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One-Step Synthesis of Heterocyclic Privileged Medicinal Scaffolds by a Multicomponent Reaction of Malononitrile with Aldehydes and Thiols

Nikolai M. Evdokimov,[†] Artem S. Kireev,[‡] Andrey A. Yakovenko,[§] Mikhail Yu. Antipin,[§,||] Igor V. Magedov,*[,†,⊥] and Alexander Kornienko*[,‡]

Department of Organic Chemistry, Timiryazev Agriculture Academy, Moscow 127550, Russia, Department of Chemistry, New Mexico Institute of Mining and Technology, Socorro, New Mexico 87801, Department of Natural Sciences, New Mexico Highlands University, Las Vegas, New Mexico 87701, Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow, Russia, and Intelbioscan Ltd., Timiryazevsky Proesd 2, Moscow 127550, Russia

intelbioscan@mtu-net.ru (I.V.M.), akornien@nmt.edu (A.K.).

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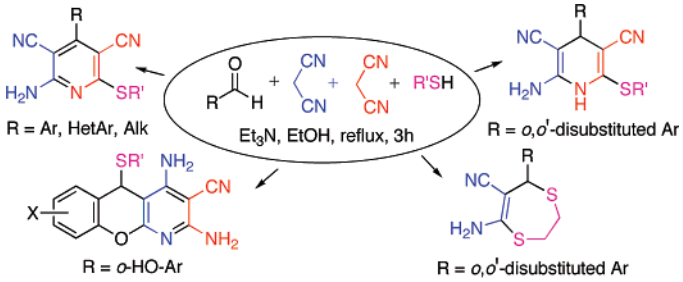

Heterocyclic privileged medicinal scaffolds involving pyridine, 1,4-dihydropyridine, chromeno[2,3-*b*]-pyridine, and dihydro-1,4-dithiepine frameworks are prepared via a single-step multicomponent reaction of structurally diverse aldehydes with various thiols and malononitrile. Mechanistic studies of the synthetic pathway leading to pyridines reveal that 1,4-dihydropyridines undergo oxidation by the intermediate Knoevenagel adducts rather than by air oxygen. The use of *o*,*o*′-disubstituted aromatic aldehydes leads to the corresponding 1,4-dihydropyridines, whereas salicylic aldehydes result in chromeno[2,3-*b*]pyridines. Reactions of ethanedithiol as a thiol component produce dimeric pyridines with sterically unencumbered aldehydes, while *o*,*o*′-disubstituted aromatic aldehydes give dihydro-1,4-dithiepines. Thus, depending on the aldehyde and thiol types, diverse libraries of medicinally relevant compounds can be prepared by a simple one-step process involving no chromatography.

Introduction

The concept of "privileged medicinal structures or scaffolds," originally introduced by Merck researchers in the course of their work on benzodiazepines, has recently emerged as one of the guiding principles of modern drug discovery.[1,2] It involves the utilization of molecular frameworks with inherent potential for biological activity. Through appropriate functional group modifications, these scaffolds are capable of providing ligands for a number of functionally and structurally discrete biological receptors. In addition, compound libraries designed on the basis of such frameworks exhibit enhanced druglike properties and result in high-quality leads. Indeed, structural analysis of 5120 commercially available drugs revealed that they were based on 1179 different scaffolds; however, half of all the drugs incorporated only 32 most frequently occurring molecular frameworks.[3] Privileged scaffolds commonly consist of rigid

[†] Timiryazev Academy.
[‡] New Mexico Institute of Mining and Technology.
[§] New Mexico Highlands University.
[||] Institute of Organoelement Compounds.
[⊥] Intelbioscan Ltd.

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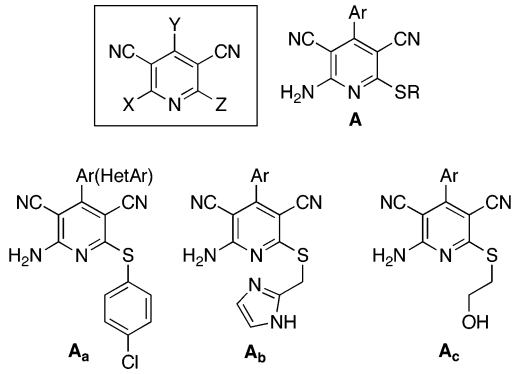

FIGURE 1. 3,5-Dicyanopyridines as privileged structures.

ring, including hetero ring, systems that present appended residues in well-defined orientations required for target recognition. Benzodiazepines represent probably the best-known privileged structures, which have produced ligands for multiple G protein-coupled receptors and ion channels among many other targets.[4]

3,5-Dicyanopyridines are an important privileged heterocyclic scaffold (Figure 1). Diversifications at positions C2, C4, and C6 (X, Y, and Z) of the pyridine core have produced a great number of compound libraries with diverse biological activities.[5] The 2-amino-4-aryl-6-sulfanyl substitution pattern (**A**) has been particularly fruitful. Thus, inspection of the patent literature reveals that compounds with the general structure **A** inhibit mitogen activated protein kinase- (MAPK-) activated protein kinase 2 (PK-2), a target for tumor necrosis factor α- (TNFα-) mediated diseases,[6a] modulate androgen receptor function,[6b] serve as potassium channel openers with applications in treating urinary incontinence,[6c] inhibit IKK2 with a potential for treating hepatitis B virus (HBV) infection,[6d] and exhibit antibacterial, antibiofilm, and antiinfective properties.[6e] Other noteworthy findings include the identification of pyridines $\mathbf{A_a}$ as potential medicinal leads in developing first therapeutic agents for the treatment of prion-induced fatal neurodegenerative diseases such as Creutzfeldt−Jacob disease (CJD) in humans, bovine spongiform encephalopathy (BSE), and scrapie in sheep.[7] A large library of compounds **A**, with variable aromatic and sulfanyl substituents, has been recently synthesized and screened for binding affinity to several forms of the prion protein.[8] Further, compounds $\mathbf{A_b}$ exhibit nanomolar selective agonistic activity for human adenosine A_{2B} receptors,[9] while substituted pyridines $\mathbf{A_c}$ display nanomolar selective full agonistic or inverse agonistic (depending on the nature of the C-4 substituent) activities for human adenosine A_1 receptors.[10] The latter findings are particularly significant due to the recent recognition of adenosine receptors as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia/ischemia, asthma, kidney disease, epilepsy, and cancer.[11]

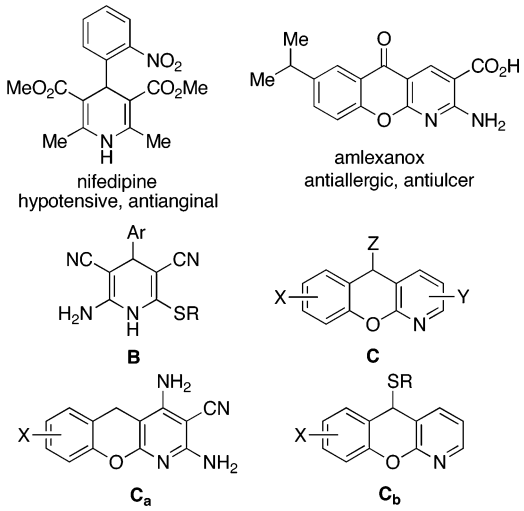

FIGURE 2. 1,4-Dihydropyridines and chromeno[2,3-*b*]pyridines as privileged structures.

1,4-Dihydropyridine and chromeno[2,3-*b*]pyridine scaffolds have also been successfully utilized for the generation of libraries for diverse medicinal applications (Figure 2). At least 10 of the most common pharmaceutical agents prescribed for a number of cardiovascular disorders incorporate the 1,4-dihydropyridine motif (e.g., nifedipine), and many are being investigated as selective agonists/antagonists of calcium, sodium, and potassium ion channels as well as G protein-coupled receptors.[2b,c] Specifically, 2-amino-3,5-dicyano-6-sulfanyldihydropyridines **B** are investigated as adenosine receptor modulators.[12] Examples of compound libraries based on chromeno[2,3-*b*]pyridine framework **C** include $\mathbf{C_a}$, found to inhibit mitogen activated protein kinase-activated protein kinase 2 and attenuate the production of proinflammatory TNFα,[13] and $\mathbf{C_b}$, reported to inhibit histamine-stimulated gastric acid secretion in animals.[14] In addition, chromenopyridines have been reported to have antiproliferative,[15a] cancer chemopreventive,[15b] antibacterial (including antitubercular),[15c,d] antimyopic,[15e] antihistaminic,[15f]

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hypotensive,[15g] antirheumatic,[15h] and antiasthmatic activities.[15i] An example of an approved drug is amlexanox, which is a commonly prescribed antiallergic and topical antiulcer agent.

