C*H$_2$*N) ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 159.4, 157.9, 153.0, 137.8, 135.1 (C), 129.3, 129.1, 128.9, 128.4, 128.0, 127.3 (CH), 119.0, 116.6, 90.0 (C), 62.3, 54.0, 49.1, 33.1 ppm. MS (ES): *m/z* (%) = 341.2/342.3/343.2 [M+1]$^+$.
Anal. Calcd for C$_{22}$H$_{20}$N$_4$: C, 77.62; H, 5.92; N, 16.46; found C, 77.48; H, 6.05; N, 16.22.

2-Amino-4-phenyl-6-(prop-2-ynyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile (2).
Procedure as above described for compound **1**. Starting from 137 mg (1 mmol) of **9**, 130 mg (45%) of the titled compound were obtained after flash column chromatography (30% ethyl acetate in hexane, then 40%, 50% and finally 60%) as a yellowish solid.

Mp 163-165 ºC. IR (KBr): 3418, 3302, 3180, 2911, 2818, 2787, 2211, 1641, 1561, 1464, 1435, 1376, 1253, 1142, 734, 702, 662, 638 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.53-7.33 (m, 3H, ArH), 7.29-7.11 (m, 2H, ArH), 5.18 (br s, 2H, NH$_2$), 3.32 (br s, 2H, NCH$_2$CCH), 3.25 (br s, 2H, NCCCH$_2$N), 2.98-2.86 (m, 2H, CH_2CH$_2$N), 2.86-2.74 (m, 2H, CH$_2$CH_2N), 2.16 (s, 1H, CCH) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 158.7, 157.8, 153.2, 135.1 (C), 129.4, 129.0, 128.0 (CH), 118.6, 116.5, 90.2, 78.1 (C), 73.8 (CH), 51.8, 49.0, 46.6, 33.2 (CH$_2$) ppm. MS (ES): m/z (%) = 289.2/290.3/291.3 [M+1]$^+$. Anal. Calcd for C$_{18}$H$_{16}$N$_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.79; H, 5.46; N, 19.24.

***N*-Propargyl-piperidin-4-one (9).**[6] A suspension of 4-piperidone hydrochloride **11** (172 mg, 1 mmol) in THF (12 mL) was treated with DIPEA (0.17 mL, 1 mmol) and tBuNH$_2$ (0.26 mL, 2.5 mmol). The mixture was cooled in an ice-bath and then propargyl bromide (0.09 mL, 1 mmol) was carefully added. The reaction was kept overnight while reaching rt. The precipitate was filtered off and washed with Et$_2$O (6×10 mL), the filtrate concentrated and the resulting residue purified by flash column chromatography. The product (106 mg, 77%) was obtained as a yellowish oil.

^{1}H NMR (CDCl$_3$, 300 MHz): δ = 3.41 (d, J = 2.4 Hz, 2H, CH_2CCH), 2.84 (t, J = 6.2 Hz, 4H, 2×CH$_2$CH_2N), 2.46 (t, J = 6.2 Hz, 4H, 2×CH_2CH$_2$N), 2.27 (t, J = 2.4 Hz, 1H, CH$_2$CCH) ppm.

***tert*-Butyl-4-oxopiperidin-*N*-carboxylate (10).**[7] A suspension of reagent **11** (1.72 g, 10 mmol) in CHCl$_3$ (20 mL) was treated at 0 ºC with K$_2$CO$_3$ (2.76 g, 20 mmol), Boc$_2$O (2.25 g, 10.3 mmol) and NEt$_3$ (1.39 mL, 10 mmol). The stirring was kept overnight while reaching rt. Water (20 mL) and CH$_2$Cl$_2$ (40 mL) were then added, layers separated and the organic fraction was further washed with water (2×40 mL), HCl 1N (3×40 mL) and NaOH 1N (3×40 mL). Solvents were removed *in vacuo* to give **10** as a colorless solid (1.89 g, 95%), m.p. 68-70 ºC (lit. 72 ºC).

