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One-Step, Three-Component Synthesis of Pyridines and 1,4-Dihydropyridines with Manifold Medicinal Utility†

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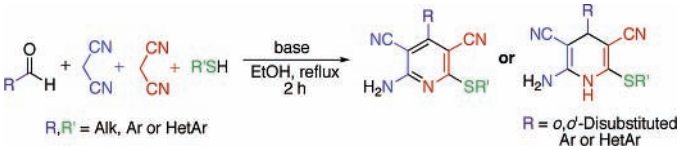
ABSTRACT



Privileged medicinal scaffolds based on the structures of 2-amino-3,5-dicyano-6-sulfanylpyridines and the corresponding 1,4-dihydropyridines have been prepared via a single-step, three-component reaction of structurally diverse aldehydes with various thiols and malononitrile. Mechanistic studies revealed that 1,4-dyhidropyridines undergo oxidation by the intermediate Knoevenagel adducts rather than by air oxygen. Although the latter process undermines the yields of pyridines, it results in the formation of substituted enaminonitriles, promising antiinflammatory agents.

The rapid assembly of molecular diversity is an important goal of synthetic organic chemistry and one of the key paradigms of modern drug discovery. 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.[1]

The usefulness of MCRs is even greater if they provide access to "privileged medicinal scaffolds." The latter are defined as molecular frameworks capable of providing ligands for a number of functionally and structurally discrete biological receptors and consequently serving as a platform for developing pharmaceutical agents for diverse applications.[2] An example of a "privileged scaffold" is a substituted pyridine framework **A**−**C** (Figure 1). Numerous patents have revealed significant and diverse medicinal utility of various compounds with this structural motif.[3] Thus, compounds with the general structure **A** inhibit MAPK-activated PK-2, a target for TNFα-mediated diseases,[3a] and modulate androgen receptor function.[3b] In addition, they serve as potassium channel openers with applications in treating urinary incontinence,[3c] inhibit IKK2 with a potential for treating

† Dedicated to Prof. Yuri I. Smushkevich on the occasion of his 70th birthday.

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(1) For recent reviews, see: (a) Ramón, D. J.; Miguel, Y. *Angew. Chem., Int. Ed*. **2005**, *44*, 1602−1634. (b) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471−1499. (c) Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screening* **2001**, *4*, 1−34. (d) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366−374.

(2) (a) The term "privileged scaffolds or structures" was originally introduced by Merck researchers in their work on benzodiazepines: Evans, B. E. et al. *J. Med. Chem*. **1988**, *31*, 2235−2246. (b) For a recent review, see: Patchett, A. A.; Nargund, R. P. *Ann. Rep. Med. Chem*. **2000**, *35*, 289−298.

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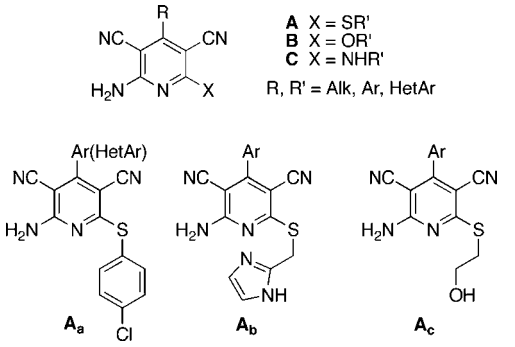

Figure 1. Substituted pyridines as "privileged structures."

HBV infection,[3d] and exhibit anti-bacterial, antibiofilm and anti-infective properties.[3e]

Other noteworthy recent findings include the identification of pyridines $\mathbf{A}_a$ as potential medicinal leads in developing therapeutic agents for the treatment of Creutzfeldt−Jacob disease[4] as well as libraries $\mathbf{A}_b$[5] and $\mathbf{A}_c$[6] as selective modulators of human adenosine receptors implicated in Parkinson's disease, hypoxia/ischemia, asthma, kidney disease, epilepsy, and cancer.[7]

Due to the vast medicinal utility of pyridine derivatives **A**, various methods to prepare these compounds have been reported.[8] 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.[5,6]

