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Synthesis and Reactivity of Some 6-Substituted-2,4-dimethyl-3-pyridinols, a Novel Class of Chain-Breaking Antioxidants

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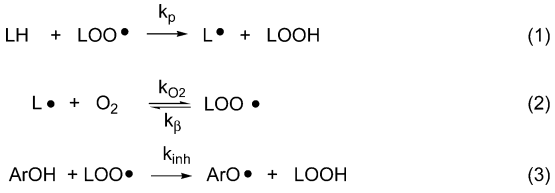
The synthesis and study of a series of 6-substituted-2,4-dimethyl-3-pyridinols having interesting antioxidant properties is reported. The general synthetic strategy leading to the compounds involved a low-temperature aryl bromide-to-alcohol conversion as the last step. 2,4-Dimethyl-3-pyridinol (**1a**), 2,4,6-trimethyl-3-pyridinol (**1b**), and 2,4-dimethyl-6-(dimethylamino)-3-pyridinol (**1d**) were thus prepared from the corresponding 3-bromopyridine precursor. The methoxy derivative 2,4-dimethyl-6-(methoxy)-3-pyridinol (**1c**) was also prepared by an alternate route via a Baeyer−Villiger reaction on the substituted benzaldehyde precursor. Novel bicyclic pyridinols **2** and **3** required prior construction of the ring structure. Thus, **2** was prepared by the use of a 6-step intramolecular Friedel−Crafts strategy, and **3** required an 11-step sequence with a thermolytic intramolecular inverse-demand Diels−Alder reaction between a pyrimidine ring and an alkyne as the key step. Basicities of the pyridinols approached physiological pH with increasing electron density in the ring. Pyridinols **1a**−**d** were found to be indefinitely stable to air oxidation while **2** and **3** decomposed upon extended exposure to the atmosphere. The reactivities of the pyridinols toward chain-carrying peroxyl radicals in homogeneous organic solution were examined by studying the kinetics of radical-initiated styrene autoxidations under controlled conditions. These experiments revealed that some of the newly synthesized pyridinols are the most effective phenolic chain-breaking antioxidants reported to date.

Introduction

Free radical chain oxidation, commonly referred to as lipid peroxidation when the reactant is a lipid, has been implicated as a key factor in a number of degenerative diseases such as atherosclerosis.[1] Polyunsaturated fatty acids and esters are the principal targets of chain-carrying peroxyl radicals in this transformation.[2] Chain-breaking antioxidants, most commonly substituted phenols, can effectively quench the propagating chain (eq 1).[3] They do so by transferring their phenolic H-atom to the propagating lipid peroxyl radical (eq 3) at a rate faster than chain propagation (eq 1). Reaction of the phenols with L•, rather than with LOO•, can be neglected at low [ArOH] and normal [O_2] since the reaction of L• with O_2 (eq 2) dominates as its rate is at or near the diffusion-controlled limit. The relevant chain propagation and inhibition steps are presented in Scheme 1.

SCHEME 1. Chain Propagation Steps for Free Radical Autoxidation and Inhibition by Phenolic Compounds



The most famous example of a phenolic antioxidant is Nature's best lipophilic antioxidant, α-tocopherol (α-TOH), the most potent form of Vitamin E. Typical propagation rate constants, k_p, for polyunsaturated lipid substrates are on the order of 10 to 100 M^{-1} s^{-1} while the inhibition rate constant for α-tocopherol, k_{inh}, is greater than 10^6 M^{-1} s^{-1}.

Extensive efforts to design synthetic antioxidants whose inhibition rate constants are greater than that of α-tocopherol have been made in recent years because of

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(1) For example: (a) Steinburg, D.; Parhsarathy, S.; Carew, T. E.; Khoo, J. C.; Witztum, J. L. *New Engl. J. Med.* **1989**, *320*, 915. (b) Chisholm, G. M.; Steinburg, D. *Free Radical Biol. Med.* **2000**, *28*, 1815.

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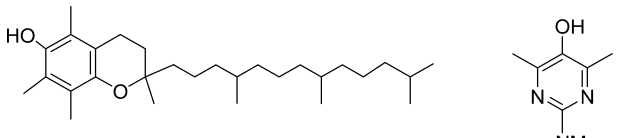
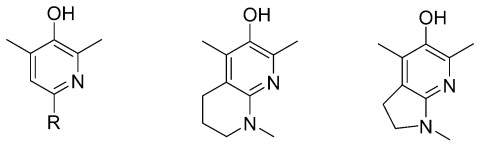
the therapeutic and industrial importance of these compounds, but this search has met with limited success due to the high reactivity of many promising candidates to oxygen.[3a−7] Recently, some of us proposed[8] that substituted 5-pyrimidinol and 3-pyridinol derivatives would possess similar reactivities toward chain-carrying peroxyl radicals as equivalently substituted phenols, but be much more stable to air oxidation. This was suggested to allow the introduction of very strongly electron-donating groups (e.g., *N*,*N*-dialkylamino) para to the O−H on the ring to enhance the reactivity of these compounds beyond that of α-TOH. Substitution of such groups on phenols leads to compounds that are unstable in air. For example, 4,6-dimethyl-2-(dimethylamino)-5-pyrimidinol, shown below, was predicted by theory to be slightly more reactive to peroxyls than α-TOH, but much more stable to air oxidation. Subsequent experimental studies have confirmed both of these predictions.[8]



α-Tocopherol (α-TOH)

In a recent communication, we predicted by theory that 6-amino-3-pyridinols should be even more reactive antioxidants than the corresponding pyrimidinols (e.g. above), while still possessing acceptable air stability.[9] We also showed that these pyridinols are, in fact, some of the best phenolic chain-breaking antioxidants known, with three derivatives (**1d**, **2**, and **3**) being 5, 28, and 88 times more



1 a. R = H
b. R = CH_3
c. R = OCH_3
d. R = $N(CH_3)_2$

2

3

active than α-TOH in intercepting peroxyl radicals. It was shown that including the para heteroatom in an aliphatic ring to form bicyclic compounds, such as α-TOH and its slightly more reactive pentamethylbenzofuranol (five-membered heterocyclic ring) analogue, further reduces the O−H bond dissociation enthalpy (BDE) and improves antioxidant efficacy.[9] This report describes synthetic efforts undertaken to prepare pyridinols **1a**−**d**, having different substituents at the 6-position on the ring, along with details of the preparation of the bicyclic compounds **2** and **3**. We provide here reliable routes for this interesting class of compounds along with some key physical properties.

