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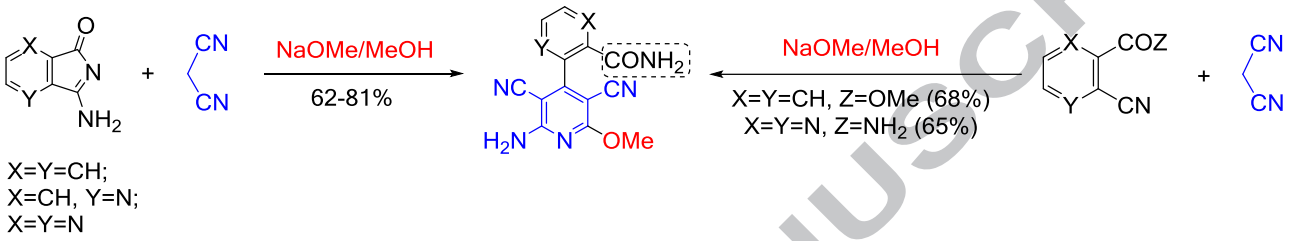

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Cyclic acyl amidines as unexpected C4-donors for fully substituted pyridine ring formation in the base mediated reaction with malononitrile

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ABSTRACT

A new one-step, pseudo four-component approach for the synthesis of fully substituted pyridines *via* ring-opening of the cyclic acyl amidine of 3-amino-1*H*-isoindol-1-one and its aza-analogues during the reaction with malononitrile in the presence of sodium methoxide, followed by pyridine ring closure is reported. This method allows the one-step preparation of previously unknown 2-(pyridin-4-yl)(hetero)aryl carboxamides in good yields under mild reaction conditions.

1. Introduction

Highly functionalized pyridine derivatives can exhibit a wide range of biological activities; in particular, they show anticancer,[1a,b] antibacterial[2a,b] and antiprion activities.[3] Compounds of the 3,5-dicyanopyridine series are considered as IKK2 inhibitors with anti-HBV activity,[4] potassium channel opening agents, bladder smooth muscle relaxants for the treatment of frequent urination and urinary incontinence,[5] human adenosine A_1 receptor nonadenosine-like agonists,[6] medicines for the prevention and treatment of cardiovascular diseases,[7a,b] as well as treatments for age-related diseases, for example sarcopenia.[8] A number of 2-amino-6-alkoxy-4-arylpyridine-3,5-dicarbonitriles also exhibited promising fluorescence properties.[9a,b] On the other hand, they are also known as corrosion inhibitors.[10]

There is no data in the literature regarding the formation of fully substituted 4-arylpyridines from the reaction of malononitrile and amidines. Only a few examples, which lead to [amino(aryl(heteroaryl)methylidene]propanedinitriles,[11a,b] 2,2'-(1*H*-isoindole-1,3(2*H*)-diylidene)dipropanedinitrile[12a-c] or pyrimidines[11a,13] have been described.

According to the known approaches for the synthesis of fully substituted pyridines, in particular 2-amino-6-alkoxy-4-arylpyridine-3,5-dicarbonitriles, malononitrile reacts with an appropriate (hetero)aromatic aldehyde in the corresponding alcohol in the presence of an alcoholate,[7a,8,14a,b] NaOH,[15a-c] KOH,[9b] K_2CO_3,[16] amine[7b,17] or with already prepared arylmethylidenemalononitriles and KOH as a base.[18a,b] In addition, Ce-V loaded alumina can be used.[19] Moreover, the orthoesters of carboxylic acids have also been explored as starting compounds.[20a-c] These transformations are generally regarded as multicomponent reactions (MCR).[9b,15b,16,17,19]

Herein, we report the development of a new method for the synthesis of fully substituted pyridines *via* a base mediated reaction of cyclic acyl amidines - 3-amino-1*H*-isoindol-1-one (**2a**) and its aza-analogues **2b**,**c** - with malononitrile in methanol.

2. Results and Discussion

The reactions of aminoisoindolone **2a** with malononitrile, cyanoacetic esters[12a,b] and other active methylene compounds, such as 2-heteroarylacetonitriles, alkyl pyridines, and barbituric acid derivatives, have previously been reported.[21] The presence of an amidine fragment in the structure of **2a** prompted us to study its condensation with active methylene compounds in order to achieve further heterocyclization with the participation of the introduced cyano group.