Recently, we have initiated a drug discovery program with a focus on privileged structures **A**. Since the lack of an efficient and general preparation method of pyridines **A** immediately impeded our efforts, we addressed it as our first goal. Because the feasibility of the assembly process **E** (Figure 2) had been previously established,[8a,5,6] we theorized

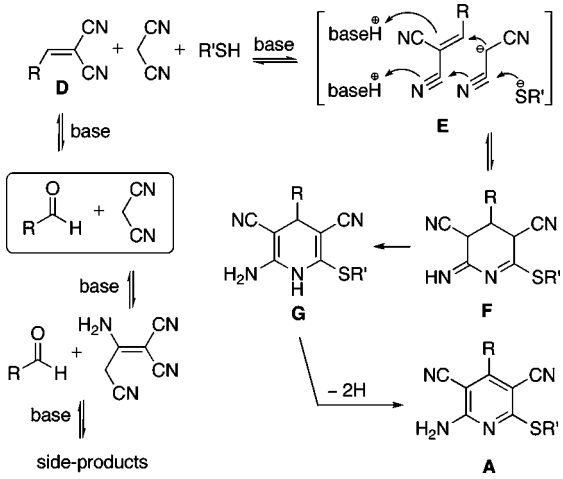

Figure 2. Relevant transformations in the proposed one-step synthesis of pyridines **A**.

that this transformation could be brought about under favorable reaction conditions by combining an aldehyde, malononitrile, and a thiol in a ratio of 1:2:1.[9]

The process would be irreversible because of the high thermodynamic stability associated with dihydropyridines **G**, stemming from the push−pull interactions involving the $H_2N-C{=}C-CN$ and $R'S-C{=}C-CN$ systems.[10] Furthermore, we envisioned that performing the reaction in an aerobic environment would promote oxidative aromatization to provide pyridines **A**. Indeed, after the 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**. This three-component process works well for any tested combination of aliphatic, aromatic or heteroaromatic aldehydes and thiols with the exception of the reaction involving 4-Et_2N-PhCHO. Conceivably, the highly stable intermediate Knoevenagel adduct $\mathbf{D}_6$ serves as a thermodynamic sink and impedes the reaction progression to dihydropyridine $\mathbf{G}_6$. The problem was solved by using a stronger base, such as DABCO. The use of DABCO improved the reaction yields in certain other cases as well. The final, optimized yields of the recrystallized products are given in Table 1.

Although the yields of 40−48% are common, the fact that in no cases do they exceed 50% was initially puzzling. Analysis of the crude product mixtures revealed no presence of dihydropyridines **G**. We suspected that due to the low

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(6) Chang, L. C. W.; von Frijtag Drabbe Künzel, J. K.; Mulder-Krieger, T.; Spanjersberg, R. F.; Roerink, S. F.; van den Hout, G.; Beukers, M. W.; Brussee, J.; Ijzerman, A. P. *J. Med. Chem.* **2005**, *48*, 2045−2053.

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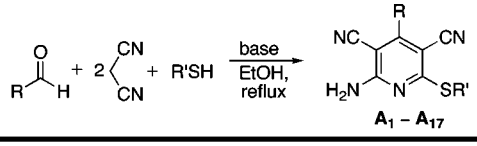
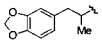
Table 1. One-Step Synthesis of Pyridines **A**



A$_1$ – A$_{17}$

pyridine	R	R′	base	yield %
A$_1$	Me	Ph	DABCO	20
A$_2$		Ph	Et_3N	40
A$_3$	4-O_2N-Ph	Ph	Et_3N	32
A$_4$	Ph	Ph	Et_3N	35
A$_5$	4-HO-Ph	Ph	Et_3N	42
A$_6$	4-Et_2N-Ph	Ph	DABCO	45
A$_7$	3,4-MeO-Ph	Ph	Et_3N	46
A$_8$	3,4,5-MeO-Ph	Ph	DABCO	43
A$_9$	4-HO_2C-Ph	Ph	Et_3N	28
A$_{10}$		Ph	DABCO	48
A$_{11}$		Ph	DABCO	29
A$_{12}$	4-Cl-Ph		Et_3N	21
A$_{13}$	4-Cl-Ph		Et_3N	31
A$_{14}$	4-Cl-Ph	Mes	Et_3N	47
A$_{15}$	4-F-Ph	$PhCH_2$	Et_3N	37
A$_{16}$	2,5-MeO-Ph	$PhCH_2$	Et_3N	44
A$_{17}$	4-MeS-Ph		Et_3N	43