Development of novel synthetic methodology to facilitate the preparation of compound libraries based on privileged structures is an intense area of research. One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials. In addition to the intrinsic atom economy and selectivity underlying such reactions, simpler procedures and equipment, time, and energy savings as well as environmental friendliness have all led to a sizable effort to design and implement MCRs in both academia and industry.[16] For example, Ugi,[16d,e] Hantzsch,[16c] and Biginelli[17] multicomponent reactions are methods of choice to prepare benzodiazepinedione, 1,4-dihydropyridine, and dihydropyrimidine privileged scaffolds, respectively (Figure 3). While many methods, including MCR, exist for the synthesis of molecular frameworks **A**, **B**, and **C**,[18] the superior features of multicomponent processes warrant their further exploration to prepare these libraries of compounds. Herein, we report our investigation of a multicomponent process involving aldehydes, thiols, and malononitrile for the synthesis of libraries of compounds based on privileged scaffolds **A**, **B**, and **C**. Details of synthetic and mechanistic studies are presented.[19]

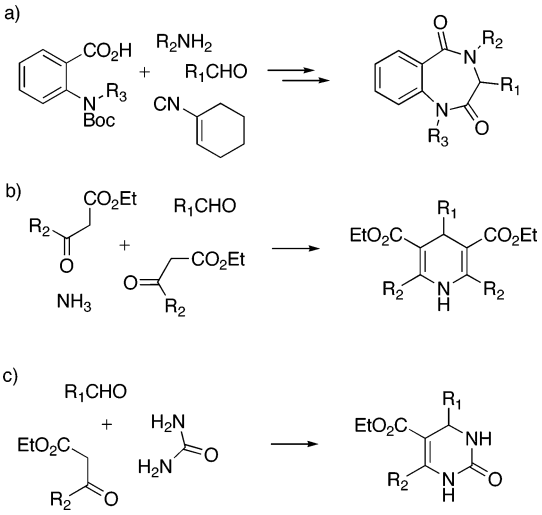

FIGURE 3. Preparation of privileged scaffolds by use of MCRs: (a) Ugi deBoc/cyclize methodology; (b) Hantzsch synthesis; (c) Biginelli synthesis.

Results and Discussion

Synthesis of Pyridines A. Due to the vast medicinal utility of pyridine derivatives **A**, various methods to prepare these compounds have been reported.[9,10,18a−h] Analysis of this literature reveals that all published approaches involve multistep sequences and their usefulness is limited by the lack of generality. For example, the syntheses of the above-mentioned $\mathbf{A_b}$ and $\mathbf{A_c}$ libraries require four steps for each member (4−12% overall yields) starting from the requisite aromatic aldehydes and purification of the target pyridines involves column chromatography.[9,10] Kambe et al.[18a] reported a potentially promising multicomponent approach utilizing a reaction of Knoevenagel reagents **D** with malononitrile and a thiol in 1:1:1 ratio to give pyridines **A** (Figure 4). The yields of compounds

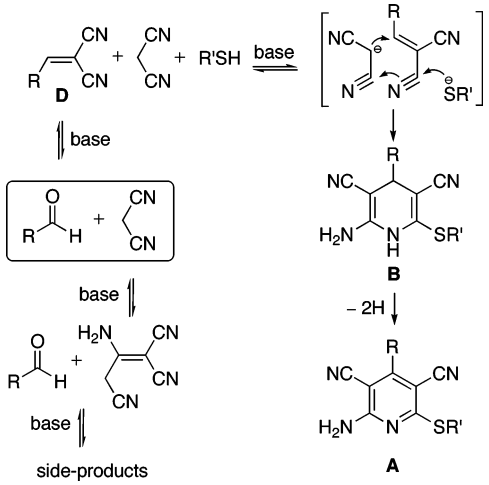

FIGURE 4. Relevant transformations in the proposed one-step synthesis of pyridines **A**.

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A were less than 50% in all cases and no explanation, other than evolution of molecular hydrogen, was provided for the transformation **B** → **A**. We theorized that often unstable compounds **D** could be obtained in situ and the synthesis of pyridines **A** could be achieved by combining an aldehyde, malononitrile, and a thiol in a ratio of 1:2:1 with suitable optimization to minimize the formation of side products.

Thus, we set out to explore this possibility and study the mechanism of Kambe's process, particularly with respect to transformation **B** → **A**, in detail. Indeed, after experimentation with different solvents, bases, and reaction temperatures, we found that simply refluxing a solution of the three reactants containing Et_3N in ethanol for 2.5−3 h followed by cooling to room temperature results in precipitation of pyridines **A**. The yields of the recrystallized products are given in Table 1 (% yield I). This multicomponent process works well for unsubstituted (**A_1**), electron-rich (**A_2**−**A_{12}**), and electron-deficient (**A_{13}**−**A_{17}**) aromatic aldehydes. Further, heteroaromatic (**A_{16}**−**A_{18}**) and aliphatic (**A_{19}**, **A_{20}**) aldehydes undergo the reaction with equal facility. In addition, variations in the thiol component are tolerated as well. Particularly noteworthy are reactions of *o*-amino- (**A_{29}**−**A_{34}**) and *o*-hydroxy-substituted (**A_{35}**, **A_{36}**) aromatic thiols that could in principle give rise to a number of unwanted cyclizations. Et_3N was found to be an adequate base for most cases with the exception of the reaction involving 4-Et_2N-PhCHO (**A_{11}**). Conceivably, the highly stable intermediate Knoevenagel adduct **D_{11}** serves as a thermodynamic sink and impedes the reaction progression to dihydropyridine **B_{11}**. The problem was solved by using more basic 1,4-diazabicyclo-[2.2.2]octane (DABCO). The use of DABCO improved the reaction yields in certain other cases as well.

Although yields of 40−48% are common, the fact that in no case do they exceed 50% was initially puzzling, albeit consistent with Kambe's results. Analysis of the crude product mixtures revealed no presence of dihydropyridines **B**. No evolution of hydrogen gas was detected, and reactions were equally successful when performed in an inert atmosphere in thoroughly deoxygenated solvent, thus ruling out atmospheric oxygen as a stoichiometric oxidant.[20] A clue was gained from reactions that involve the use of *o*,*o*′-disubstituted aromatic and heteroaromatic aldehydes, which give dihydropyridines **B** exclusively in high yields (Table 3, vide infra). We reasoned that such a divergence in the reaction paths was caused by the resistance of compounds **B_{37}**−**B_{46}** toward oxidation, because this would generate sterically crowded bis-*o*,*o*′-disubstituted biaryl systems. Importantly, the apparent 2-fold increase of product yields pointed to the possibility that pyridines **A_1**−**A_{36}** are formed through the oxidation of dihydropyridines **B_1**−**B_{36}** by an intermediate whose reductive consumption cuts the reaction yields in half. In a search for this reduced species, we isolated all components present in the crude product mixture after pyridine **A_1** was removed by filtration and elucidated their structures by use of various NMR and MS techniques. These efforts led to the identification of enaminonitrile **F_1** as an equilibrium *E*,*Z* mixture

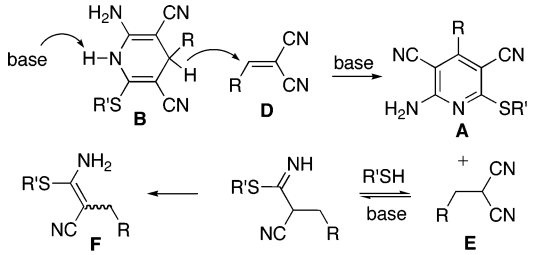

FIGURE 5. Proposed mechanistic pathway consistent with the experimental observations.

(Figure 5), whose yield of 34% practically matches that of **A_1** (35%). Similarly, **F_7** was isolated from the reaction leading to pyridine **A_7**, albeit in slightly smaller 38% yield (compared to 46% for **A_7**) after chromatographic purification.