Aminoisoindolone **2a** is typically synthesized by the sodium methoxide catalysed cyclization of 2-cyanobenzamide, which is in turn prepared from 2-cyanoester **1**[22] or from phthalamide.[23] Based on this knowledge and the known cyclization of pyridine cyano ester **6** into the corresponding analogue **2b** under the action of ammonia,[12b,24] we successfully combined these approaches for the direct and efficient preparation of aminoisoindolone **2a** from cyanoester **1**[25] by treatment with bubbling ammonia in methanol in the presence of catalytic sodium methoxide at reflux (Scheme 1). The structure of **2a**

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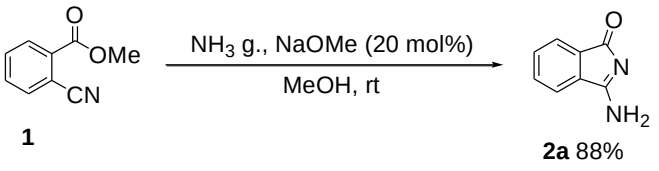
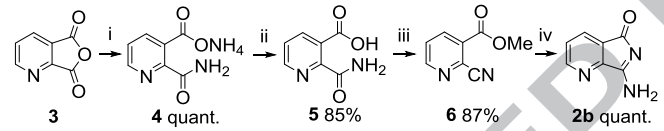
coincides with that previously reported,[26] pertaining to the same tautomeric form.



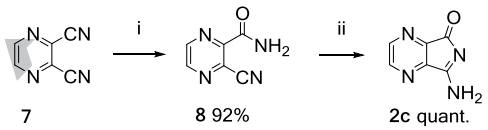
Scheme 1. Improved synthesis of 3-amino-1*H*-isoindol-1-one (**2a**).

The aza-analogue of aminoisoindolone **2a**, 7-amino-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (**2b**), was obtained using modified literature methods[12b,27] (Scheme 2). In particular, a commercially available 7N methanolic ammonia solution was used instead of an aqueous solution for the conversion of quinolinic anhydride furo[3,4-*b*]pyridine-5,7-dione (**3**) into ammonium 2-carbamoylpyridine-3-carboxylate (**4**). This allowed the yield of the target compound **5** to be increased from 70% to 85%. For the best isolation of 2-carbamoyl pyridine-3-carboxylic acid (**5**), ammonium salt **4** (the structure of co-crystals of salt **4** with acid **5** was confirmed by X-Ray study, see ESI, S1) was dissolved in a minimum amount of cold water and carefully acidified to a slightly acidic pH with 12M HCl while cooling on ice. After drying, acid **5** was reacted with methyl chloroformate for the preparation of methyl 2-cyanopyridine-3-carboxylate (**6**). In the final step, methyl ester **6** was treated with cold saturated 3M ethanolic ammonia instead of bubbling ammonia as previously described.[12b] After standing the reaction mixture in a refrigerator overnight, a fine crystalline precipitate of **2b** was formed in 74% overall yield.



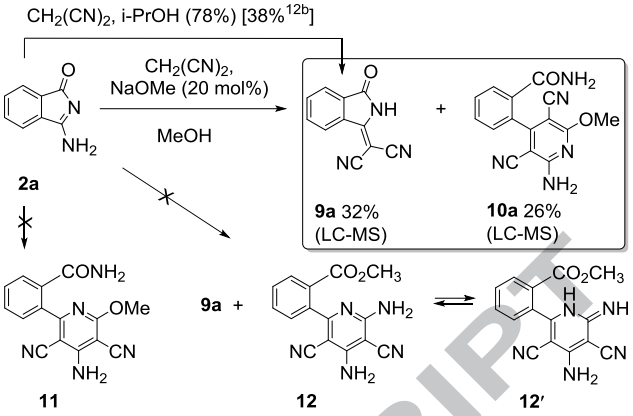
Scheme 2. Improved synthesis of 7-amino-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (**2b**). Reagents and conditions: (i) 7N NH_3/MeOH, 0 °C; (ii) 12M HCl, 0 °C; (iii) $ClCO_2Me$, TEA, CH_2Cl_2, 0 °C; (iv) 3M NH_3/EtOH, 0 °C.