Results and Discussion

Synthesis. (a) General Strategy: The Hydroxylation Step. Several parameters were important in devising a general synthetic strategy. For example, *p*-aminopyridinols are electron-rich and can be reactive with molecular oxygen. This suggests that introduction of the OH group should be performed as late in the sequence as possible to avoid decomposition of unstable intermediates. Furthermore, the hydroxylation step should be performed under very mild conditions given the expected moderate stabilities of some of the pyridinols. A sequence starting with construction of the appropriate mono- or bicyclic aminopyridine precursor was envisioned, followed by a hydroxylation procedure. The Boyland−Sims peroxidation, the only general method to directly para-hydroxylate activated pyridine rings,[10] is known to fail for aminopyridines when the ortho position is vacant.[11] Some direct hydroxylations with aq H_2O_2 (AcOH, 100 °C) have been reported,[12] but in all cases very low yields were obtained. It is likely that such a reaction will have very low selectivity for the electron-rich substrates **1d**, **2**, and **3** due to their expected high oxidizabilities. Baeyer−Villiger approaches call for the appropriately substituted aldehydes, which are themselves difficult to prepare.[12b] Diazonium precursors have been shown to give undesired coupling products upon attempted hydrolysis ($CuSO_4$, H_2O, 100 °C).[13] A procedure by Van Boeckel et al., which utilized a low-temperature bromide/lithium exchange, followed by a nitrobenzene quench[14] to obtain a 6-amino-3-pyridinol from the corresponding 6-amino-3-bromopyridine[15] piqued our interest, and we set out to use it in a general way to prepare the simplest aminopyridinol, **1d**, from the readily prepared 3-bromo precursor. This approach is illustrated in Scheme 2.

The appropriate starting material leading to **1d**, 2-amino-4,6-lutidine, is commercially available and inexpensive. It was brominated regioselectively para to the amino group to give pyridine **4**,[16] which was methylated under Eschweiler−Clark conditions to afford **5**. Hydroxylation of arylbromides via aryllithium intermediates

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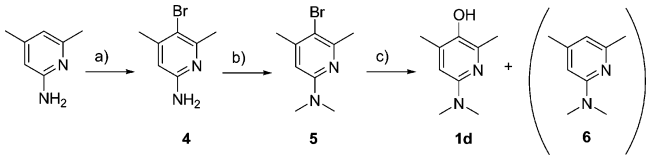
SCHEME 2. Synthesis of Monocyclic Pyridinol 1d[a]



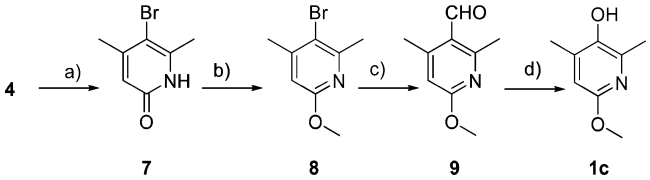
[a] Reagents and conditions: (a) dibromodimethylhydantoin, DCM, −40 °C, 45 min, 67%; (b) HCOOH, *i*-PrOH, H_2CO (aq), reflux, 100%; (c) (1) *n*-BuLi, THF, −78 °C, (2) 2,6-dimethylnitrobenzene, 63%.

has been reported in the literature. Reagents that have been used for the oxygenation step include bis(trimethylsilyl)peroxide,[17] lithium *tert*-butylhydroperoxide,[18] or trimethylborate/CH_3CO_3H.[13] However, all of these reagents contain active peroxy bonds and problems in their compatibility with electron-rich aminopyridines or aminopyridinols were expected. Therefore, we followed the protocol used by Van Boeckel et al.[15] Briefly, bromide **5** underwent smooth lithium/bromide exchange with *n*-BuLi in THF at −78 °C and the resulting pyridyllithio reagent was quenched with 2,6-dimethylnitrobenzene (vide infra) to afford compound **1d** as a yellow solid in 63% isolated yield. Purification consisted of a base/acid extraction, which eliminated the need for purification by column chromatography. Another advantage of the synthesis outlined in Scheme 2 is that a variety of exocyclic amine substituents can be introduced by reductive alkylation of **4**. This would provide antioxidants having a range of lipophilicity, a parameter that has been shown to be important in determining antioxidant efficacy for some applications.

Clear advantages of this hydroxylation protocol for our targets were the low reaction temperature (−78 °C) and the fact that nitroarenes, which are usually not considered oxidants, are compatible with electron-rich pyridines. Indeed, as will be shown, this protocol was successfully and reproducibly applied to all of our target substrates. However, the yields of the reaction were modest to low. Poor chromatography of the pyridinols could be partially avoided by using Et_3N-deactivated silica gel as the stationary phase. A more significant problem in this step was the formation of large amounts of the reduced pyridine (i.e. **6** in the case of **1d**) due to quenching of the pyridyllithio species. Cava et al. have found that the formation of the reduced product is caused by abstraction of an ortho proton from $PhNO_2$ by the aryllithium intermediate.[19] Therefore, for the present study, 2,6-dimethylnitrobenzene was selected as the electrophile rather than nitrobenzene. This reagent gave comparable or slightly higher yields than nitrobenzene and it was easier to remove from the crude product because of its reduced polarity. It did not, however, eliminate the formation of the reduced byproduct. Follow-up studies, aimed at developing a means to avoid this serious side reaction, were fruitless.