6-Amino-2-benzyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline-5,7-dicarbonitrile (13). A solution of benzaldehyde (0.1 mL, 1 mmol) in dry toluene (2.5 mL) under argon was treated with malononitrile (66.1 mL, 1 mmol) and then piperidine (0.01 mL, 0.1 mmol) was slowly added. The solution gradually became cloudy while a brownish oil appeared. After 12h of stirring at rt, piperidone **8** (147.6 mg, 0.78 mmol) and further piperidine (0.01 mL, 0.1 mmol) were added. After 6h, the precipitate was collected by filtration, washed with cold toluene (6×5 mL) and dried under vacuum. AcONH$_4$ (107 mg, 1.39 mmol) was dissolved in AcOH (1.7 mL) while heating. The previously obtained precipitate was then added and the mixture refluxed for 10h. After this time, TLC showed the formation of a sole product. Solvent was partially removed *in vacuum* and the resulting oil was treated with sat. NaHCO$_3$ (20 mL) and extracted with ethyl acetate (3×20 mL). The organic fractions were dried (MgSO$_4$) and concentrated, giving rise to a colorless solid (45.5 mg, 16% from starting ketone).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.42-7.36 (m, 3H, ArH), 7.24-7.11 (m, 7H, ArH), 5.02 (br s, 2H, NH_2), 3.45 (s, 2H, NCH_2Ph), 3.16 (s, 2H, CCH_2N), 2.95 (t, J = 5.9 Hz, 2H, CH_2CH$_2$N), 2.59 (t, J = 6.0 Hz, 2H, CH$_2$CH_2N) ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 150.2, 148.7, 144.9, 137.4, 135.8 (C), 129.3, 129.1, 129.0, 128.5, 128.2, 127.4 (CH), 124.4, 115.6, 115.2, 96.6, 96.4 (C), 62.2, 54.5, 48.3, 29.6 (CH$_2$) ppm. MS (ES): m/z (%) = 365.2/366.3 [M+1]$^+$.

4-(N-Methyl-N-propargylamino)-butan-2-one (14). N-Methylprop-2-yn-1-amine (1.7 mL, 20 mmol) and toluene (20 mL) were charged in a flask fitted with a reflux condenser under argon. But-3-en-2-one (2.3 mL, 28 mmol) was dropwise added at rt and the mixture heated at reflux for 4h. HCl 1N was then added up to pH=1 and after addition of Et$_2$O (20 mL), layers were separated, the aqueous one being treated with further Et$_2$O (2×20 mL). The aqueous fractions were basified to pH=8 and extracted with CH$_2$Cl$_2$ (3×50 mL), the organic fractions dried (MgSO$_4$), filtrated and concentrated. The resulting brown oil (2.63 g, 94%) was used without further purification.

IR (KBr): 3286, 2946, 2098, 1712, 1358, 1165 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 3.32 (d, J = 2.4 Hz, 2H, CH_2CCH), 2.72 (t, J = 7.0 Hz, 2H, CH$_2$CH_2N), 2.58 (t, J = 7.0 Hz, 2H, CH_2CH$_2$N), 2.29 (s, 3H, CH_3N), 2.21 (t, J = 2.4 Hz, 1H, CH$_2$CCH), 2.16 (s, 3H, CH_3CO) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 207.5, 78.2 (C), 73.3 (CH), 50.0, 45.5, 41.8, 41.6 (CH$_3$, 3×CH$_2$), 29.9 (CH$_3$) ppm. EM (ES): m/z (%) = 140.2/141.2 [M+1]$^+$.

2-Amino-6-(2-(methyl(prop-2-ynyl)amino)ethyl)-4-phenylnicotinonitrile (15). AcONH$_4$ (115 mg, 1.5 mmol), dry toluene (3 mL), 2-benzylidenemalononitrile **12** (308 mg, 2 mmol) and 4-(N-methyl-N-propargylamino)-butan-2-one **14** (137 mg, 1 mmol) were mixed and heated under reflux for 4h in a Dean-Stark system. Solvents were then removed *in vacuum* and the resulting residue purified by flash column chromatography (30% ethyl acetate in hexane, then 40%, 50% and finally 60%) yielding the titled compound (42 mg, 14%) as a brown oil, that crystallized as a yellowish solid (from ethyl acetate).

