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Catalyst-free three-component synthesis of 2-amino-4,6-diarylpyridine-3-carbonitriles under solvent-free conditions

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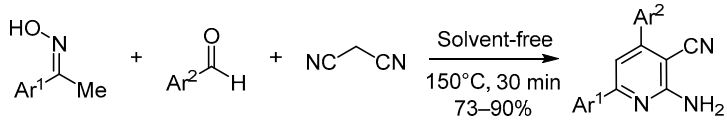


Ar^1, Ar^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, thiophen-3-yl

A novel efficient one-pot synthesis of 2-amino-4,6-diarylpyridine-3-carbonitriles is described. Method involves heating the mixture of an acetophenone oxime, aldehyde, and malononitrile without any catalyst under solvent-free conditions to give the title compounds in good to high yields.

Keywords: acetophenone oximes, 2-amino-4,6-diarylpyridine-3-carbonitriles, solvent-free synthesis.

Due to their productivity, atom economy, straightforward reaction design, convergence and facile execution, multicomponent reactions (MCRs) have emerged as a highly efficient tool in modern synthetic organic chemistry and are widely used for the preparation of chemically and biologically important compounds.[1–3]

A major challenge for synthetic chemists is to carry out organic reactions in green solvents or without conventional organic solvents to develop environment-friendly synthetic procedures. One of the most promising approaches is solvent-free organic synthesis. These reactions provide greater selectivity, proceed with enhanced reaction rates, give cleaner products, and involve simple manipulations.[4–6]

The pyridine nucleus is an important class of nitrogen-containing heterocyclic compounds, since it is widespread in natural products,[7] and it is also broadly used in medicinal chemistry and drug synthesis.[8] Pyridines are also used in coordination chemistry,[9] supramolecular structures,[10] and organocatalysis.[11] Among them, 2-aminopyridine-3-carbonitrile derivatives are known to have multiple biological activities, such as antiviral, antibacterial, and fungicidal activities.[12–14] They have been also reported as novel IKK-β serine-threonine protein kinase inhibitors,[15] A_2A adenosine receptor antagonists,[16] and potent inhibitors of HIV-1 integrase.[17] Therefore, the synthesis of these valuable *N*-containing heterocycles is of great significance.

So far, several synthetic methods have been reported for the preparation of 2-amino-4,6-diarylpyridine-3-carbonitrile ring systems. The most common synthetic method involves the condensation of chalcone or carbonyl compounds with malononitrile and ammonium acetate by conventional heating in the presence of different catalysts.[18–24,25a] Furthermore nitrile oxides with ylidene malononitriles[25b] and oxime acetates[25c] have been used as starting materials. However, some of these procedures have certain limitations such as harsh reaction conditions, use of rare earth Lewis acid catalysts with long reaction times, high temperatures, toxic benzene as solvent, or tedious workup with microwave assistance, and low yields. Although a large number of reactants and functional groups have been successfully explored in literature, to the best of

our knowledge, no report has been published concerning the use of acetophenone oximes as starting materials for the preparation of 2-amino-4,6-diarylpyridine-3-carbonitriles. Due to the fact that acetophenone oxime is commercially available, it is a readily accessible starting material for performing the reaction. It should also be mentioned that the preparation of oximes is very facile in organic chemistry.

During the course of our studies on the development of new routes to the synthesis of heterocyclic compounds,[26–30] herein, we disclose a novel and efficient procedure for the synthesis of 2-amino-4,6-diarylpyridine-3-carbonitrile derivatives **4a–j** by condensation of acetophenone oximes **1**, aromatic aldehydes **2**, and malononitrile (**3**) without use of any catalyst under solvent-free conditions at 150°C in 73–90% yields (Scheme 1). TLC and ^{1}H NMR spectroscopic analysis of the reaction mixtures clearly indicated formation of the corresponding 2-amino-4,6-diarylpyridine-3-carbonitriles **4a–j** in good to excellent yields. No product other than compounds **4a–j** could be detected by NMR spectroscopy. The results are summarized in Table 1. In the ^{13}C NMR spectra of the products, the C–C≡N atom has the chemical shift in the 88.3–89.0 ppm region due to the anisotropic effect of the nitrile group.[19]