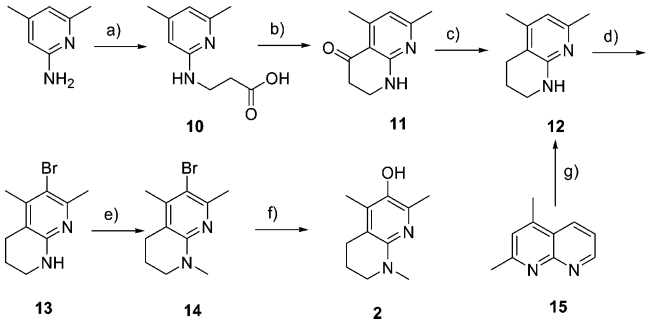
Syntheses of **1a** and **1b**, which are known compounds,[20] proceeded by conversion of the requisite bromopyridine

SCHEME 3. Synthesis of Pyridinol 1c[a]



[a] Reagents and conditions: (a) NaONO, H_3PO_2, H_2O, 5 °C, 87%; (b) Ag_2CO_3, CH_3I, CH_2Cl_2, 24 h, 90%; (c) (1) *n*-BuLi, THF, −78 °C, (2) DMF, 87%; (d) (1) *m*-CPBA, $CHCl_3$, (2) KOH, MeOH, 33%.

SCHEME 4. Synthesis of Pyridinols Containing an Annulated Aliphatic Six-Membered Ring[a]



[a] Reagents and conditions: (a) acrylic acid, py, reflux, 24 h, 30%; (b) PPA, 125 °C, 40 min, 75%; (c) BH_3·THF, THF, reflux, 18h, 83%; (d) dibromodimethylhydantoin, DCM, −78 °C, 93%; (e) HCOOH, H_2CO(aq), *i*-PrOH, reflux, 77%; (f) (1) *n*-BuLi, THF, −78 °C, (2) 2,6-dimethylnitrobenzene, 25%; (g) H_2, 10% Pd/C, EtOH, overnight, 74%.

to the pyridinol by the same lithiation−hydroxylation sequence. Compound **1c** was prepared from the corresponding bromide **8**, which in turn was prepared by methylation (Ag_2CO_3/CH_3I) of 3-bromo-2,4-dimethyl-6-hydroxypyridine **7**. Compound **7** was obtained from amine **4** by hydrolysis of the corresponding diazonium salt in the presence of H_3PO_2. Generally, under these conditions deaminated products form, but in our case hydrolysis prevails over reduction of the diazonium salt. We attribute this to the neighboring pyridine nitrogen. A Baeyer−Villiger sequence was used to generate **1c** from the corresponding aldehyde precursor **9**, as shown in Scheme 3. The reactions leading to the aldehyde intermediate proceeded in high yield but the Baeyer−Villiger reaction also gave the product pyridinol in only modest yields, offering no advantage to this alternate procedure.

(b) Pyridinols with an Annulated Six-Membered Ring. The construction of the bicyclic pyridinol **2** required the formation of a tetrahydronaphthyridine structure prior to bromination and hydroxylation. A Friedel−Crafts approach was used for the annulation process (Scheme 4).[21] A sluggish Michael reaction of 2-amino-4,6-lutidine with acrylic acid in refluxing pyridine afforded amino acid **10**. The subsequent ring closure proceeded in either hot polyphosphoric acid (PPA) or hot methanesulfonic acid. The reduction of aryl ketone **11** was achieved by reacting it with excess BH_3−THF complex at reflux to afford **12** in 83% yield and in high purity. Alternatively, **12** was obtained in 74% recrystallized yield

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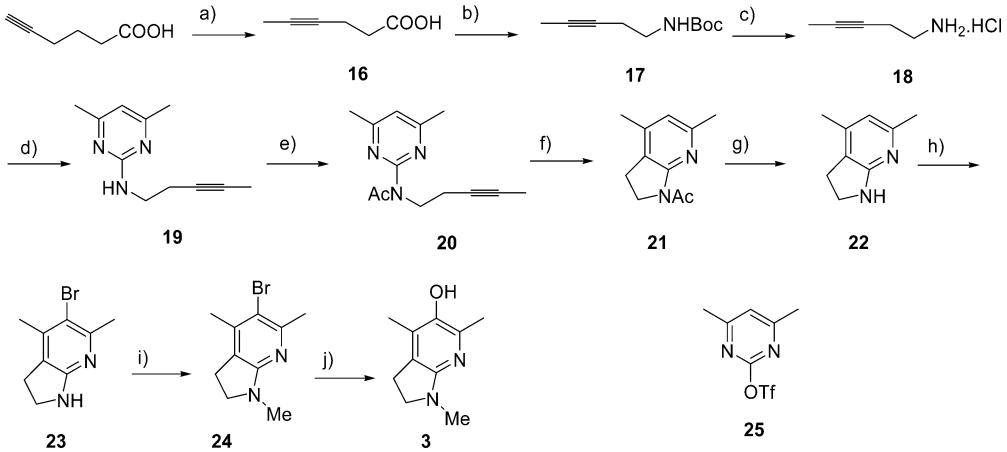
SCHEME 5. Synthesis of Pyridinols Containing an Annulated Aliphatic Five-Membered Ring[a]



[a] Reagents and conditions: (a) 15 M KOH, reflux, 4 h, 80%; (b) Ph_2PON_3, Et_3N, *t*-BuOH, reflux, 79%; (c) HCl, ether, 70%; (d) 4,6-dimethylpyrimidinyltriflate (**25**), Et_3N, DMF, 1 d, 93%; (e) Ac_2O, DMAP, 100 °C, 20 h, 91%; (f) Ph_2O, 1 d, reflux, 82%; (g) KOH, MeOH, reflux, 100%; (h) dibromodimethylhydantoin, DCM, −78 °C, 83%; (i) HCOOH, H_2CO(aq), *i*-PrOH, reflux, 84%; (j) (1) *n*-BuLi, THF, −78 °C, (2) 2,6-dimethylnitrobenzene, 27%.

from 2,4-dimethyl-[1,8]-naphthyridine (**15**) by selective catalytic hydrogenation.