Thus, in a clarified mechanistic route for this transformation (Figure 5), the reduction of the intermediate Knoevenagel adducts **D** by dihydropyridines **B** results in the formation of alkylated malononitriles **E**, whose further reaction with a thiol leads to the irreversible formation of highly thermodynamically stable enaminonitriles **F**. Importantly, the lack of reactivity of dihydropyridines **B_{37}**−**B_{46}** toward intermediates **D_{37}**−**D_{46}** in this pathway is nicely explained by the crowded nature of both the C-4 position in these dihydropyridines and the β-carbon of the corresponding Knoevenagel Michael acceptors. The mechanistic investigation of biological reduction processes mediated by the cofactor NAD(P)H is an intense area of research, and many simplified chemical model systems have been utilized for this purpose. Specifically, kinetic studies of the reaction of Hantzsch 1,4-dihydropyridines with benzylidenemalononitrile indicated that this redox process is likely to involve a single-step hydride transfer route as opposed to a multistep e^--H^+-e^--H^+ sequence.[21] Clearly, such a mechanism would be more sensitive to the steric accessibility of the C-4 position in compounds **B** and the β-position in intermediates **D**.

Indeed, reacting substituted malononitriles **E** with R′SH in ethanol in the presence of Et_3N affords enaminonitriles **F**. More importantly, the yields of pyridines **A** are unaffected if the starting aldehydes, malononitrile, and thiols are used in the ratio of 1:1.5:0.5, a fact that we regard as strong evidence in support of the proposed mechanism. We repeated the reactions using this ratio of the reactants, and the yields based on the amount of the starting thiols are shown in Table 1 (% yield II). These yields are quite acceptable when a valuable starting thiol is used, while the aldehyde is expendable and half of its amount can be sacrificed.

In an attempt to improve the aldehyde-based yields, we experimented with adding various external oxidizing agents in the hope that these would outcompete the Knoevenagel intermediates **D** in oxidation of dihydropyridines **B**. Weak oxidizing agents such as R′SSR′ or bubbled oxygen gas do not have an effect on product yields, whereas a strong oxidizing agent such as chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone, TCQ) leads to complete reaction failure, presumably due to thiol oxidation. The breakthrough was achieved, however, when TCQ was added to the reaction mixtures of electron-rich aromatic aldehydes (**A_2**−**A_7**) incrementally, with the first portion added immediately after the pyridine products started to precipitate from the refluxing mixtures (ca. 40−50 min after the beginning of the

(20) The role of atmospheric oxygen as a catalytic oxidant or oxidation promoter cannot be ruled out on the basis of our mechanistic studies. Furthermore, such a possibility is supported by the observations of Chen and co-workers,[8] who studied this process concurrently and independently. Using mass-spectrometric monitoring of the reaction mixtures, these investigators found that the pyridines **A** were formed only when the reaction vessels were open to the atmosphere. Due to the significance of biological NADH oxidation by molecular oxygen, a reaction catalyzed by NADH oxidases (Nox), further work in collaboration with Chen's group is underway to clarify the role of oxygen in these reactions.

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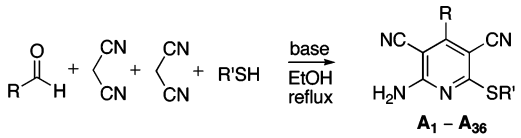
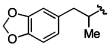
TABLE 1. One-Step Synthesis of Pyridines A



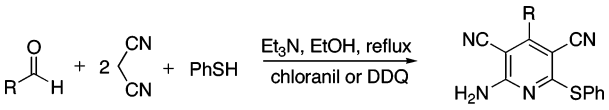
pyridine	R	R′	base	% yield I[a]	% yield II[b]	pyridine	R	R′	base	% yield I[a]	% yield II[b]
A_1	Ph	Ph	Et_3N	35	72	A_{19}	Me	Ph	DABCO	20	39
A_2	3,4,5-MeO-Ph[c]	Ph	Et_3N	44	83	A_{20}		Ph	DABCO	29	55
A_3	4-MeO-Ph	Ph	Et_3N	43	86	A_{21}	4-Cl-Ph		Et_3N	21	42
A_4	3-BnO-Ph	Ph	Et_3N	32	64	A_{22}	4-Cl-Ph		Et_3N	31	60
A_5	2,3-MeO-Ph	Ph	Et_3N	34	65	A_{23}	4-Cl-Ph	Mes	Et_3N	47	92
A_6	2,5-MeO-Ph	Ph	Et_3N	35	70	A_{24}	4-F-Ph	$PhCH_2$	Et_3N	37	73
A_7	3,4-MeO-Ph	Ph	Et_3N	46	88	A_{25}	2,5-MeO-Ph	$PhCH_2$	Et_3N	44	88
A_8	3-HO-4-MeO-Ph	Ph	Et_3N	47	94	A_{26}	3-Br-4-Me_2N-Ph		Et_3N	31	59
A_9	2,4-MeO-Ph	Ph	Et_3N	40	80	A_{27}	4-MeS-Ph		Et_3N	43	83
A_{10}	4-HO-Ph	Ph	Et_3N	42	80	A_{28}			Et_3N	20	40
A_{11}	4-Et_2N-Ph	Ph	DABCO	45	88	A_{29}	Me	2-NH_2-Ph	DABCO	25	49
A_{12}	3-Br-4-Me_2N-Ph	Ph	Et_3N	34	69	A_{30}	4-Cl-Ph	2-NH_2-Ph	Et_3N	32	63
A_{13}	4-HO_2C-Ph	Ph	Et_3N	28	55	A_{31}		2-NH_2-Ph	Et_3N	36	70
A_{14}	4-Cl-Ph	Ph	Et_3N	45	92	A_{32}	3,4,5-MeO-Ph	2-NH_2-Ph	Et_3N	44	85
A_{15}	4-O_2N-Ph	Ph	Et_3N	32	57	A_{33}	3,4-MeO-Ph	2-NH_2-Ph	Et_3N	45	90
A_{16}		Ph	Et_3N	28	55	A_{34}	4-MeS-Ph	2-NH_2-Ph	Et_3N	40	83
A_{17}		Ph	Et_3N	40	79	A_{35}		2-HO-Ph	Et_3N	38	74
A_{18}		Ph	Et_3N	48	96	A_{36}	3,4,5-MeO-Ph	2-HO-Ph	Et_3N	32	64

[a] Reactions are performed with an aldehyde, malononitrile, and a thiol in a ratio of 1:2:1; the yield is based on the starting aldehyde. [b] Reactions are performed with an aldehyde, malononitrile, and a thiol in a ratio of 1:1.5:0.5; the yield is based on the starting thiol. [c] Here and throughout the rest of the paper symbol Ph represents $C_6H_{(5-n)}$, where $n = 0$, 1, 2, etc.

reflux). In these cases, reaction yields increase to over 50% based on the starting aldehydes (Table 2). However, the addition of TCQ has no effect on reactions of benzaldehyde or other electron-deficient aldehydes (**A_1**, **A_{14}**, **A_{16}**). The substitution of TCQ by a stronger oxidant, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), solves the problem and raises the yields above 50% in these cases as well.

Because the oxidant is added after the reactions have proceeded to a considerable degree and, conceivably, a significant amount of intermediate **F** has been formed, we hypothesized that the increase in yield occurs through oxidation not of dihydropyridines **B** but rather of intermediates **F**. After the addition of another equivalent of malononitrile, these should give additional amounts of pyridines **A**. To obtain experimental

TABLE 2. Reactions Performed in the Presence of an Oxidant



pyridine	R	% yield no oxidant	% yield with TCQ	% yield with DDQ
A_2	3,4,5-MeO-Ph	42	67	--
A_3	4-MeO-Ph	43	67	--
A_4	3-BnO-Ph	32	58	--
A_5	2,3-MeO-Ph	32	65	--
A_6	2,5-MeO-Ph	35	56	--
A_7	3,4-MeO-Ph	46	66	66
A_1	Ph	35	37	61
A_{14}	4-Cl-Ph	45	45	72
A_{16}		28	27	61

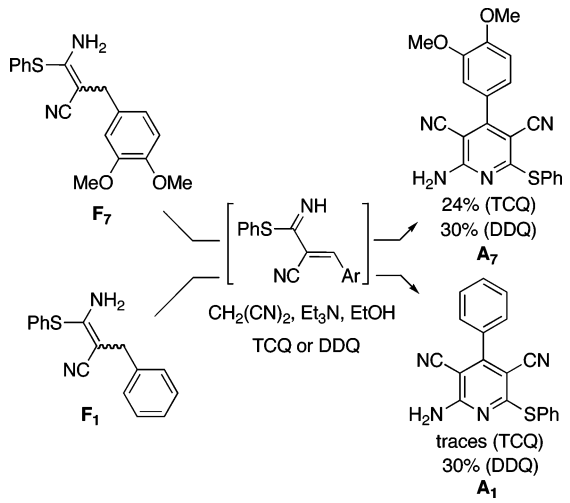
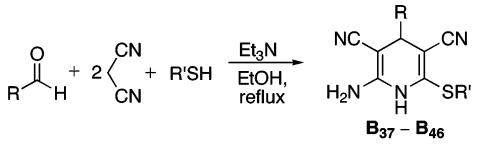


FIGURE 6. Experiments supporting the reaction mechanism in the presence of an oxidant.