The diaza derivative 7-amino-5*H*-pyrrolo[3,4-*b*]pyrazin-5-one (**2c**),[28] could be synthesized from 3-cyanopyrazine-2-carboxamide (**8**),[29a,b] which in turn was obtained by analogy with the known method for the partial hydrolysis of dinitriles (Scheme 3).[30] Thus, pyrazine-2,3-dicarbonitrile (**7**)[31] in MeOH was treated with 35% H_2O_2 solution and 0.5% $(NH_4)_2MoO_4$ aqueous solution to afford cyanocarboxamide **8** in 92% yield. Upon treatment with an equimolar amount of NaOMe in MeOH, compound **8** was converted into amidine **2c** in quantitative yield.[32]



Scheme 3. Reagents and conditions: (i) H_2O_2 (35%), 0.5% aq. $(NH_4)_2MoO_4$, MeOH; 6 h, rt; (ii) NaOMe, MeOH, rt.

In order to optimize conditions for the known catalyst-free reaction between amidine **2a** and malononitrile[12b] and to increase the yield of the expected (3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)propanedinitrile (**9a**), we carried out this reaction in the presence of catalytic sodium methoxide to activate the methylene compound. However, this modification led to an unexpected result (Scheme 4).



Scheme 4. Preliminary results for the reaction of **2a** with malononitrile.

After heating the reaction mixture of **2a** with a 3-fold excess of malononitrile and catalytic NaOMe (20 mol%), until the starting amidine **2a** disappeared (~10 h according to TLC), and complete cooling, a small amount of orange crystals of an individual compound was filtered off. The molecular ions, according to LC-MS, had values of 294 $[M+H]^+$ and 292 $[M–H]^+$ which differed significantly from the molecular mass of 195 a. u. of the expected product **9a**.

The ^1H NMR spectrum of the isolated compound revealed a singlet with an integration of 3H at δ 4.00 ppm, which could correspond to an aromatic methoxy group, two singlets with an integration of 1H at δ 7.24 and δ 7.98 ppm, which could be assigned to two different NH protons, and signals from aryl protons. The ^{13}C NMR spectrum showed a set of 15 carbon atoms signals, in particular, at δ 115.3 and δ 115.7 ppm, which could correspond to two nitrile groups. In the IR spectrum, a narrow band characteristic of a CN group at 2218 cm^{-1}, an amide CO at 1686 cm^{-1} and a C=N band at 1638 cm^{-1} were observed. The absence of characteristic bands in the ester region indicated that the methoxy group was indeed an ether function.

After evaporation of the mother liquid, the residue was diluted with distilled water, acidified to neutral pH with AcOH and the resulting brown precipitate filtered off. A study of this material by LC-MS showed that it was mainly a mixture of an unknown compound and predominantly the desired product **9a** with molecular ions 196 $[M+H]^+$, 194 $[M–H]^+$, that could not be completely separated. It was suggested that the unknown compound was a result of the reaction of aminoisoindolone **2a** with two molecules of malononitrile, and that (3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)propanedinitrile (**9a**) is the intermediate in this process.

It was assumed that the process occurred in a manner similar to that of the previously described transformation of formamidine, which afforded 2,4-diaminopyridine-3,5-dicarbonitrile in the reaction with malononitrile dimer[33] or similar to the intramolecular cyclization of the arylmethylidene derivative of malononitrile dimer.[34] On this basis, a probable structure of 2-aryl substituted pyridines **11** or **12** could be assumed for the product obtained. In turn, the ability of pyridin-2- and -4-amines to undergo a tautomeric equilibrium with the corresponding pyridin-2(1*H*)- and -4(1*H*)-imines also did not contradict the tautomeric structure of **12'**, which was consistent with the presence of two one-proton singlets in the ^1H NMR spectrum of the unknown compound (Scheme 4).