The bromination of **12** at −78 °C proceeded well, but care had to be taken that over-bromination, presumably on the benzylic positions, did not take place. After the reaction, product **13** was precipitated by adding aqueous KOH and $Na_2S_2O_3$. The methyl derivative **14** was obtained under the usual Eschweiler−Clark conditions. The bromide was converted to the corresponding pyridinol by the standard hydroxylation method to obtain **2** in 25% isolated yield.

(c) Pyridinols with an Annulated Five-Membered Ring. Bicyclic pyridinols with an annulated five-membered ring (i.e. with a dihydropyrrolopyridine system) represented the synthetically most challenging class of pyridinol reported here. Simple dihydropyrrolopyridine structures have been prepared from chloride precursors,[22] by radical cyclizations[23] or by sluggish hydrogenations of aza-indoles.[24] All of these reactions required precursors that were not readily available with the desired substitution pattern of the pyridinol product. After some unsuccessful attempts with intramolecular Friedel−Crafts chemistry, a sequence with Van der Plas's reaction as the key step was selected.[25] This reaction consists of an intramolecular inverse electron demand Diels−Alder reaction between an alkyne and pyrimidine ring followed by a cycloreversion (vide infra). The whole sequence is depicted in Scheme 5.

Compound **18** is a known compound, but the literature procedures are lengthy[26,27] or give very low yields when repeated.[28] The alternative synthesis shown in Scheme 5 was very easy to scale up and provided crystalline **18**. 5-Hexynoic acid was treated with concentrated aqueous base, which isomerized the triple bond to give acid **16**.[29] This compound was mixed with diphenylphosphoryl azide in refluxing *t*-BuOH, which induced a one-pot acid azidation, Curtius rearrangement, and alcoholysis.[30] The crude Boc-protected amine **17** was deprotected with 1.0 M ethereal HCl and salt **18** was isolated in good yield simply by filtration.

Coupling of this salt with triflate **25**, prepared from 4,6-dimethyl-2-pyrimidinol and triflic anhydride,[31] was achieved by a nucleophilic aromatic substitution in distilled DMF and in the presence of excess Et_3N to afford amine **19**. The two methyls on the pyrimidine ring reduced the coupling rate considerably compared to nonsubstituted pyrimidines[27] and it was for this reason that the triflate proved superior over other activating groups such as chloride[27] and tosylate. Acetylation of **19** was accomplished by heating in acetic anhydride in the presence of DMAP, giving acetamide **20**. The next step was the Van der Plas reaction.[27] After 3 d of reflux in nitrobenzene (210 °C), a common solvent for this reaction, **21** was formed with good conversion. It was found, however, that the reaction proceeded significantly faster and cleaner in refluxing diphenyl ether (250 °C), allowing an easy workup consisting of an acid/base extraction to give light-colored recrystallized product **21** in 82% yield. The presence of two methyl groups on the pyrimidine ring, even though one is eliminated as MeCN, avoids a potential selectivity issue in the cycloreversion step. Subsequently, acetamide **21** was subjected to basic methanolysis which cleaved the acetamide group. The rest of the synthesis was performed by a sequence similar to that of the annulated six-membered analogue **2**. Thus, **22** was brominated to give **23**, which was then converted into the methylated compound **24** by an Eschweiler−Clark methylation. The bromide **24** was hydroxylated to give **3** in 27% isolated yield after column chromatography.

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TABLE 1. Some Relevant Properties of Pyridinols 1a–d, 2, and 3

compd	half-life (h)[a]	mp (°C)	pK_a [c]	k_{inh} ($M^{-1}s^{-1}$)[d]	k_{inh}/k_{inh}(α-TOH)
1a	≫24[b]	102	5.45	$(5.8 \pm 2.3) \times 10^3$	0.0018
1b	≫24[b]	129	5.95	$(2.2 \pm 0.3) \times 10^4$	0.0069
1c	≫24[b]	77	6.75	$(2.9 \pm 0.4) \times 10^5$	0.091
1d	≫24[b]	132	6.97	$(1.6 \pm 0.6) \times 10^7$	5
2	30	126 (dec)	>7.0	$(8.8 \pm 3.2) \times 10^7$	28
3	14	115 (dec)	>7.0	$(2.8 \pm 1.8) \times 10^8$	88
α-TOH	≫24[b]	n/a	n/a	3.2×10^6 [e]	1

[a] Estimated from decay of UV absorbance at λ_{max} in aerated *tert*-butylbenzene (ca. 0.3 mM) at 37 °C. Values taken from ref 9. [b] No significant change in UV signal observed in 24 h. [c] The pK_a value for the protonated form of the pyridinol (see Supporting Information). [d] Obtained from autoxidations of styrene in chlorobenzene at 303 K. [e] Value for α-TOH taken from ref 3a.

Some Relevant Properties. Since the stability of electron-rich phenols upon exposure to air has been a major hurdle in the successful design of novel phenolic antioxidants with enhanced activities relative to α-tocopherol, we first sought to examine the stabilities of our newly synthesized pyridinols in organic solutions. For this purpose, we simply monitored the absorbance of the intact (i.e., non-oxidized) chromophore as a function of time in aerated *tert*-butylbenzene. The results are presented in Table 1.