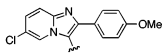
evidence in support of this mechanism, we independently treated $\mathbf{F_7}$ and $\mathbf{F_1}$ with TCQ and DDQ in the presence of 1 equiv of malononitrile (Figure 6). Indeed, $\mathbf{A_7}$ is formed from $\mathbf{F_7}$ with both TCQ and DDQ, explaining the increase in reaction yield for $\mathbf{A_7}$ in the presence of either oxidant (Table 2). In contrast, $\mathbf{A_1}$ is formed from $\mathbf{F_1}$ only with DDQ and not with TCQ, clarifying the reason for this reagent's failure to increase the yields of reactions with electron-deficient aldehydes.

To investigate the scope of this process with respect to the active methylene component, we explored the corresponding reactions of cyanoacetamide. The direct replacement of malononitrile with cyanoacetamide gives no pyridine products. Furthermore, the reactions of cyanoacetamido-derived Knoevenagel products with malononitrile and PhSH as well as those of malononitrile-derived Knoevenagel products with cyanoacetamide and PhSH give only 3,5-dicyanopyridines **A** (Figure 7). Clearly, the Michael/retro-Michael process leads to the formation of the necessary malononitrile-derived Knoevenagel product in the first type of reaction and the release of malononitrile from its Knoevenagel adduct in the second. Evidently, the higher acidity of malononitrile compared to that of cyanoacetamide and higher Michael acceptor ability of the malononitrile-derived Knoevenagel product combine to give 3,5-dicyanopyridines exclusively. In addition, the higher electrophilicity of malononitrile-derived Knoevenagel product toward a hydride transfer leads to the formation of the reduced intermediate **E** only. While investigation of other active methylene compounds is an attractive future project, it appears that the properties of malononitrile play a crucial role in the successful outcome of this multistage reaction.

TABLE 3. One-Step Synthesis of Dihydropyridines B



$\mathbf{B_{37}}$ – $\mathbf{B_{46}}$

dihydropyridine	R	R′	yield %
B_{37}	2,6-Cl-Ph	Ph	90
B_{38}	2,6-Cl-Ph	Mes	96
B_{39}	2-Cl-6-F-Ph	Ph	62
B_{40}	2-Cl-6-F-Ph	Mes	84
B_{41}		Ph	86
B_{42}		Ph	68
B_{43}	2,6-Cl-Ph		77
B_{44}	2,6-Cl-Ph	2-NH_2-Ph	39
B_{45}	2-Cl-6-F-Ph	2-NH_2-Ph	28
B_{46}		2-NH_2-Ph	69

Synthesis of 1,4-Dihydropyridines B. In agreement with our mechanistic understanding of the reaction leading to pyridines **A**, the use of sterically encumbered aldehydes, such as *o,o′*-disubstituted aromatic aldehydes, leads to the formation of 1,4-dihydropyridines **B** in good yields (Table 3). A range of thiols is tolerated, including the use of *o*-aminophenylmercaptan ($\mathbf{B_{44}}$–$\mathbf{B_{46}}$). The reactions of this thiol were initially presumed to give another unknown product since the ^{1}H NMR signal of the dihydropyridine N-H (ca. 9.5 ppm) that is consistently observed in all dihydropyridine products in DMSO-d_6, as well as the -NH_2

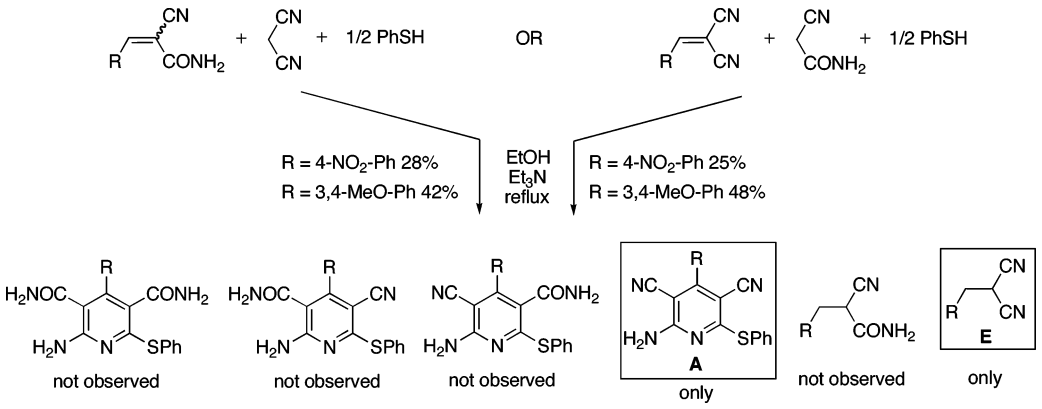
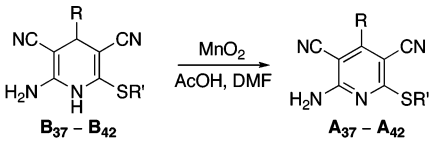


FIGURE 7. Synthesis of 3,5-dicyanopyridines involving Michael/retro-Michael processes.

TABLE 4. Aromatization of Dihydropyridines B



$\mathbf{B_{37}}$ – $\mathbf{B_{42}}$ $\mathbf{A_{37}}$ – $\mathbf{A_{42}}$

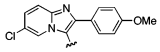
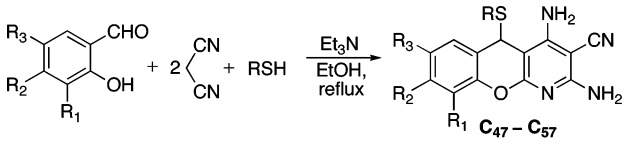
pyridine	R	R′	yield %
$\mathbf{A_{37}}$	2,6-Cl-Ph	Ph	88
$\mathbf{A_{38}}$	2,6-Cl-Ph	Mes	85
$\mathbf{A_{39}}$	2-Cl-6-F-Ph	Ph	92
$\mathbf{A_{40}}$	2-Cl-6-F-Ph	Mes	80
$\mathbf{A_{41}}$		Ph	78
$\mathbf{A_{42}}$		Ph	93

TABLE 5. One-Step Synthesis of Chromenopyridines



$\mathbf{C_{47}}$ – $\mathbf{C_{57}}$

chromeno-pyridine	R_1	R_2	R_3	R	yield %
$\mathbf{C_{47}}$	H	H	H	Ph	86
$\mathbf{C_{48}}$	H	H	H		55
$\mathbf{C_{49}}$	H	H	H	$PhCH_2$	51
$\mathbf{C_{50}}$	H	H	Me	Ph	69
$\mathbf{C_{51}}$	H	H	Me	$PhCH_2$	52
$\mathbf{C_{52}}$	H	H	Me		63
$\mathbf{C_{53}}$	H	H	Me	Mes	56
$\mathbf{C_{54}}$	OMe	H	H	Ph	57
$\mathbf{C_{55}}$	H	Et_2N	H	Ph	63
$\mathbf{C_{56}}$	H	OH	H	Ph	63
$\mathbf{C_{57}}$	H	H	NO_2	4-F-Ph	73

of *o*-aminophenylsulfanyl group, is absent in compounds $\mathbf{B_{44}}$−$\mathbf{B_{46}}$. Therefore, we obtained a crystal structure of compound $\mathbf{B_{44}}$ and confirmed that it is indeed the desired dihydropyridine (see Supporting Information). Evidently, the intramolecular hydrogen exchange between the -NH_2 of *o*-aminophenylsulfanyl and the N-H of the dihydropyridine ring is fast on the NMR time scale.

Probably due to the fact that aromatization of the dihydropyridine ring in $\mathbf{B_{37}}$−$\mathbf{B_{46}}$ would give rise to sterically hindered bis-*o*,*o*′-disubstituted biaryl systems, we were unable to achieve oxidation of these dihydropyridines under the reaction conditions of their synthesis from aldehydes, malononitrile, and thiols. However, treatment of isolated $\mathbf{B_{37}}$−$\mathbf{B_{42}}$ with a suspension of MnO_2 in AcOH/*N*,*N*-dimethylformamide (DMF) cleanly gives pyridines $\mathbf{A_{37}}$−$\mathbf{A_{42}}$ in good yields (Table 4). This oxidation further broadens the range of pyridines accessible via this multicomponent methodology, extending it to the use of sterically encumbered aldehydes. Unfortunately, in our hands the oxidative aromatization fails with dihydropyridines containing easily oxidizable substituents ($\mathbf{B_{43}}$−$\mathbf{B_{46}}$).