However, X-ray diffraction indicated that the studied compound was not a derivative of 2-, but of 4-arylpyridine, namely, 2-(2-amino-3,5-dicyano-6-methoxypyridin-4-

yl)benzamide (**10a**) (Fig. 1). Therefore, in the ^{1}H NMR spectrum, the signal at δ 4.00 ppm corresponds to the protons of the methoxy group and the two one-proton singlets at δ 7.24 and δ 7.98 ppm correspond to the non-equivalent NH protons of the $CONH_2$ group. In addition, a broad signal with an integration of ~2H at δ 7.65 ppm, which belongs to the amino group attached to the pyridine ring, can be distinguished as a part of the multiplet in the region of δ 7.57-7.65 ppm.

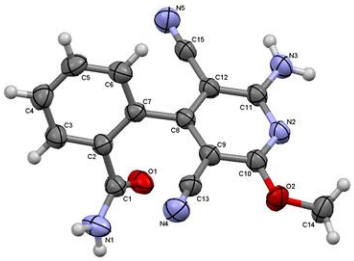


Figure 1. Structure of **10a** according to the X-ray diffraction study. Thermal ellipsoids are shown at 50% probability level.

A subsequent study of this transformation showed that product **10a** was formed exclusively when the reaction was carried out in absolute methanol with a 1.5-fold excess of malononitrile and a stoichiometric amount of sodium methoxide. It was necessary to heat the reaction mixture at reflux for an extended time (12 h, TLC monitoring) for reaction completion.

In order to confirm that dinitrile **9a** is an intermediate in the pathway from **2a** to the target pyridine **10a**, compound **9a** was synthesised in 78% yield according to a known protocol[12b] (Scheme 4). When **9a** was reacted with excess malononitrile in the presence of NaOMe, as expected, it resulted in pyridine **10a** formation. It should be noted that an LC-MS study of crude product **9a** showed that in the absence of sodium methoxide, the reaction of malononitrile with **2a** stopped at the stage of their bimolecular condensation.

We then investigated the substrate scope of this reaction with regard to the cyclic acyl amidines of the heterocyclic series: 7-amino-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (**2b**) and 7-amino-5*H*-pyrrolo [3,4-*b*]pyrazin-5-one (**2c**) (Scheme 5). Pyrrolopyridine **2b** was significantly more reactive compared to acylamidine **2a**; almost half the time (6 h) was required for complete conversion to 2'-amino-3',5'-dicyano-6'-methoxy-2,4'-bipyridine-3-carboxamide (**10b**). The reaction was, presumably, accompanied by the formation of azaphthalocyanines, since the colour of the reaction mixture gradually deepened from yellowish to blue-green. The crystals of the 2-pyridyl nicotinamide derivative **10b**, which gradually formed on the flask wall during the reaction, also had a greenish tint. The ^{1}H NMR spectrum of compound **10b** revealed characteristic signals of non-equivalent protons of the $CONH_2$ group, one of which was clearly observed at δ 7.60 ppm, and the other at δ 8.28 ppm which overlapped with the signals of the pyridine ring protons in the δ 8.24-8.28 ppm region. A broadened singlet of the amino group of the pyridine moiety was also observed at δ 7.91 ppm.

Pyrrolopyrazine **2c** was the least reactive of the three cyclic amidines tested in the reaction with malononitrile. To complete its transformation into the target 3-(2-amino-3,5-dicyano-6-methoxypyridin-4-yl)pyrazine-2-carboxamide (**10c**), it was necessary to heat the reaction mixture at reflux for 13 h. One of the reasons for such a long reaction time is likely to be the poor solubility of intermediate **9c**, which partially precipitated as an amorphous cream coloured material, then gradually dissolved with further formation of product **10c** as small shiny flesh-coloured crystals.