The introduction of a basic nitrogen atom in the aromatic ring of phenolic compounds can potentially create a problem for their efficacy as antioxidants in protic solvents should the basic pyridine nitrogen (or the *p*-amine substituent in the case of **1d**, **2**, and **3**) be protonated to a significant extent at equilibrium. The basicity of these compounds is also relevant to issues associated with the isolation and purification of those pyridinols presented here. The pyridinium ion itself has a pK_a of 5.25 but it was expected that the electron-donating substituents in the target pyridinols may raise this value substantially. Titrations of the dibasic phenolate salts of **1a–3** with dilute HCl in MeOH/H_2O (1/3) were therefore performed to provide some insight into their acid/base equilibria. These results are also collected in Table 1 with additional details available as Supporting Information.

Last, the rate of the reaction between the pyridinol and a peroxyl radical is of definitive importance for the overall antioxidant activity. We found that standard methyl linoleate autoxidations[32] are greatly inhibited in the presence of compounds **1d**, **2**, and **3**. Styrene autoxidations[3a] inhibited by **1a–d**, **2**, and **3** were well-behaved and provided inhibition rate data (k_{inh}) for each of the six compounds.[33] The stoichiometric factor *n* (number of peroxyl radicals trapped by each molecule of antioxidant) was determined to be 2 for all of the compounds, similar to phenols and pyrimidinols. These data are collected in Table 1.

Inspection of the table shows clear and consistent trends. In the subseries **1d**, **2**, and **3**, the half-life in aerated solution decreases. For bicyclic members **2** and **3**, heating results in decomposition indicated by the formation of dark brown material. Both trends are indicative of the anticipated decrease in aerobic stability upon increasing the electron-density in the aromatic ring. In an analogous manner, basicity increases as electron-donating substituents are incorporated. Titrations for **2** and **3** yielded somewhat distorted plots, probably due to decomposition of the very electron-rich pyridinoxide anions. Yet, it was evident from the curves that the pK_a values for the protonated forms of these compounds were higher than 7.0 (7.0–7.2) and were thus approaching physiological pH values. The anticipated substituent effect was also markedly clear from the k_{inh} values. An increase of as many as 4.5 orders of magnitude was observed between the values of **1a** and **3**.

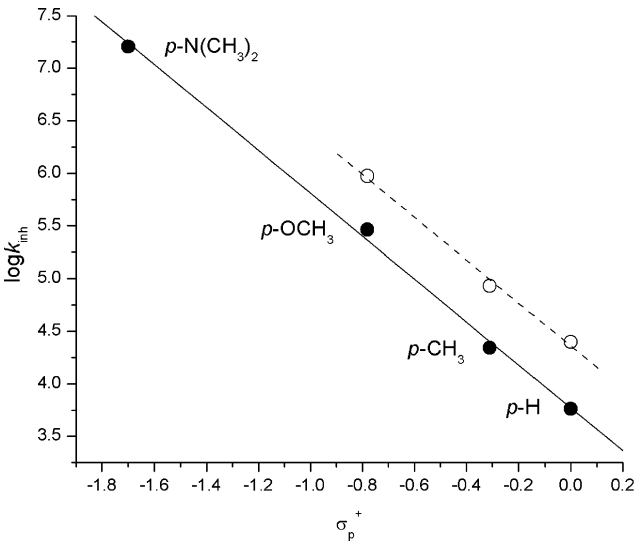

FIGURE 1. Inhibition rate constants plotted as a function of the σ_p^+ constant of the substituent para to the hydroxyl group in 2,4-dimethyl-3-pyridinols (closed symbols, solid line) and 2,6-dimethylphenols (open symbols, dashed line).

The bond dissociation enthalpy (BDE) of the phenolic O–H bond plays a central role[34,35] in determining antioxidant efficacy, compounds having lower BDEs generally being better antioxidants. The introduction of electron-donating groups at the para position relative to the phenolic OH leads to compounds with lower BDEs. This effect is obviously a factor that controls the reactivity of the pyridinols studied here. It is difficult to obtain BDEs for **1a–c** by the radical equilibration electron paramagnetic resonance (REqEPR) technique as we have done[9] for **1d**, **2**, and **3** due to the asymmetry and relatively low persistence of their corresponding 3-pyridinoxyl radicals. It is well-known, however, that phenolic O–H BDEs correlate very well with σ_p^+ substituent constants,[36] and as such, k_{inh} for **1a–d** should also correlate well with these substituent constants if the O–H BDE is indeed a factor that controls the reactivity of the pyridinols studied here. A plot of log k_{inh} for **1a–d** as a function of σ_p^+ of

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the 6-substituent, as shown in Figure 1 (closed symbols and solid line), yields a straight line that is essentially parallel to that for the equivalently substituted phenols (open symbols and dashed line).[3a] The lower *y*-intercept for the 3-pyridinols is expected on the basis of our theoretical calculations, which indicate that the O−H BDEs in pyridinols are roughly 1−1.5 kcal/mol higher than those of equivalently substituted phenols.[8a,9] The parallel lines confirm that substituent effects on the O−H BDEs of 3-pyridinols are essentially equivalent to those on phenols as was predicted by our theoretical calculations.[8a,9]

Summary

A series of 6-substituted-2,4-dimethyl-3-pyridinols was synthesized by using a common general strategy. The introduction of the reactive hydroxyl group in the final step allowed for easy scale-up and storage of all intermediates up to the stable penultimate pyridyl bromides. The hydroxylation step was a relatively low-yielding step, but it proved reproducible and generally applicable. Thus, a general route to this interesting class of compounds has been established. The stabilities of the pyridinols toward air oxidation are in qualitative agreement with their previously calculated ionization potentials. The basicity of the pyridinols increased as the electron density in the ring increased and it approached physiological pH values for the bicyclic compounds **2** and **3**. The rate constants for inhibition of styrene autoxidations were determined for all of the pyridinols and the more electron-rich compounds proved to be the best antioxidants. The rate constants correlate with σ_p^+ for the pyridinol series **1a**−**d**, a result that is fully consistent with that observed for the analogous phenols.