Synthesis of Chromenopyridines C. The use of salicylic aldehydes in this multicomponent methodology results in the formation of products whose mass spectrometric and combustion analysis data are consistent with the dihydropyridine structure. Also, yields that are significantly over 50% rule out an oxidative process characteristic of pyridine synthesis. Yet NMR and Fourier transform infrared (FTIR) analyses reveal the presence of only one cyano and two amino groups as well as the absence of the dihydropyridine N-H, indicating the formation of a different product. To elucidate the structures of these new compounds, we obtained a crystal of $\mathbf{C_{50}}$ and subjected it to X-ray analysis. The latter showed the new compounds to have a benzopyrano-[2,3-*b*]pyridine framework (see Supporting Information).

The reaction works well for all salicylaldehyde and thiol combinations tested (Table 5). Similarly to compounds **A** and

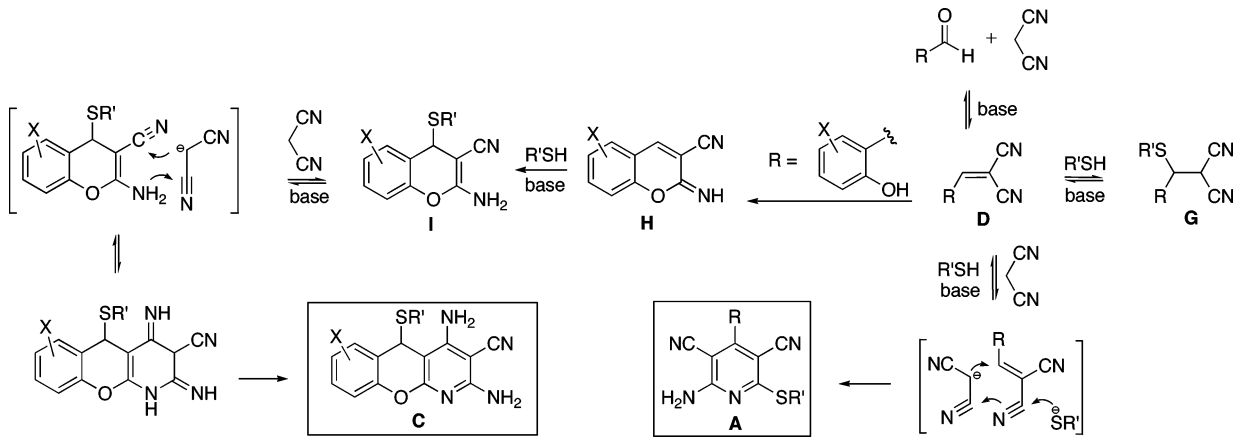


FIGURE 8. Proposed reaction path for salicylic aldehydes.

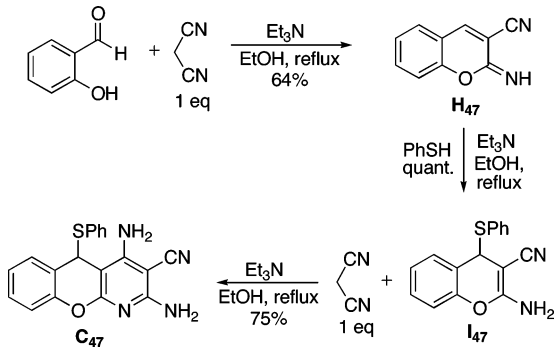


FIGURE 9. Experimental support for the proposed mechanistic divergence.

B, chromenopyridines **C** precipitate from refluxing ethanolic solutions. Normally, the solids are taken up into DMF and filtered from a yellow undissolved material. Upon the addition of water to the DMF solutions, compounds $\mathbf{C_{47}}-\mathbf{C_{57}}$ crystallize and their yields are given in Table 5.

Our proposed mechanistic interpretation of the divergence in reaction paths for aldehydes containing no *o*-hydroxyl group, which lead to formation of pyridines **A** and dihydropyridines **B**, as opposed to salicylic aldehydes, that result in chromenopyridines **C**, is shown in Figure 8. Base-catalyzed Michael addition of thiols to Knoevenagel adducts **D** to form **G** is generally reversible and nonproductive. Therefore, the reaction path leading to pyridines **A** (or dihydropyridines **B**) is operative. In contrast, Knoevenagel intermediates **D**, produced from salicylaldehydes, undergo intramolecular cyclization to give powerful Michael acceptors **H** that react with strongly nucleophilic thiols to form thermodynamically stable chromenes **I** irreversibly. Finally, the addition of another equivalent of malononitrile results in chromenopyridines **C**.

In support of the proposed mechanism, we obtained experimental evidence for each of the key steps in Figure 8. Thus, *o*-hydroxybenzaldehyde reacts with 1 equiv of malononitrile to form iminochromene $\mathbf{H_{47}}$ in 64% isolated yield after recrystallization (Figure 9). This compound undergoes addition with thiophenol to afford phenylsulfanylchromene $\mathbf{I_{47}}$ in quantitative yield. Finally, when $\mathbf{I_{47}}$ is treated under the same reaction conditions with another equivalent of malononitrile, benzopyranopyridine $\mathbf{C_{47}}$ forms in good isolated yield.

Interestingly, the yellow material that precipitates along with compounds **C**, but can be easily separated due to its lack of solubility, has been identified as structures **K** (Figure 10). Presumably, malononitrile is somewhat competitive with thiols for the addition to compounds **H** and this reactivity leads to a series of transformations shown in Figure 10. Indeed, several literature reports describe the formation of compounds **K** in the reaction of salicylic aldehydes with excess malononitrile under basic conditions.[22] None of the reported aldehyde-based yields exceeded 50%, supporting our proposal involving the reductive consumption of iminochromenes **H**. In further support, we have indeed isolated compounds **J** from our reaction mixtures.

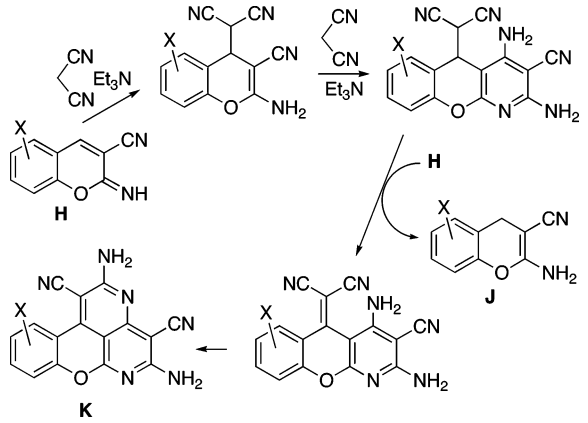


FIGURE 10. Proposed pathway for the formation of heterocycles **K**.

Further Medicinal Scaffolds. When ethanedithiol is used with unencumbered aldehydes, dimeric products **L** are obtained (Figure 11). Interestingly, the reactions of *o*,*o*′-disubstituted aldehydes do not give dimeric products but rather lead to dihydro-1,4-dithiepines **M**. Evidently, the sterically hindered *β*-position of the Knoevenagel Michael acceptors in this case slows down a nucleophilic attack by malononitrile anion, opening the door for a double attack by ethanedithiol on the two electrophlic positions to take place.

Inspection of the patent literature reveals that various dihydro-1,4-dithiepines and 1,4-dithiepine-fused heterocycles have been reported to have pesticidal,[23a] insecticidal,[23b] antibacterial,[23c] antidepressant,[23d] psychotropic,[23e] and anticonvulsant−sedative[23f]

(22) (a) Tkach, I. I.; Reznichenko, A. V.; Lukyanets, E. A. *Khim. Geterotsikl. Soedin.* **1992**, 1043−1052. (b) See ref 18n. (c) O'Callaghan, C. N.; McMurry, T. B. H.; O'Brien, J. E.; Draper, S. M. *J. Chem. Res.* **1997**, 312−313.