Mp 114-116 ºC. IR (KBr): 3437, 3306, 3181, 2214, 1648, 1577, 1556, 1047 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.59-7.54 (m, 2H, ArH), 7.52-7.46 (m, 3H, ArH), 6.67 (s, 1H, CHCN), 5.34 (br s, 2H, NH_2), 3.41 (d, J = 2.3 Hz, 2H, NCH_2CCH), 2.84 (s, 4H, CH$_2$CH$_2$N), 2.37 (s, 3H, CH_3N), 2.24 (t, J = 2.3 Hz, 1H, NCH$_2$CCH) ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 164.2, 160.3, 154.7, 136.8 (C), 129.9, 129.0, 128.3 (CH), 117.2 (C), 113.8 (CH), 87.7, 78.5 (C), 73.5 (CH), 54.8, 45.7 (CH$_2$), 41.9 (CH$_3$), 36.8 (CH$_2$) ppm. MS (EI): m/z (%) = 290.2/291.2/292.2 [M]$^+$. Anal. Calcd for C$_{18}$H$_{18}$N$_4$: C, 74.46; H, 6.25; N, 19.30. Found: C, 74.19; H, 5.98; N, 19.43.

N-Methyl-N-propargylacetoacetamide (16).[13] *tert*-Butyl acetoacetate (0.75 mL, 4.5 mmol) was diluted in toluene (5 mL) and N-methyl-N-propargylamine (0.34 mL, 4.1 mmol) added. The mixture was refluxed for 14h and then diluted in Et$_2$O (20 mL) after cooling. HCl 1N (10 mL) was then added and layers separated. The organic layer was treated with further HCl 1N (2×20 mL), the aqueous fractions combined, extracted once with Et$_2$O (20 mL) and basified with NaOH 50%. When reaching pH=7-8, the aqueous fraction was extracted with ethyl acetate (3×150 mL). The organic fractions were separately dried (Na$_2$SO$_4$) and filtered. The first organic fraction (obtained in Et$_2$O) showed a mixture of product and starting material and was purified by flash

column chromatography (10% ethyl acetate in hexane to 60%), giving rise to 85 mg of a yellowish oil; the second one (360 mg of a dark brownish oil, obtained in ethyl acetate) was used without further purification. Total yield: 71%.

Mixture of rotamers.^{1}H NMR (CDCl$_3$, 300 MHz): δ = 4.21 (d, J = 2.4 Hz, 2H, CH_2CCH of major rotamer), 4.00 (d, J = 2.3 Hz, 2H, CH_2CCH of minor rotamer), 3.59 (s, 2H, CH$_2$CO of minor rotamer), 3.53 (s, 2H, CH$_2$CO of major rotamer), 3.02 (s, 3H, CH$_3$N of major rotamer), 3.00 (s, 3H, CH$_3$N of minor rotamer), 2.32 (t, J = 2.4 Hz, 1H, CCH of minor rotamer), 2.26 (s, 3H, CH$_3$CO of minor rotamer), 2.25 (s, 3H, CH$_3$CO of major rotamer), 2.22 (t, J = 2.5 Hz, 1H, CCH of major rotamer) ppm.

6-Amino-5-cyano-2-methyl-4-phenyl-*N*-(prop-2-ynyl)nicotinamide (17). Compound **18** (193 mg, 0.62 mmol) was treated under argon at rt with CH$_2$Cl$_2$ (13 mL) and TFA (0.95 mL). After 7 days, solvents were removed *in vacuum* and the residue was basified with NaOH 2N (50 mL). CHCl$_3$ (30 mL) was added until the observed solid was dissolved and layers were then separated. The aqueous layer was extracted with CHCl$_3$ (2×20 mL). The organic fractions were washed once with NaOH 2N (5 mL) and with water (10 mL). The collected aqueous fractions were then acidified (pH 3-4) by adding HCl conc. to pH=3-4 and extracted with isopropanol-CHCl$_3$ 1:3 (3×30mL). The organic fractions were dried over MgSO$_4$ and solvents were evaporated to yield 6-amino-5-cyano-2-methyl-4-phenylpyridine-3-carboxylic acid (116 mg, 74%), which was used without further purification.

Colorless solid. Mp 228-230 ºC. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.51-7.44 (m, 3H, ArH), 7.38-7.29 (m, 2H, ArH), 7.20 (br s, 2H, NH$_2$), 2.40 (s, 3H, CH$_3$) ppm. EM (EI): m/z (%) = 253.0/254.0/255.0 [M]$^+$; 236.0/237.0 [M-17]$^+$.