oxygen concentration in refluxing ethanol oxidation of compounds **G** is slow and these intermediates undergo a competing transformation, undermining the final yields of pyridines **A**. However, performing the reactions in the presence of known 1,4-dihydropyridine oxidizing agents[11] such as DDQ,[12] R′SSR′,[13] or bubbling oxygen through the refluxing mixtures[14] does not have an effect on product yields. A clue was gained from reactions that involve the use of ortho,ortho′-disubstituted aromatic and hetero-aromatic aldehydes, which give dihydropyridines **G** exclusively in high yields (Table 2).

We reasoned that such a divergence in the reaction paths was caused by the resistance of compounds **G$_{18–24}$** toward oxidation, because this would generate sterically crowded bis-ortho,ortho′-disubstituted biaryl systems. Importantly, the apparent 2-fold increase of product yields pointed to the possibility that compounds **A$_{1–17}$** are formed not through the oxidation of 1,4-dihydropyridines **G$_{1–17}$** by oxygen, but rather 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$_4$** was removed by filtration and elucidated their structures using various NMR and MS

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(12) Wallace, D. J.; Gibb, A. D.; Cottrell, I. F.; Kennedy, D. F.; Brands, K. M. J.; Dolling, U. H. *Synthesis* **2001**, 1784−1789.
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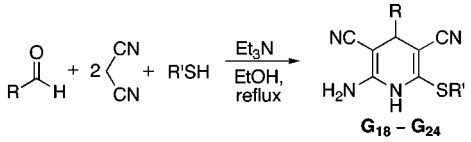
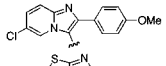
(14) See: Mashraqui, S. H.; Karnik, M. A. *Tetrahedron Lett.* **1998**, *39*, 4895−4898 and references therein.

Table 2. One-Step Synthesis of Dihydropyridines **G**



G$_{18}$ – G$_{24}$

dihydropyridine	R	R′	yield %
G$_{18}$	2,6-Cl-Ph	Ph	90
G$_{19}$	2,6-Cl-Ph	Mes	96
G$_{20}$	2,6-Cl-Ph		77
G$_{21}$	2-Cl-6-F-Ph	Ph	62
G$_{22}$	2-Cl-6-F-Ph	Mes	84
G$_{23}$		Ph	86
G$_{24}$		Ph	68

techniques. These efforts led to the identification of enaminonitrile **J$_4$** as an equilibrium *E*,*Z*-mixture (Figure 3), whose

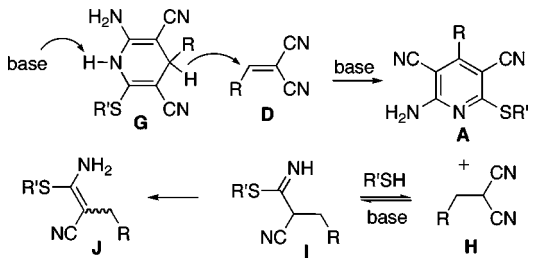


Figure 3. Proposed mechanistic pathway consistent with the experimental observations.

yield of 34% practically matches that of **A$_4$** (35%). Thus, in a clarified mechanistic route for this transformation (Figure 3), the reduction of the intermediate Knoevenagel adducts **D$_{1–17}$** by dihydropyridines **G$_{1–17}$** results in the formation of alkylated malononitriles **H$_{1–17}$**, whose further reaction with a thiol leads to the irreversible formation of highly thermodynamically stable[10] enaminonitriles **J$_{1–17}$**. Importantly, the lack of reactivity of dihydropyridines **G$_{18–24}$** toward intermediates **D** in this pathway is nicely explained by the crowded nature of the C-4 position in these compounds. Because of its relevance to the biological NADH reduction processes, the mechanism of a reaction of Hantzsch 1,4-dihydropyridines with benzylidenemalononitrile has been thoroughly studied and found to involve a single-step hydride transfer route as opposed to a multistep $e^-−H^+−e^-−H^+$ sequence.[15] Clearly, the former mechanism would be more sensitive to the steric accessibility of the C-4 position in compounds **G**.