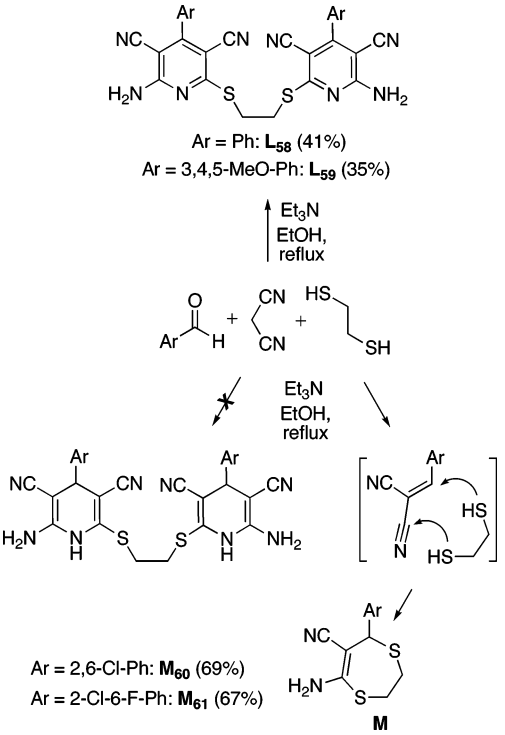


FIGURE 11. Reactions of ethanedithiol with sterically unencumbered and *o*,*o*′-disubstituted aldehydes.

activities. In addition, bis-sulfone derivatives of these compounds have been recently identified as potent calcium channel[24] and human neuropeptide galanin hGAL-1 receptor antagonists.[25] It follows that dihydro-1,4-dithiepenes also serve as privileged medicinal scaffolds, and many structures based on this molecular framework should be accessible via the one-step synthesis described here.

Finally, enaminonitriles **F**, which are formed as side products in yields identical to those of pyridines **A**, have significant medicinal potential. The *E*,*Z* mixtures of compounds **F** themselves[26] and their analogues (e.g., U0126[27] in Figure 12) are currently being investigated as potent mitogen activated protein kinase kinase (MEK) inhibitors with potential applications as antiinflammatory agents with a novel mechanism of action. The tetrasubstituted olefinic scaffold presents the appended residues for recognition by biological receptors in well-defined orientations in a fashion similar to ring-based privileged structures. Furthermore, the push−pull interaction of the amino and the cyano groups allows for a facile *E*,*Z* equilibration (clearly evident from NMR experiments) and makes it possible to present the substituents attached to the olefin from the two opposite geometries resulting in improved "pharmacological promiscuity."[2c,d,3]

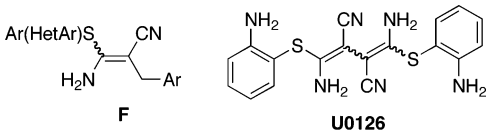


FIGURE 12. Enaminonitriles investigated as potential antiinflammatory agents.

Conclusions

In summary, one-step multicomponent reactions of structurally diverse aldehydes with various thiols and malononitrile result in the formation of substituted pyridines, 1,4-dihydropyridines, chromeno[2,3-*b*]pyridines, dihydro-1,4-dithiepines, and enaminonitriles, each representing a privileged medicinal scaffold. The reaction conditions consist of a simple reflux in ethanol, and in most cases pure products precipitate upon cooling of the reaction mixtures. *Where products fail to precipitate, a small quantity of crystalline structurally related, previously synthesized library member can be added to facilitate the process.* We have started utilizing this experimental nuance with other compound libraries as well and consider it a very useful technique in library preparation.

The mechanistic studies of these reactions reveal that pyridine yields of 50% or less are accounted for by the reductive consumption of the intermediate Knoevenagel adducts. Therefore, the thiol-based yields in most cases can be doubled by using half the original amount of the thiol, while the aldehyde-based yields can be increased to over 50% by adding an oxidant, such as chloranil or DDQ. These investigations raise the possibility that many other heterocycle-forming transformations, which involve the ultimate oxidative aromatization step and which *are often presumed to be effected with air oxygen or hydrogen release*, may proceed via mechanisms similar to the one described here. Efforts to verify this hypothesis are underway in our laboratories.

Furthermore, the mechanistic investigations explain the formation of 1,4-dihydropyridines and dihydro-1,4-dithiepines when *o*,*o*′-disubstituted aromatic aldehydes are used. In addition, each of the steps in the proposed mechanism for the synthesis of chromeno[2,3-*b*]pyridines can be reproduced in separate experiments.

Further exploration of this chemistry and biological evaluation of the synthesized libraries are in progress and will be reported in due course.

Experimental Section[28]

Synthesis of 2-Amino-4-(alkyl or aryl or heteroaryl)-6-(alkyl or aryl or heteroarylsulfanyl)-3,5-pyridinedicarbonitriles (A_1−A_{36}) and 2-Amino-4-(aryl or heteroaryl)-6-(aryl or heteroarylsulfanyl)-1,4-dihydro-3,5-pyridinedicarbonitriles (B_{37}−B_{46}): Method 1. To a solution of selected aldehyde (1.5 mmol) and malononitrile (3.1 mmol) in 5 mL of ethanol was added Et_3N or

(23) (a) Phillips, R. B.; Roush, D. M. U.S. Patent 4814325 A 19890321, 1989. (b) Ghosh, R.; Bishop, N. D.; Peacock, F. C. Ger. Offen. DE 1812762 19690703, 1969. (c) Wagner, H. A. U.S. Patent 3158619 19641124, 1964. (d) Sindelar, K.; Protiva, M.; Dlabac, A. Czech. Patent CS 219786 B 19850915, 1985. (e) Protiva, M.; Sindelar, K.; Dlabac, A.; Metysova, J. Belg. Patent BE 892476 A1 19820701, 1982. (f) Farge, D.; Leger, A.; Ponsinet, G. Eur. Pat. Appl. EP 17523 19801015, 1980.

(24) Bullington, J. L.; Dodd, J. H.; Hall, D. A. PCT Int. Appl. WO 2000077009 A1 20001221, 2000.

(25) Scott, M. K.; Ross, T. M.; Lee, D. H. S.; Wang, H.-Y.; Shank, R. P.; Wild, K. D.; Davis, C. B.; Crooke, J. J.; Potocki, A. C.; Reitz, A. B. *Bioorg. Med. Chem.* **2000**, *8*, 1383−1391.

(26) Hobbs, F. W., Jr. PCT Int. Appl. WO 2000056706 A1 20000928, 2000.

(27) (a) Duncia, J. V.; et al. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2839−2844. (b) Favata, M. F.; Horiuchi, K. Y.; Manos, E. J.; Daulerio, A. J.; Stradley, D. A.; Feeser, W. S.; Van Dyk, D. E.; Pitts, W. J.; Earl, R. A.; Hobbs, F.; Copeland, R. A.; Magolda, R. L.; Scherle, P. A.; Trzaskos, J. M. *J. Biol. Chem.* **1998**, *273*, 18623−18632.

(28) General experimental details are provided in the Supporting Information.

1,4-diazabicyclo[2.2.2]octane (DABCO), (0.1 mmol) dropwise at room temperature. The resulting mixture was heated to 50 °C and a desired thiol (1.6 mmol) was added. The reaction mixture was refluxed for 2.5−3 h and then allowed to cool to room temperature. The formed precipitate (here, and in the following procedures, a structurally similar analogue can be added to facilitate crystallization if no precipitation occurs) was isolated by filtration and the filtrate was concentrated under reduced pressure. To the dark residue was added methanol (2 mL), which resulted in the crystallization of an additional 5−10% of the product. The solids were combined and recrystallized from acetonitrile (3 mL) or methanol (3 mL) to yield a corresponding pure pyridine **A** or 1,4-dihydropyridine **B**.

Optimized Synthesis of 2-Amino-4-(alkyl or aryl or heteroaryl)-6-(alkyl or aryl or heteroarylsulfanyl)-3,5-pyridinedicarbonitriles (A_1−A_{36}): Method 2. To a solution of selected aldehyde (1.5 mmol), malononitrile (2.25 mmol), and Et_3N or DABCO (0.1 mmol) in 4 mL of ethanol was added a desired thiol (0.75 mmol) dropwise at room temperature. The resulting mixture was refluxed for 40−90 min and then worked up as described for method 1.