Scheme 1

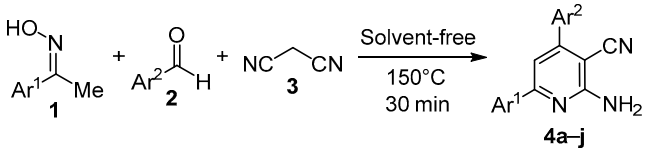


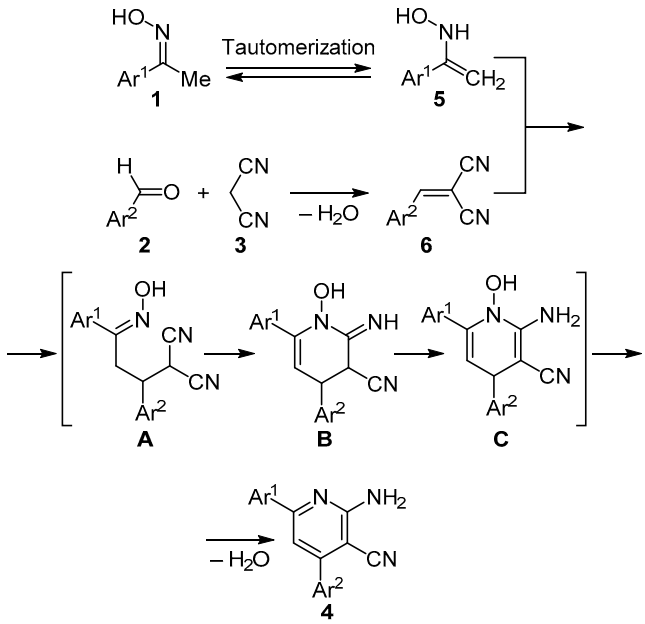
Table 1. Yields of 2-aminopyridine-3-carbonitrile derivatives **4a–j**

Compound	Ar^1	Ar^2	Yield, %	Ref.
4a	Ph	Ph	88	22
4b	Ph	4-MeC_6H_4	83	22
4c	Ph	4-$MeOC_6H_4$	85	19
4d	Ph	Thiophen-3-yl	73	22
4e	Ph	4-ClC_6H_4	90	18
4f	4-MeC_6H_4	Ph	85	20
4g	4-$MeOC_6H_4$	Ph	76	22
4h	4-ClC_6H_4	Ph	81	20
4i	4-$MeOC_6H_4$	4-ClC_6H_4	78	24
4j	4-$MeOC_6H_4$	4- $MeOC_6H_4$	89	24

Mechanistically, it is reasonable to assume that the first step may involve nucleophilic attack of the *N*-hydroxyenamine tautomer **5** of oxime **1** on alkylidenemalononitrile **6**, obtained by condensation of aromatic aldehyde **2** with malononitrile (**3**), to give intermediate **A**, followed by cycloaddition, isomerization, and aromatization through intermediates **B** and **C** to afford 2-aminopyridine-3-carbonitrile **4** (Scheme 2).

In conclusion, we have synthesized a series of 2-amino-3-cyanopyridine derivatives which are of potential synthetic and pharmacological interest by one-pot three-component reaction between acetophenone oximes, aldehydes, and malononitrile under solvent-free conditions. The availability of the starting materials, solvent-free conditions without need of catalyst, and short reaction times are the main advantages of this approach. To the best of our knowledge, there is no previous report in the literature regarding the use of acetophenone oxime as starting material for the synthesis of 2-aminopyridine-3-carbonitriles.

Scheme 2



Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker NMR Avance spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ with TMS as internal standard. Elemental analyses (CHNSO) were conducted on an ECS 4010 Costech elemental combustion system. Melting points were determined using a Thermo Scientific Electrothermal IA9000 Series Programmable Digital Melting Point apparatus in a capillary tube and are not corrected. The progress of reaction was followed with TLC using silica gel SILG/UV 254 and 365 plates, and the crude products were purified by column chromatography using silica gel 60 mesh and *n*-hexane–EtOAc as eluent.

All chemicals were purchased from Merck and Fluka companies. All synthesized products are known compounds, their physical and spectroscopic data were in accordance with those previously reported.[18–20,22,24]

Preparation of 2-aminopyridine-3-carbonitriles 4a–j (General method). A mixture of acetophenone oxime **1** (2.0 mmol), aldehyde **2** (2.0 mmol), and malononitrile (**3**) (2.5 mmol) was stirred at 150°C for 30 min. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and the residue was purified by column chromatography using *n*-hexane–EtOAc, 1:4, as eluent to afford the pure products.