Experimental Section

2-Amino-5-bromo-4,6-dimethylpyridine (4). The title compound was prepared according to the literature[16] (with 0.5 equiv of 1,3-dibromo-5,5-dimethylhydantoin) in lower yield but higher purity, typically 67% yield after recrystallization from EtOAc: mp 136 °C (lit.[16] mp 108−110 °C). The literature yield and purity are very likely incorrect since 92% of pure **4** was reported after recrystallization while there was a reported 1:10 ratio of regioisomers in the crude mixture.

5-Bromo-4,6-dimethyl-2-(dimethylamino)pyridine (5). Bromide **4** (1.2 g, 5.94 mmol) was heated at reflux overnight in a mixture of formic acid (20 mL) and 37% formaline (20 mL). The reaction mixture was cooled and most volatiles were removed under reduced pressure. The residue was shaken with a mixture of 1.0 M aq NaOH and CH_2Cl_2 (2×). The organic layers were collected, dried ($MgSO_4$), and filtered. The filtrate was concentrated and purified by column chromatography (3:1 hexanes:EtOAc) to afford a yellowish low-metling solid product (1.06 g, 78%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.21 (s, 1H, Ar-H), 3.02 (s, 6H, N-Me), 2.53 (s, 3H, 6-Me), 2.29 (s, 3H, 4-Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.9, 155.1, 147.9, 110.6, 105.6, 38.4, 26.0, 24.11; HRMS (FAB) for $C_9H_{13}BrN_2$ [M − H] 227.0184, found 227.0174.

2,4-Dimethyl-6-(dimethylamino)-3-hydroxypyridine (1d). Bromide **5** (890 mg, 3.86 mmol) was dissolved in THF (10 mL) and the solution was cooled to −78 °C. To this was added *n*-BuLi (2.5 M in hexanes, 3.5 mL, 8.8 mmol) and the yellow reaction mixture was stirred at −78 °C for 15−30 min (the Br/Li exchange was monitored by TLC and was quantitative). Then dry 2,6-dimethylnitrobenzene (2.6 mL, 19.80 mmol) was added, resulting in the solution turning brown. After being stirred for 2 h at −78 °C, the reaction mixture was warmed to room temperature and quenched with saturated aq Na_2CO_3. This mixture was extracted with ether (3×) to remove **6** and 2,6-dimethylnitrobenzene. The aqueous phase was cooled in an ice bath and carefully neutralized by adding concentrated HCl dropwise. The yellow mixture was extracted with EtOAc (3×). The organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a yellow solid product (400 mg, 63%) that was a single highly fluorescent spot by TLC. NMR revealed that the product was ≥95% pure. The product could be recrystallized by dissolving it quickly in a minimum amount of hot ether/hexanes (1/1), cooling, storing at −30 °C, filtering, washing, and drying. This protocol yielded yellow crystals which were stable under argon in the freezer for over a year. Mp 132 °C; λ_{max} (MeOH) 328 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.19 (br s, 1H, Ar-H), 4.75 (br s, OH), 2.96 (br s, 6H, N-Me), 2.29 (br s, 3H, 6-Me), 2.16 (br s, 3H, 4-Me); ^{1}H NMR ($CDCl_3$ + drop of D_2O, 300 MHz) same shifts as without D_2O, but sharp signals and no −OH signal; ^{13}C NMR ($CDCl_3$ + drop of D_2O, 75 MHz) δ 154.8, 143.0, 141.1, 136.5, 106.3, 39.3, 19.3, 16.8; 2D NOESY-NMR ($CDCl_3$ + drop of D_2O, 400 MHz) couplings Ar-H × N-Me, Ar-H × 4-Me; IR (film) ν (cm^{-1}) 3400, 3000, 2920, 1610, 1480, 1420, 1402, 1260; HRMS (FAB) for $C_9H_{14}N_2O$ [M] 166.1106, found 116.1108. Anal. Calcd for $C_9H_{14}N_2O$: C 65.03, H 8.49, N 16.85. Found: C 64.82, H 8.71, N 16.59.

5-Bromo-4,6-dimethylpyridin-2(1*H*)-one (7). Amine **4** (6.00 g, 29.8 mmol) was mixed with a 50% aqueous solution of hypophosphorous acid (25 mL, 241 mmol) and water (55 mL). The mixture was cooled to about 2 °C and a solution of sodium nitrite (2.40 g, 34.8 mmol) in water (12 mL) was added with vigorous stirring keeping the temperature below 5 °C. The mixture was stirred for 30 min at a lower temperature and then for an additional 12 h at room temperature. The mixture was neutralized to pH 6−7 and kept at 5 °C for 6 h. The resulting precipitate was filtered and washed with water. After drying under high vacuum, a white solid was obtained (5.25 g, 87%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.32 (s, 1H, Ar-H), 2.45 (s, 3H, 6-Me), 2.27 (s, 3H, 4-Me); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 161.6, 151.0, 144.5, 116.3, 102.2, 23.0, 20.2; mp 255−257 °C (lit.[37] mp 257−259 °C).

3-Bromo-6-methoxy-2,4-dimethylpyridine (8). Silver carbonate (9.55 g, 34.7 mmol) and iodomethane (16.5 mL, 266 mmol) were added to bromide **7** (5.20 g, 25.3 mmol) dissolved in CH_2Cl_2 (260 mL) with protection from light. The reaction mixture was stirred until all starting material was consumed (overnight) and the inorganic solids were removed by filtration and washed with CH_2Cl_2 (3 × 40 mL). The filtrate was concentrated in vacuo to yield a rust colored oil (5.02 g, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.43 (s, 1H, Ar-H), 3.85 (s, 3H, O-Me), 2.54 (s, 3H, 2-Me), 2.30 (s, 3H, 4-Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.0, 154.4, 149.5, 115.3, 109.4, 53.42, 25.20, 23.28; HRMS for $C_8H_{10}NOBr$ [M + Na] 237.9838, found 237.9840.