To a mixture of 6-amino-5-cyano-2-methyl-4-phenylpyridine-3-carboxylic acid (50.6 mg, 0.20 mmol) in CH$_2$Cl$_2$ (0.5 mL) at 0 ºC, EDCI (38.3 mg, 0.20 mmol), DIPEA (40 µl, 0.24 mmol), *N*-propargylamine (15 µl, 0.24 mmol) and HOBt (27 mg, 0.20 mmol) were added. Stirring was kept overnight while the mixture reached rt. Water (10 mL) and further CH$_2$Cl$_2$ (15 mL) were then added. Layers were separated and the organic layer was washed with water (5 mL) and sat. NaHCO$_3$ (3×10 mL) and dried (MgSO$_4$). Solvents were removed *in vacuum* and the resulting residue was purified by flash column chromatography (1% to 2.5% MeOH in CH$_2$Cl$_2$) to yield the titled compound **17** (22.4 mg, 39%) as a white-off solid.

Mp 178-180 ºC. IR (KBr): 3393, 3332, 3288, 3178, 2219, 1665, 1641, 1561, 1290, 1252, 761, 706, 648, 529 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.61 (t, J = 5.4 Hz, 1H, NH), 7.47-7.39 (m, 3H, ArH), 7.38-7.30 (m, 2H, ArH), 7.06 (s, 2H, NH$_2$), 3.72 (dd, J = 5.4, 2.1 Hz, 2H, NCH$_2$), 3.00 (t, J = 2.1 Hz, 1H, CCH), 2.30 (s, 3H, CH$_3$) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 166.3, 159.6, 158.7, 152.0, 135.4 (C), 129.0, 128.3, 128.2 (CH), 122.0, 116.4, 86.6, 80.2 (C), 73.0 (CH), 28.0 (CH$_2$), 22.6 (CH$_3$) ppm. EM (EI): m/z (%) = 290.1/291.1 [M]$^+$; 236.1/237.1/238.1 [M-54]$^+$. Anal. Calcd for C$_{17}$H$_{14}$N$_4$O: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.11; H, 4.91; N, 19.54.

***tert*-Butyl 6-amino-5-cyano-2-methyl-4-phenylpyridine-3-carboxylate (18).** AcONH$_4$ (116 mg, 1.5 mmol), dry toluene (3 mL), benzylidenemalononitrile (308.3 mg, 2 mmol) and *tert*-butyl acetoacetate (0.17 mL, 1 mmol) were mixed and heated under reflux for 4h in a Dean-stark system. Solvents were then removed *in vacuum* and the resulting residue purified by flash column chromatography (5% ethyl acetate in hexane, then 10%, 20% and finally 30%) yielding the titled compound (126 mg, 41%) as a colorless solid.

Mp 215-217 ºC. IR (KBr): 3399, 3331, 3149, 3064, 3002, 2972, 2931, 2220, 1703, 1660, 1552, 1498, 1476, 1447, 1367, 1299, 1257, 1150, 1076, 865, 844, 811, 798, 759, 742, 699, 563 cm^{-1}.
^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.48-7.43 (m, 3H, ArH$_{meta}$, ArH$_{para}$), 7.38-7.32 (m, 2H, ArH$_{ortho}$), 5.41 (br s, 2H, NH$_2$), 2.50 (s, 3H, CH$_3$), 1.18 [s, 9H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 166.5, 160.2, 158.8, 153.5, 135.9 (C), 129.5, 128.7, 128.2 (CH), 121.8, 116.1, 89.1, 82.4 (C), 27.6, 23.5 (CH$_3$) ppm. EM (IE): *m/z* (%) = 309.2/310.2 [M]$^+$; 253.2/254.1/252.1/255.1 [M-57]$^+$; 236.2/ 235.1/ 237.1/238.1 [M-73]$^+$. Anal. Calcd for C$_{18}$H$_{19}$N$_3$O$_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.75; H, 6.08; N, 13.43.