2-Amino-4-phenyl-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (A_1). Yield 35% (method 1), 72% (method 2); mp 215−216 °C (CH_3CN); ^{1}H NMR (DMSO-d_6) δ 7.51 (m, 3H), 7.58 (m, 7H), 7.80 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 166.7, 160.2, 159.2, 135.4, 134.5, 130.9, 130.2, 130.0, 129.3, 129.1, 129.0, 127.7, 115.8, 115.5, 93.9, 87.7; IR (KBr) 3360, 3058, 2212, 2208, 1620, 1544, 1516, 1460, 1264, 760, 746, 704, 688 cm^{-1}. Anal. Calcd for $C_{19}H_{12}N_4S$ (328.399): C, 69.49; H, 3.69; N, 17.06; S: 9.76. Found: C, 69.38; H 3.61; N, 16.92; S, 9.90.

2-Amino-4-(2,6-dichlorophenyl)-6-(phenylsulfanyl)-1,4-dihydro-3,5-pyridinedicarbonitrile (B_{37}). Yield 90%; mp 317−318 °C (CH_3CN); ^{1}H NMR (DMSO-d_6) δ 5.63 (s, 1H), 5.85 (br s, 2H), 7.37 (q, J = 7.0 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.50−7.60 (m, 5H), 9.07 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 152.2, 143.3, 135.9, 131.7, 130.8, 130.4, 129.2, 120.6, 118.2, 116.2, 115.8, 88.6, 52.6; IR (KBr) 3476, 3356, 3084, 2986, 2208, 2196, 2172, 1700, 1652, 1586, 1568, 1528, 1512, 1492, 1440, 1396, 1258, 788, 740, 686, 630, 548 cm^{-1}. Anal. Calcd for $C_{19}H_{12}N_4SCl_2$ (399.305): C, 57.15; H, 3.04; N, 14.04; S, 8.03. Found: C, 57.02; H, 3.10; N, 14.17; S, 7.86.

Isolation of Enaminonitriles (F_1 and F_7). After a pyridine **A** was removed by filtration, the filtrate was concentrated under reduced pressure. The brown residue was dissolved in chloroform (20 mL) and presorbed on silica gel, and the enaminonitrile **F** was isolated by column chromatography (16%−40% EtOAc/hexanes) as an inseparable *E*,*Z*-isomeric mixture.

(*E* + *Z*)-3-Amino-2-benzyl-3-(phenylsulfanyl)acrylonitrile (F_1). Yield 34%; R_f 0.3 (25% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 3.52 (s, 2H), 3.65 (s, 2H), 4.20 (br s, 2H), 4.46 (br s, 2H), 7.52−7.26 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 154.8, 152.5, 139.2, 137.4, 134.6, 134.0, 130.0, 129.8, 129.6, 129.2, 129.0, 128.7, 128.3, 128.0, 127.1, 126.7, 121.5, 120.0, 81.7, 79.0, 35.02, 34.8. HRMS *m*/*z* (ESI) calcd for $C_{16}H_{15}N_2S$ (M + H)$^+$ 267.0956, found 267.0921.

Synthesis of 2-Amino-4-(aryl or heteroaryl)-6-(phenylsulfanyl)-3,5-pyridinedicarbonitriles (A) in the Presence of Oxidant: Method 1. To a solution of selected aldehyde (0.45 mmol) and malononitrile (0.9 mmol) in 3 mL of ethanol was added Et_3N (0.01 mmol) dropwise at room temperature. The resulting mixture was heated to 50 °C and thiophenol (0.45 mmol) was added. The reaction mixture was refluxed for 40 min and then the first portion of oxidant (0.25 mmol) was added. After that, the brown reaction mixture was refluxed for an additional 20 min and then the second portion of oxidant (0.2 mmol) was added. The reaction mixture was refluxed for an additional 20 min and then allowed to cool to room temperature. The formed precipitate was isolated by filtration and washed with methanol (2 × 3 mL) to yield a corresponding pure pyridine A.

Method 2. To a solution of selected enaminonitrile **F** (0.18 mmol), malononitrile (0.18 mmol), and an oxidant (0.18 mmol) in 3 mL of ethanol was added Et_3N (0.01 mmol) dropwise at room temperature. The reaction mixture was refluxed for 40 min and then allowed to cool to room temperature. The formed precipitate was isolated by filtration and washed with methanol (2 × 3 mL) to yield a corresponding pure pyridine **A**.

Synthesis of 3,5-Dicyanopyridines (A_7 and A_{14}) Involving Michael/Retro-Michael Process: Method 1. To a solution of cyanoacetamide (1 mmol) and arylidenemalononitrile (1 mmol) in 4 mL of ethanol was added Et_3N (0.1 mmol) dropwise at room temperature. The resulting mixture was heated to 60 °C and thiophenol (0.5 mmol) was added. The reaction mixture was refluxed for 30 min and then allowed to cool to room temperature. The formed precipitate was isolated by filtration and washed with methanol (3 × 2 mL) to yield a corresponding pure pyridine **A**.

Method 2. To a solution of 3-aryl-2-cyanoacrylamide (1 mmol) and malononitrile (1 mmol) in 4 mL of ethanol was added Et_3N (0.1 mmol) dropwise at room temperature. The resulting mixture was heated to 60 °C and thiophenol (0.5 mmol) was added. The reaction mixture was refluxed for 30 min and then allowed to cool to room temperature. The formed precipitate was isolated by filtration and washed with methanol (3 × 2 mL) to yield a corresponding pure pyridine **A**.

Synthesis of 2-Amino-4-(aryl or heteroaryl)-6-(arylsulfanyl)-3,5-pyridinedicarbonitriles (A_{37}−A_{42}) through the Oxidative Aromatization Reaction of 2-Amino-4-(aryl or heteroaryl)-6-(arylsulfanyl)-1,4-dihydro-3,5-pyridinedicarbonitriles (B_{37}−B_{42}). To a suspension of manganese dioxide (0.75 mmol) in 1.5 mL of glacial acetic acid was added a selected compound **B** (0.5 mmol). DMF (2 mL) was added to the suspension to fully solubilize compound **B**. The mixture was refluxed for 15−20 min, the formed black precipitate was filtered off, and the filtrate was poured into ice−water (80 mL). The formed precipitate was isolated by filtration and recrystallized from methanol (3−5 mL) to yield a corresponding pure pyridine **A**.

2-Amino-4-(2,6-dichlorophenyl)-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (A_{37}). Yield 88%; mp 209−210 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 7.52 (s, 3H), 7.64 (s, 2H), 7.78 (s, 2H), 8.13 (br s, 2H), 10.23 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 167.3, 160.0, 154.9, 144.6, 135.6, 133.6, 133.2, 132.0, 130.6, 130.1, 129.5, 126.9, 121.2, 114.5, 114.2, 93.5, 87.7; IR (KBr) 3632, 3388, 3252, 3204, 2216, 1656, 1620, 1588, 1556, 1476, 1444, 1440, 1436, 1430, 1420, 1410, 1404, 1398, 1310, 1262, 1200, 1020, 884, 814, 796, 776, 748, 706, 688 cm^{-1}. HRMS *m*/*z* (ESI) calcd for $C_{19}H_{11}Cl_2N_4S$ (M + H)$^+$ 397.0081, found 397.0087.

Synthesis of 2,4-Diamino-5-(aryl or heteroarylsulfanyl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles (C_{47}−C_{57}). To a solution of selected salicylaldehyde (1.5 mmol), malononitrile (3 mmol) and a desired thiol (1.5 mmol for **C_{54}**, 2.3 mmol for **C_{55}**) in 7 mL of ethanol was added Et_3N (0.1 mmol) dropwise at room temperature. The resulting mixture was refluxed for 3−3.5 h and then allowed to cool to room temperature. The formed precipitate was isolated by filtration. The product was dissolved in DMF (3 mL), and the remaining undissolved material was removed by filtration. To the filtrate was added water (4 mL), which resulted in crystallization of the product. The formed crystals were isolated by filtration to yield a corresponding pure chromenopyridine **C**.

2,4-Diamino-9-methoxy-5-(phenylsulfanyl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (C_{54}). Yield 57%; mp 254−255 °C (DMF); ^{1}H NMR (DMSO-d_6) δ 3.72 (s, 3H), 5.74 (s, 1H), 6.30 (br s, 2H), 6.74 (dd, J = 1.4, 7.9 Hz, 1H), 6.80 (br s, 2H), 6.84 (dd, J = 1.2, 7.3 Hz, 2H), 6.90 (dd, J = 1.4, 7.9 Hz, 1H), 7.01 (t, J = 7.9 Hz, 1H), 7.12 (t, J = 7.3 Hz, 2H), 7.28 (dt, J = 1.2, 7.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 160.3, 160.1, 156.9, 147.5, 141.3, 136.4, 131.3, 129.4, 128.8, 123.9, 123.0, 120.5, 117.1, 111.9, 86.7, 70.9, 56.5, 43.4; IR (KBr) 3452, 3340, 3272, 2866, 2208, 1656, 1630, 1606, 1590, 1486, 1408, 1350, 1270, 1220, 1172, 1116, 1096, 794, 778, 764, 748, 710 cm^{-1}. Anal. Calcd for $C_{20}H_{16}N_4O_2S$ (376.442): C, 63.81; H, 4.29; N, 14.89; S, 8.52. Found: C, 63.95; H 4.08; N, 14.81; S, 8.63.