2-Amino-4,6-diphenylpyridine-3-carbonitrile (4a). Yield 0.48 g (88%), white solid, mp 178–180°C (mp 176–

177°C[22]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.40 (2H, s, NH_2); 7.23 (1H, s, H Py); 7.46–8.06 (10H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 88.6; 113.3; 116.0; 117.2; 128.6; 128.7; 129.8; 130.2; 136.7; 137.9; 151.0; 155.1; 158.8; 161.3. Found, %: C 79.67; H 4.93; N 15.42. $C_{18}H_{13}N_3$. Calculated, %: C 79.68; H 4.83; N 15.49.

2-Amino-4-(4-methylphenyl)-6-phenylpyridine-3-carbonitrile (4b). Yield 0.47 g (83%), white solid, mp 162–164°C (mp 160–161°C[22]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (3H, s, CH_3); 5.38 (2H, s, NH_2); 7.23–8.02 (10H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.4; 88.6; 113.2; 119.9; 127.3; 128.4; 128.6; 128.8; 128.9; 129.5; 130.1; 138.2; 151.3; 154.0; 161.0. Found, %: C 79.78; H 5.21; N 14.81. $C_{19}H_{15}N_3$. Calculated, %: C 79.98; H 5.30; N 14.73.

2-Amino-4-(4-methoxyphenyl)-6-phenylpyridinecarbonitrile (4c). Yield 0.51 g (85%), white solid, mp 190–192°C (mp 192–195°C[19]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.86 (3H, s, OCH_3); 5.39 (2H, s, NH_2); 7.06 (2H, dd, *J* = 6.7, *J* = 2.1, H Ar); 7.17 (1H, s, H Py); 7.46–8.01 (7H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 55.5; 88.7; 110.7; 114.4; 117.5; 126.3; 128.8; 129.6; 130.7; 138.0; 150.9; 155.7; 159.7; 161.4; 162.9. Found, %: C 75.58; H 5.11; N 13.83. $C_{19}H_{15}N_3O$. Calculated, %: C 75.73; H 5.02; N 13.94.

2-Amino-6-phenyl-4-(thiophen-3-yl)pyridine-3-carbonitrile (4d). Yield 0.40 g (73%), white solid, mp 208–210°C (mp 213–214°C[22]). ^{1}H NMR spectrum, δ, ppm: 5.37 (2H, s, NH_2); 6.94 (1H, s, H Py); 7.44–7.56 (7H, m, H Ph, H thiophene); 7.79 (1H, s, H thiophene). ^{13}C NMR spectrum, δ, ppm: 88.9; 111.4; 118.3; 126.0; 126.5; 126.9; 127.2; 127.3; 128.7; 128.9; 129.5; 131.2; 133.2; 136.3; 152.4. Found, %: C 69.17; H 4.08; N 15.06; S 11.47. $C_{16}H_{11}N_3S$. Calculated, %: C 69.29; H 4.00; N 15.15; S 11.56.

2-Amino-4-(4-chlorophenyl)-6-phenylpyridine-3-carbonitrile (4e). Yield 0.55 g (90%), white solid, mp 229–231°C (mp 229–230°C[22]). ^{1}H NMR spectrum, δ, ppm: 5.41 (2H, s, NH_2); 6.87 (1H, s, H Py); 7.45–7.57 (9H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 88.6; 111.7; 116.9; 118.8; 125.3; 128.4; 128.7; 129.1; 129.2; 129.6; 129.7; 129.9; 130.3; 154.8; 161.0. Found, %: C 70.62; H 3.82; N 13.78. $C_{18}H_{12}ClN_3$. Calculated, %: C 70.71; H 3.96; N 13.74.