***tert*-Butyl 5-amino-4,6-dicyano-3-methylbiphenyl-2-carboxylate (19).** MeOH (30 mL), toluene (30 mL), *tert*-butyl acetoacetate (6.63 mL, 40 mmol), benzaldehyde (4.06 mL, 40 mmol), malononitrile (2.52 mL, 40 mmol) and AcONH$_4$ (3.24 g, 42 mmol) were mixed and heated under reflux for 24h. Solvents were then removed *in vacuum* and then toluene (30 mL) and water (3 mL) were added to continue refluxing for additional 24h. The reaction was concentrated and the residue partially purified by re-precipitation in CH$_2$Cl$_2$-CHCl$_3$-hexane. The observed brown oil was discarded and the resulting fraction was concentrated and purified by flash column chromatography (5% hexane in CH$_2$Cl$_2$) to yield pure compound (570 mg, 4%) as a colorless solid.

Mp 200-202 ºC. IR (KBr): 3461, 3352, 3248, 2976, 2226, 2218, 1725, 1645, 1563, 1371, 1307, 1283, 1216, 1148, 843, 753, 701 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.52-7.38 (m, 3H, ArH$_{meta}$, ArH$_{para}$), 7.37-7.31 (m, 2H, ArH$_{ortho}$), 5.35 (br s, 2H, NH$_2$), 2.55 (s, 3H, CH$_3$), 1.15 [s, 9H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 165.7, 151.8, 148.3, 145.3, 136.3 (C), 129.5, 128.6, 128.6 (CH), 127.0, 115.1, 115.1, 97.5, 96.0, 82.8 (C), 27.6, 19.4 (CH$_3$) ppm. EM (ES): *m/z* (%) = 356.3/357.2/358.3 [M+23]$^+$; 334.2/335.2 [M+1]$^+$; 278.2/279.3/280.2 [M-57+2]$^+$; 260.2/ 261.2/ 262.0 [M-73]$^+$. Anal. Calcd for C$_{20}$H$_{19}$N$_3$O$_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.87; H, 5.91; N, 12.85.

***tert*-Butyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate (20).**[15] A solution of benzaldehyde (4.06 mL, 40 mmol) in dry toluene (100 mL) under argon was treated with malononitrile (2.52 mL, 40 mmol) and then piperidine (0.40 mL, 4 mmol) was slowly added. The solution became gradually cloudy while a brownish oil appeared. After 12h of stirring at rt, *tert*-butyl acetoacetate (6.63 mL, 40 mmol) and further piperidine (0.1 mL, 1 mmol) were added. After 6h, the precipitate was collected by filtration, washed with cold toluene (6×20 mL) and dried under vacuum, to yield the titled compound (9.68 g, 78%) as a light pink solid.

^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.34-7.26 (m, 2H, ArH), 7.25-7.16 (m, 3H, ArH), 4.46 (br s, 2H, NH$_2$), 4.38 (s, 1H, C*H*Ph), 2.34 (s, 3H, CH$_3$), 1.24 [s, 9H, C(CH$_3$)$_3$] ppm.

2-Amino-6-methyl-4-phenylnicotinonitrile (21).[5] AcONH$_4$ (19.3 g, 250 mmol) was dissolved in AcOH (315 mL) while heating. Compound **20** (7.8 g, 25 mmol) was then added and the mixture refluxed for 16h. Solvent was partially removed *in vacuum* and the resulting oil was treated with sat. NaHCO$_3$ (1000 mL) to pH=6-7. A yellowish solid precipitated and was collected by filtration, washed with water (6×100 mL) and re-dissolved in ethyl acetate (50 mL). The aqueous layer was treated with HCl 1N to pH=2-3 and extracted with ethyl acetate to confirm that no compounds were recovered from the aqueous layer. The re-dissolved precipitate was washed with water (2×20 mL) and sat. NaCl (2×20 mL), dried (MgSO$_4$) and concentrated. The resulting crude was purified by re-precipitation in CHCl$_3$-hexane (50:5). Yellowish solid (345 mg, 6.6 %).
^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.60-7.40 (m, 5H, Ph), 6.82 (br s, 2H, NH$_2$), 6.56 (s, 1H, CHCCH$_3$), 2.32 (s, 3H, CH$_3$) ppm.

Acknowledgements

References and Notes

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12. This analysis has been carried out by Mr. César Pastor, SIDI, Facultad de Ciencias, UAM, Madrid, Spain. Single-crystal data and CIF file of compound **15** (CCDC 763716) have been deposited at the Cambridge Crystallographic Data Centre and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1123-336-033; or email: deposit@ccdc.ac.uk).

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