Synthesis of 2-Imino-2*H*-chromene-3-carbonitrile (H_{47}). To a solution of salicylaldehyde (1.83 g, 15 mmol) and malononitrile (0.99 g, 15 mmol) in 20 mL of ethanol was added Et_3N (0.1 mmol) dropwise at room temperature. The resulting mixture was refluxed for 30 min and then allowed to cool to room temperature. The formed precipitate was isolated by filtration and washed with methanol (3 × 3 mL) to yield **H_{47}** (1.63 g, 64%) as a yellow-red solid; ^{1}H NMR (DMSO-d_6) δ 4.90 (dd, J = 3.8, 23.4 Hz, 1H), 6.7 (br s, 1H), 7.09 (s, 1H), 7.24 (dd, J = 7.4, 17.6 Hz, 1H), 7.41−7.61 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 161, 160.9, 157.5, 152.1, 130.7, 129.5, 124.6, 118.5, 117.4, 116.8, 114.0, 113.4, 84.4, 71.1, 35.3, 31.0. HRMS *m*/*z* (ESI) calcd for $C_{10}H_6N_2ONa$ $(M + Na)^+$ 193.0378, found 193.0372.

Synthesis of 2-Amino-4-(phenylsulfanyl)-4*H*-chromene-3-carbonitrile (I_{47}) from 2-Imino-2*H*-chromene-3-carbonitrile (H_{47}). To a solution of **H_{47}** (183 mg, 1 mmol) in 7 mL of ethanol was added Et_3N (0.1 mmol) dropwise at room temperature. The resulting mixture was heated to 55 °C and thiophenol (110 mg, 1 mmol) was added. The reaction mixture was refluxed for 4 h and then allowed to cool to room temperature. The formed precipitate was isolated by filtration and washed with methanol (3 × 3 mL) to yield **I_{47}** (276 mg, quant) as a yellow solid; ^{1}H NMR (DMSO-d_6) δ 5.32 (s, 1H), 6.78 (d, J = 7.98 Hz, 1H), 7.03 (br s, 2H), 7.12−7.39 (m, 8H); ^{13}C NMR (DMSO-d_6) δ 162.6, 149.6, 136.3, 131.3, 129.5, 129.4, 129.2, 129.0, 125.0, 121.8, 120.3, 115.9, 54.1, 47.4, 47.3. HRMS *m*/*z* (ESI) calcd for $C_{16}H_{12}N_2OSNa$ $(M + Na)^+$ 303.0562, found 303.0564.

Synthesis of 2,4-Diamino-5-(phenylsulfanyl)-5*H*-chromeno-[2,3-*b*]pyridine-3-carbonitrile (C_{47}) from 2-Amino-4-(phenylsulfanyl)-4*H*-chromene-3-carbonitrile (I_{47}). To a solution of **I_{47}** (95 mg, 0.34 mmol) and malononitrile (22 mg, 0.34 mmol) in 7 mL of ethanol was added Et_3N (0.1 mmol) dropwise at room temperature. The resulting mixture was refluxed for 4 h and then allowed to cool to room temperature. The formed precipitate was isolated by filtration. The product was dissolved in DMF (3 mL), and the remaining undissolved material was removed by filtration. To the filtrate was added water (4 mL), which resulted in the crystallization of the product. The formed crystals were isolated by filtration to yield a corresponding pure chromenopyridine **C_{47}** (88.6 mg, 75%); mp 215−217 °C (DMF); ^{1}H NMR (DMSO-d_6) δ 5.75 (s, 1H), 6.47 (br s, 2H), 6.78 (t, J = 6.6 Hz, 3H), 6.92 (br s, 2H), 7.10 (t, J = 7.4 Hz, 3H), 7.17−7.30 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 160.4, 160.2, 157.0, 151.4, 136.5, 131.2, 129.4, 129.2, 128.9, 128.8, 124.3, 122.4, 117.1, 116.3, 86.8, 70.9, 43.4, 43.3. HRMS *m*/*z* (ESI) calcd for $C_{19}H_{15}N_4OS$ $(M + H)^+$ 346.0888, found 347.0958.

Synthesis of 2-Amino-6-[(2-{[6-amino-3,5-dicyano-4-aryl-2-pyridinyl]sulfanyl}ethyl)sulfanyl]-4-aryl-3,5-pyridinedicarbonitriles (L_{58} and L_{59}). To a solution of selected aldehyde (1.5 mmol), malononitrile (2.3 mmol), and 100 μL of Et_3N in 4 mL of ethanol was added ethanedithiol (0.4 mmol) dropwise at room temperature. The resulting mixture was refluxed for 40−90 min and then allowed to cool to room temperature. The formed precipitate was isolated by filtration and the filtrate was concentrated under reduced pressure. To the dark residue was added methanol (2 mL), which resulted in the crystallization of an additional 5−10% of the product. The solids were combined and recrystallized from methanol (3 mL) to yield a corresponding pure pyridine **L**.

2-Amino-6-[(2-{[6-amino-3,5-dicyano-4-(3,4,5-trimethoxyphenyl)-2-pyridinyl]sulfanyl}ethyl)sulfanyl]-4-(3,4,5-trimethoxyphenyl)-3,5-pyridinedicarbonitrile (L_{59}). Yield 35%; mp 279−280 °C (CH_3CN); ^{1}H NMR (DMSO-d_6) δ 3.77 (s, 4H), 3.80 (s, 6H), 3.84 (s, 12H), 6.87 (d, J = 2.5 Hz, 4H), 7.71 (br s, 4H); ^{13}C NMR (DMSO-d_6) δ 166.7, 160.5, 158.7, 153.5, 129.6, 115.8, 107.8, 87.0, 60.9, 57.1, 29.8; IR (KBr) 3420, 3220, 2364, 2216, 1656, 1632, 1588, 1550, 1536, 1530, 1506, 1464, 1420, 1340, 1260, 1128, 1002, 780, 706, 532 cm^{-1}. HRMS *m*/*z* (ESI) calcd for $C_{34}H_{31}N_8O_6S_2$ $(M + H)^+$ 711.1808, found 711.1805.

Synthesis of 5-Amino-7-aryl-3,7-dihydro-2*H*-1,4-dithiepine-6-carbonitrile (M_{60} and M_{61}). To a solution of selected *o*,*o*′-disubstituted aldehyde (1.5 mmol) and malononitrile (1.5 mmol) in 4 mL of ethanol was added Et_3N (0.1 mmol) dropwise at room temperature. The resulting mixture was heated to 50 °C and ethanedithiol (1.5 mmol) was added dropwise. The reaction mixture was refluxed for 40 min and then allowed to cool to room temperature. The formed precipitate was isolated by filtration and washed with ethanol (2 × 1 mL) to yield a corresponding pure dihydrodithiepine **M**.

(*Z*)-5-Amino-7-(2,6-dichlorophenyl)-3,7-dihydro-2*H*-1,4-dithiepine-6-carbonitrile (M_{60}). Yield 69%; mp 208−210 °C (CH_3CN); ^{1}H NMR (DMSO-d_6) δ 2.97 (m, 1H), 3.06−3.16 (m, 2H), 3.38 (td, J = 13.8, 5.8 Hz, 1H), 5.84 (d, J = 5.5 Hz, 1H), 6.91 (br s, 2H), 7.34 (m, 1H), 7.49 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 161.4, 136.3, 135.6, 134.0, 130.4, 129.0, 118.9, 82.9, 47.9, 36.2, 34.5; IR (KBr) 3448, 3396, 3336, 3200, 2360, 2180, 1652, 1608, 1528, 1432, 786 cm^{-1}. HRMS *m*/*z* (ESI) calcd for $C_{12}H_{11}Cl_2N_2S_2$ $(M + H)^+$ 316.9740, found 316.9763.

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Supporting Information Available: Full compound characterization data, X-ray structures of **B_{44}** and **C_{50}**, X-ray data for **B_{44}**·H_2O (CIF and PDF), complete references 1 and 27a, and copies of ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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