2-Amino-6-(4-methylphenyl)-4-phenylpyridine-3-carbonitrile (4f). Yield 0.48 g (85%), white solid, mp 168–170°C (mp 182–183°C[20]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (3H, s, CH_3); 5.35 (2H, s, NH_2); 7.12 (1H, s, H Py); 7.27 (2H, d, *J* = 9.2, H Ar); 7.20–7.54 (3H, m, H Ar); 7.60–7.65 (2H, m, H Ar); 7.90 (2H, d, *J* = 8.1, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.5; 88.4; 110.9; 118.3; 127.5; 128.2; 128.6; 129.4; 129.8; 134.1; 136.0; 138.6; 151.4; 154.0; 158.8; 161.3. Found, %: C 79.81; H 5.26; N 14.72. $C_{19}H_{15}N_3$. Calculated, %: C 79.98; H 5.30; N 14.73.

2-Amino-6-(4-methoxyphenyl)-4-phenylpyridine-3-carbonitrile (4g). Yield 0.46 g (76%), white solid, mp 166–168°C (mp 166–167°C[22]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.87 (3H, s, OCH_3); 5.39 (2H, s, NH_2); 7.03 (2H, dd, *J* = 6.8, *J* = 2.0, H Ar); 7.18 (1H, s, H Py); 7.46–7.62 (5H, m, H Ar); 7.97 (2H, dd, *J* = 6.8, *J* = 2.1, H Ar). ^{13}C NMR spectrum, δ, ppm: 56.4; 89.0; 112.0; 115.4; 118.5; 128.3; 129.8; 130.2; 130.6; 131.1; 139.1; 155.7; 160.7; 161.4; 161.9. Found, %: C 75.67; H 4.91; N 13.89. $C_{19}H_{15}N_3O$. Calculated, %: C 75.73; H 5.02; N 13.94.

2-Amino-6-(4-chlorophenyl)-4-phenylpyridine-3-carbonitrile (4h). Yield 0.49 g (81%), white solid, mp 243–244°C (mp 238–241°C[20]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.35 (2H, s, NH_2); 7.18 (1H, d, *J* = 0.8, H Ar); 7.45 (2H, d, *J* = 8.1, H Ar); 7.51–7.55 (3H, m, H Ar); 7.60–7.64 (2H, m, H Ar); 7.95 (2H, d, *J* = 8.1, H Ar). ^{13}C NMR spectrum, δ, ppm: 88.7; 111.9; 115.8; 117.3; 125.8; 128.5; 128.6; 129.1; 129.3; 129.5; 129.7; 130.2; 155.1; 155.2; 162.1. Found, %: C 70.69; H 3.84; N 13.61. $C_{18}H_{12}ClN_3$. Calculated, %: C 70.71; H 3.96; N 13.74.

2-Amino-4-(4-chlorophenyl)-6-(4-methoxyphenyl)-pyridine-3-carbonitrile (4i). Yield 0.52 g (78%), white solid, mp 195–197°C (mp 195–196°C[24]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.81 (3H, s, OCH_3); 6.97 (2H, s, NH_2); 7.03 (2H, d, *J* = 8.2, H Ar); 7.24 (1H, s, H Py); 7.62 (2H, d, *J* = 8.2, H Ar); 7.71 (2H, d, *J* = 8.2, H Ar); 8.14 (2H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 55.5; 88.6; 111.7; 115.4; 118.5; 127.3; 128.6; 128.8; 129.5; 129.8; 130.5; 138.5; 156.8; 159.3; 162.4; 162.9. Found, %: C 67.81; H 4.14; N 12.42. $C_{19}H_{14}ClN_3O$. Calculated, %: C 67.96; H 4.20; N 12.51.

2-Amino-4,6-bis(4-methoxyphenyl)pyridine-3-carbonitrile (4j). Yield 0.59 g (89%), white solid, mp 160–162°C (mp 159–160°C[24]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.70 (3H, s, OCH_3); 3.86 (3H, s, OCH_3); 5.38 (2H, s, NH_2); 6.97 (2H, d, *J* = 8.2, H Ar); 7.12 (1H, s, H Py); 7.31 (2H, d, *J* = 8.2, H Ar); 7.53 (2H, d, *J* = 8.2, H Ar); 7.96 (2H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 54.4; 56.4; 88.3; 111.3; 115.1; 118.6; 129.1; 129.8; 130.6; 131.4; 135.2; 140.9; 155.9; 160.2; 161.3; 162.4. Found, %: C 72.37; H 5.06; N 12.59. $C_{20}H_{17}N_3O_2$. Calculated, %: C 72.49; H 5.17; N 12.68.

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of compounds **4g**,**j** is available from the journal website http://link.springer.com/journal/10593.

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