2,4-Dimethyl-6-methoxynicotinaldehyde (9). Bromide **8** (4.00 g, 18.4 mmol) was dissolved in THF (53 mL) and the solution was cooled to −78 °C. To this was added *n*-BuLi (2.5 M in hexanes, 7.8 mL, 19.4 mmol) and the reaction mixture was stirred at −78 °C for 1 h (the Br/Li exchange was monitored by TLC and was quantitative). Then dry DMF (2.8 mL, 36.1 mmol) was added and stirring was continued at −78 °C for 30 min. The cold mixture was poured into a stirred aqueous solution of sodium bicarbonate (5% $NaHCO_3$). The mixture was extracted with ether (3×) and the combined organic extracts were washed with brine (3×) and dried over K_2CO_3. Rotary evaporation yielded a white solid (2.92 g, 89%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.42 (s, 1H, aldehyde), 6.37 (s, 1H, Ar-H), 3.91 (s, 3H, O-Me), 2.69 (s, 3H, 2-Me), 2.50 (s, 3H, 4-Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.4, 165.5, 162.5, 153.1, 123.3, 111.1, 54.07, 23.38, 21.17; HRMS for $C_9H_{11}NO_2$ [M + H] 166.0862, found 166.0856; mp 80.5−81 °C.

6-Methoxy-2,4-dimethylpyridin-3-ol (1c). A solution of *m*-CPBA (0.61 g, 3.50 mmol) and *p*-toluenesulfonic acid (9 mg, 0.05 mmol) in chloroform (3.5 mL) was slowly added to a

solution of nicotinaldehyde **9** (0.49 g, 2.97 mmol) in chloroform (3.5 mL). After being stirred for 24 h at room temperature the solution was treated with aqueous NaOH (1M) until a pH of 8.5 was reached. The mixture was extracted with chloroform (3×) and the organic layer was dried over Na_2SO_4 and concentrated to yield a yellow oil (0.23 g, 43%). This crude product was dissolved in a solution of KOH (0.26 g, 4.62 mmol) in methanol (5 mL). The solution was heated at reflux for 2 h. The solvent was then evaporated. The resulting solids were dissolved by addition of water and ether. The aqueous layer was washed with additional ether and then brought to pH 8.5 with aqueous hydrochloric acid (1 M). The formed precipitate was extracted with EtOAc (3×). The ethyl acetate extracts ware combined, dried over $MgSO_4$, and concentrated to yield a pale orange solid (0.15 g, 33% over both steps). Mp 77−79 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.36 (s, 1H, Ar-H), 4.4 (br s, OH), 3.82 (s, 3H, O-Me), 2.36 (s, 3H, 2-Me), 2.19 (s, 3H, 4-Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.9, 144.1, 141.3, 137.6, 108.9, 53.95, 18.95, 16.52; HRMS for $C_8H_{11}NO_2$ [M + H] 154.0862, found 154.0865.

3-(4,6-Dimethylpyridin-2-ylamino)propanoic Acid (10). 2-Amino-4,6-lutidine (8.5 g, 70 mmol) and acrylic acid (6 g, 84 mmol) were heated at reflux in pyridine (60 mL) overnight. The mixture was concentrated and dried thoroughly (to remove traces of pyridine and acrylic acid). The following protocol gave good quality product albeit in low yield: the residue was dissolved in water containing NaOH (3.1 g, 77 mmol) and filtered through Celite. The filtrate was cooled in an ice bath and slowly acidified with concentrated H_2SO_4. Around pH 3−4 a precipitate formed, which was filtered and washed with water and acetone affording an off-white solid (4 g, 30%) sufficiently pure for further reactions. An analytical sample was obtained by recrystallization from water and then from *i*-PrOH followed by extensive drying. The product (as an *i*-PrOH-solvate) was obtained as white crystals. Mp 84 °C; ^{1}H NMR (d_3-MeOD, 300 MHz) δ 6.87 (s, 1H, Ar-H), 6.77 (s, 1H, Ar-H), 3.86 (t, 2H, NCH_2, J = 5.0 Hz), 2.82 (t, 2H, CH_2CO, J = 5.0 Hz), 2.72 (s, 3H, 6-Me), 2.41 (s, 3H, 4-Me); ^{13}C NMR (d_3-MeOD, 75 MHz) δ 180.9, 157.7, 156.6, 150.1, 115.4, 109.0, 41.3, 38.5, 22.6, 20.2; HRMS for $C_{10}H_{14}N_2O_2$ [M + H] 195.1128, found 195.1118.

5,7-Dimethyl-2,3-dihydro-1*H*-[1,8]naphthyridin-4-one (11). Polyphosphoric acid (25 g) was added to amino acid **10** (3.1 g, 16 mmol). The mixture was heated to 125 °C for 40 min. The mixture was cooled, and the PPA was slowly decomposed by addition of ice and solid NaOH (exothermic!!). Subsequently, the basic suspension was stored at 0 °C for several hours and the precipitate was filtered, washed with water, and dried. This afforded the ring-closed product as an orange powder (2.1 g, 75%). An analytical sample was obtained by column chromatography (5% MeOH in CH_2Cl_2) to yield a yellow solid. Mp 142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.24 (s, 1H, Ar-H), 6.21 (br s, 1H, NH), 3.50 (t, 2H, NCH_2, J = 6.5 Hz), 2.61 (t, 2H, CH_2CO, J = 5.0 Hz), 2.49 (s, 3H, 6-Me), 2.27 (s, 3H, 4-Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.0, 162.6, 162.2, 152.8, 117.6, 110.3, 39.7, 39.0, 24.6, 22.6; HRMS for $C_{10}H_{12}N_2O$-[M + H] 177.1022, found 177.1013.