Also consistent with this mechanistic pathway are the following observations. First, performing the reactions lead-

(15) Zhu, X.-Q.; Zou, H.-L.; Yuan, P.-W.; Liu, Y.; Cao, L.; Cheng, J.-P. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1857−1861.

ing to pyridines **A** under inert atmosphere in thoroughly deoxygenated ethanol has no effect on reaction outcome. Second, yields of pyridines **A** are unaffected if the starting aldehydes, malononitrile, and thiols are used in a ratio of 1:1.5:0.5. Finally, reacting substituted malononitriles **H** with R′SH in ethanol in the presence of Et_3N affords enaminonitriles **J**.

While these transformations are fascinating due to the richness of chemistry involved, it is important to point out that a great number of the intermediates in these synthetic pathways have established themselves as "privileged medicinal structures". In addition to the diverse medicinal utility of the pyridines **A**, 1,4-dihydropyridines of the general structure **K** (Figure 4), which encompasses compounds **G**,

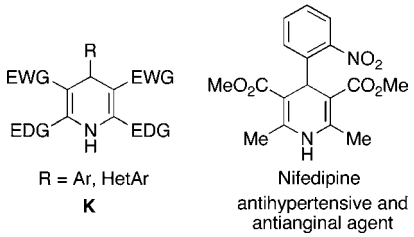


Figure 4. Substituted 1,4-dihydropyridines as "privileged structures."

have become a mainstay in the treatment of cardiovascular disorders due to their ability to inhibit Ca^{2+} entry into the cells of cardiac and vascular muscle. While there are already 10 therapeutic agents (e.g., nifedipine) that are based on the scaffold **K**, extensive investigations are ongoing not only to uncover novel pharmaceuticals but also to use these privileged structures as a tool to study calcium channels.[16]

Last, the enaminonitriles **J** that are formed as side products in yields identical to those of pyridines **A** have significant medicinal potential. The *E*,*Z*-mixtures of compounds **J** themselves[17] and their analogues (e.g., U0126[18] in Figure 5)

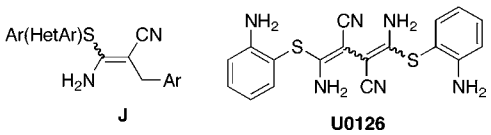


Figure 5. Enaminonitriles investigated as potential antiinflammatory agents.

are currently being investigated as potent MEK inhibitors with potential applications as antiinflammatory agents with a novel mechanism of action.

In summary, one-step, three-component reactions of structurally diverse aldehydes with various thiols and malononitrile result in the formation of substituted pyridines, 1,4-dihydropyridines and enaminonitriles, each representing a privileged medicinal scaffold. Armed with a clear mechanistic understanding of this intriguing process we are pursuing further studies to uncover the reaction conditions necessary for selective, high yielding synthesis of each one of these three products.

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Supporting Information Available: Experimental procedures and characterization of compounds $\mathbf{A_{1-17}}$ and $\mathbf{G_{18-24}}$, copies of ^1H and ^{13}C NMR spectra for *E*,*Z*-mixture $\mathbf{J_4}$, and the complete refs 2a and 18. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For a review discussing 1,4-dihydropyridines as privileged structures, see: Triggle, D. J. *Cell. Mol. Neurobiol.* **2003**, *23*, 293−303. For a review of structure−activity relationship studies, see: Goldmann, S.; Stoltefuss, J. *Angew. Chem., Int. Ed.* **1991**, *30*, 1559−1578.

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

(18) Duncia, J. V. et al. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2839−2844.