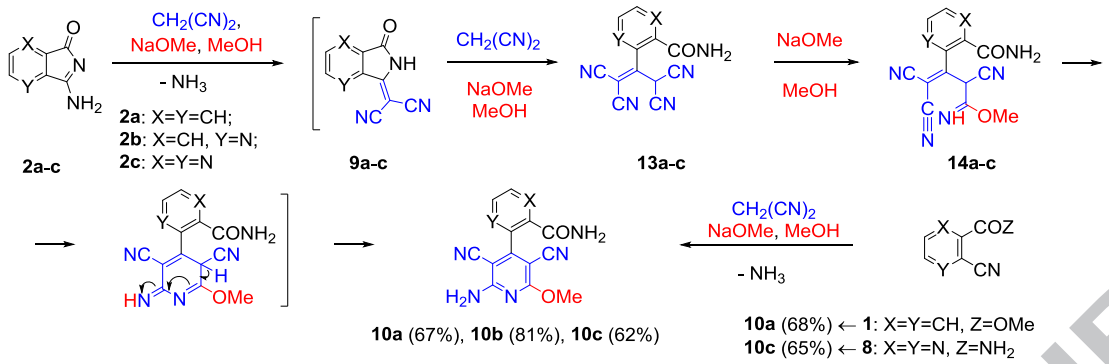
As in the case of compounds **10a** and **10b**, the ^{1}H NMR spectrum of carboxamide **10c** revealed two singlets of non-equivalent protons of the $CONH_2$ group at δ 7.93 and δ 8.48 ppm and a broad singlet of the amino group of the pyridine moiety at δ 8.10 ppm.

A reasonable pathway for this MCR resulting in the transformation of acylamidines **2a-c** into the corresponding fully substituted 4-arylpyridines **10a-c** is presented in Scheme 5. The limiting step is obviously acyleneamine **9a-c** pyrrole ring opening under the action of the second malononitrile anion generated in the presence of NaOMe to afford intermediates **13a-c** and **14a-c**.

The formation of intermediate tetranitriles **13a-c** could not be determined using LC-MS in any case. They precede the target fully substituted pyridines **10a-c**, analogous to the reactions of aldehydes[14a,15a,16-18a,b] or orthoesters[20a,b] with malononitrile. The formation of compounds **13a-c** in several cases was indirectly indicated only by the presence of additional spots on TLC. Further cyclization occurs by sequential addition of the methoxide anion to one of the cyano groups to form intermediate iminoesters **14a-c**, which then add to the cyano group at the δ-position with subsequent dihydropyridine ring closure and tautomeric conversion leading to the corresponding aminopyridines **10a-c**.

According to the literature, the formation of substituted 4-arylpyridines from amidines and malononitrile was unexpected. In this case, the amidine motif of the 3-amino-1*H*-isoindol-1-one (**2a**) behaves as a pseudo-aldehyde group, since the C4 carbon atom for 4-aryl pyridines, like **10a**, is usually supplied by the appropriate (hetero)aromatic aldehyde.[7-9b, 14-17] At the same time, there are a number of reports describing the preparation of polysubstituted pyridines from enamines.[34,35a-c] Therefore, considering that intermediate **9a** has also an enamine structure, it is possible to envisage its conversion into 4-arylpyridine **10a**.

The synthesized 4-arylpyridines **10a-c** are characterized by high melting points and poor solubility in methanol. A notable feature of their ^{1}H NMR spectra (DMSO-d_6) is the significant non-equivalence of the proton signals of the carboxamide $CONH_2$ group. The difference between the NH chemical shifts for **10a**, **10b**, and **10c** is $\Delta\delta$ 0.74, 0.68, and 0.55 ppm, respectively, which is primarily due to restricted amide bond rotation.[36] At the same time, the difference between the amide proton signals for 3-cyanopyrazine-2-carboxamide (**8**) is only $\Delta\delta$ 0.32 ppm. In addition, the oxygen and hydrogen atoms of the amide group in the crystal are involved in relatively strong hydrogen bonds.

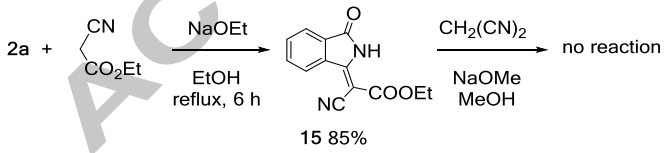


Scheme 5. Plausible mechanism for the formation of (2-amino-3,5-dicyano-6-methoxypyridin-4-yl) substituted carboxamides (**10a-c**).

During the study of the formation pathway for amides **10a-c**, it was suggested that these compounds could be formed directly from the starting nitriles from which amidines **2a-c** were synthesized in the presence of sodium methoxide. A report on the reaction of ethyl cyanobenzoate with active methylene compounds[37] and data regarding the reaction of some nitriles with one molecule of malononitrile under the action of bases[35a,38a-c] were also in favour of our assumption.

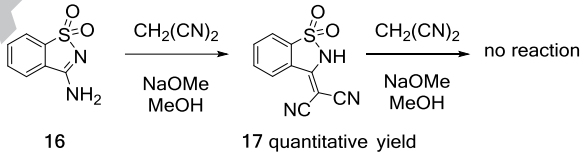
Therefore, methyl cyanobenzoate **1** and 2-cyano pyrazinecarboxamide **8** were examined as model compounds in the direct reaction with malononitrile. As expected, upon heating a mixture of ester **1** with a 3-fold excess of malononitrile in methanol with sodium methoxide, a bright-orange suspension was formed, from which pyridine **10a** was isolated in 68% yield. The reaction of pyrazine cyano amide **8** with a 3-fold excess of malononitrile and methanolic sodium methoxide also led to formation of the desired amide **10c** in 65% yield (Scheme 5).

When studying the behaviour of other active methylene compounds of ethyl cyanoacetate in the above transformation, it was found that the reaction stopped with the formation of the known product **15**[12a] derived from exocyclic amino group substitution by the ethylidene residue. This allowed us to simplify its preparation compared with known methods proceeding *via* the catalyst free heating of aminoisoindolone **2a** and ethyl cyanoacetate at 140 °C[12a] or at 150 °C.[12b] The attempted pyrrole ring opening of compound **15** under the action of a generated malononitrile carbanion proved to be unsuccessful (Scheme 6).



Scheme 6. Attempted reaction of ethyl cyanoacetate derivative **15** with malononitrile.

In order to expand the scope of this transformation, the reaction of malononitrile with 1,2-benzisothiazol-3-amine 1,1-dioxide **16**, in which the CO group is replaced by a sulfonyl group, was investigated. However, as shown by the LC-MS results and ^{1}H and ^{13}C NMR-spectroscopy, in this case the reaction stopped at the condensation of **16** with one equivalent of malononitrile to give (1,1-dioxido-1,2-benzisothiazol-3(2*H*)-ylidene)propanedinitrile **17** in quantitative yield (Scheme 7). An LC-MS study of the residue after evaporation of the combined filtrates also did not show the presence of the expected molecular ion, which could be formed from the substituted pyridine. This also indicates that benzizothiazole derivative **17** did not undergo further reaction with a second molecule of malononitrile.



Scheme 7. Reaction of 1,2-benzisothiazol-3-amine 1,1-dioxide **16** with malononitrile.

Compound **17** was previously obtained from 3-chloro-1,2-benzisothiazole 1,1-dioxide but was not characterised.[39] Compared to all four unresolved multiplets in the ^{1}H NMR spectrum (DMSO-d_6) of the starting amidine **16**, the aromatic proton signals of sulfone amide **17** were clearly observed and shifted slightly by 0.1-0.17 ppm to a lower field. At the same time, the NH proton signal was not observed, possibly due to rapid exchange with the water in DMSO-d_6.

3. Conclusion

A simple pseudo four-component method for the synthesis of fully substituted 4-arylpyridines based on 3-amino-1*H*-isoindol-1-one and its aza-analogues under mild reaction conditions has been developed. Unlike the more common approach using aromatic aldehydes, this method employs stable and readily available precursors and allows pyridine derivatives that, in addition to typical functional groups, contain an amide function at the (*α*)*ortho*-position of the obtained 4-(hetero)aromatic ring. Further studies of the scope and the limitations of this transformation with the variation of different components are in progress in our lab.

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Supplementary Material

Supplementary data (X-Ray diffraction studies of compounds **4**, **5** and **10a**, experimental procedures, ^{1}H and ^{13}C spectra) associated with this article can be found, in the on-line version, at http://

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Cyclic acyl amidines as unexpected C4-donors for fully substituted pyridine ring formation in the base mediated reaction with malononitrile

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Highlights

Pyridines are formed by the reaction of 3-amino-1*H*-isoindol-1-one with malononitrile.

This one-step, pseudo four-component reaction is catalyzed by sodium methoxide.

Aza-analogues of 3-amino-1*H*-isoindol-1-one form 4-(hetero)aryl pyridines.

Fully substituted pyridines formed have amide function at 4-(hetero)aromatic ring.

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