5,7-Dimethyl-1,2,3,4-tetrahydro[1,8]naphthyridine (12). Ketone **11** (2.1 g, 11.9 mmol) was dissolved in THF (10 mL). To this BH_3·THF (1.0 M in THF, 32 mL, 32.0 mmol) was added slowly. The reaction mixture was heated at reflux overnight. After cooling, concentrated HCl was added to decompose the amine−borane complexes. After the solution was stirred for 10 min at room temperature, an aq 15 M KOH solution was added until basic pH was reached. The THF was removed under reduced pressure and the residue was cooled in ice. The solid was filtered, washed with water, and dried. The product was obtained as a yellow solid (1.6 g, 83%). An analytical sample was obtained by recrystallization from hexanes to give white needles. Mp 114 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.25 (s, 1H, Ar-H), 5.02 (br s, 1H, NH), 3.35 (m, 2H, NCH_2), 2.58 (t, 2H, Ar-CH_2, J = 6.4 Hz), 2.27 (s, 3H, 6-Me), 2.09 (s, 3H, 4-Me), 1.94 (p, 2H, CH_2, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 153.8, 146.0, 114.7, 111.7, 41.7, 24.0, 23.5, 22.3, 18.8; 2D NOESY-NMR ($CDCl_3$, 400 MHz) couplings Ar-H × 4-Me, Ar-H × 6-Me, Ar-CH_2 × 4-Me, Ar-CH_2 × CH_2CH_2; HRMS for $C_{10}H_{14}N_2$ [M + H] 163.1230, found 163.1224. Anal. Calcd for $C_{10}H_{14}N_2$: C 74.03, H 8.70, N 17.27. Found: C 73.94, H 8.71, N 17.20. NMR data have been reported.[38] **Alternative procedure:** 2,4-Dimethyl[1,8]naphthyridine **15**[39] (6.8 g, 43.0 mmol) and 10% Pd/C (0.5 g) were stirred in EtOH (70 mL) overnight under H_2 atmosphere. The catalyst was removed by filtration over Celite and the solvent removed by concentration giving an off-white solid (6.96 g, 42.9 mmol) in near quantitative yield. The product was recrystallized from hexanes to afford 5.2 g of yellow needles (74%).

6-Bromo-5,7-dimethyl-1,2,3,4-tetrahydro[1,8]naphthyridine (13). Amine **12** (1.6 g, 9.8 mmol) was dissolved in CH_2Cl_2 (30 mL). The solution was cooled to −78 °C and 1,3-dibromo-5,5-dimethylhydantoin (1.54 g, 5.4 mmol) was added portionwise. To avoid over-bromination of the electron-rich starting material, the following protocol worked best: the dry ice/acetone bath was removed for the duration of 1−1.5 min after which the reaction mixture was recooled to −78 °C and checked by TLC. Usually, after a few of these cycles, clean and full conversion was achieved. The cooling bath was removed, saturated aq $Na_2S_2O_3$ (10 mL) was immediately added, and the contents of the flask was swirled thoroughly to destroy the remaining 1,3-dibromo-5,5-dimethylhydantoin. After the solution was warmed to room temperature while stirring, water and excess solid KOH were added. The CH_2Cl_2 was removed under reduced pressure and the basic suspension was filtered. The precipitate was washed with water and dried. This gave the product as a yellow solid (2.2 g, 93%). An analytical sample was obtained by recrystallization from MeOH/water to give yellow needles (according to NMR, the crystals retained 4.7% MeOH in the lattice even after extensive drying). Mp 146 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.95 (br s, 1H, NH), 3.32 (m, 2H, NCH_2), 2.65 (t, 2H, Ar-CH_2, J = 7.6 Hz), 2.44 (s, 3H, 6-Me), 2.24 (s, 3H, 4-Me), 1.91 (p, 2H, CH_2, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.6, 152.7, 145.2, 113.7, 111.9, 41.4, 25.7, 25.0, 22.1, 19.3; HRMS for $C_{10}H_{13}BrN_2$ [M + H] 241.0335, found 241.0340.

6-Bromo-1,5,7-trimethyl-1,2,3,4-tetrahydro[1,8]naphthyridine (14). Bromide **13** (1.1 g, 4.56 mmol) was heated at reflux overnight in a mixture of formic acid (10 mL) and 37% formaline (10 mL). The reaction mixture was cooled and most volatiles were removed by evaporation. Enough aq 15 M KOH was added to make the solution basic and the suspension was then cooled in an ice bath. The precipitate was filtered, washed with water, and dried to give the product as a brown solid (0.9 g, 77%) of satisfactory purity. An analytical sample was prepared by running the solid though a plug of silica gel with 3:1 hexanes:EtOAc as the eluent. This gave white needles. Mp 75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.24 (t, 2H, NCH_2, J = 5.5 Hz), 3.06 (s, 3H, N-Me), 2.66 (t, 2H, Ar-CH_2, J = 6.5 Hz), 2.46 (s, 3H, 6-Me), 2.22 (s, 3H, 4-Me), 1.95 (p, 2H, CH_2, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.0, 152.3, 143.8, 114.9, 111.4, 50.0, 37.2, 26.2, 25.9, 22.2, 19.5; HRMS for $C_{11}H_{15}BrN_2$ [M + H] 255.0491, found 255.0491.

2,4,8-Trimethyl-5,6,7,8-tetrahydro[1,8]naphthyridin-3-ol (2). Bromide **14** (800 mg, 3.13 mmol) was dissolved in THF (20 mL) and the solution was cooled to −78 °C. Then *n*-BuLi (2.5 M in hexanes, 2.88 mL, 7.2 mmol) was added and the yellow reaction mixture was stirred at −78 °C for 15−30 min (the Br/Li exchange was monitored by TLC and was quantitative). Dry 2,6-dimethylnitrobenzene (2.1 mL, 15.4 mmol) was then added, resulting in a brown mixture. After being stirred

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for 2 h at −78 °C, the reaction mixture was warmed and quenched with saturated aq NH_4Cl. The THF layer was separated and the aqueous layer extracted once with EtOAc. The organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (1:1 hexanes:EtOAc) to afford a yellow solid (150 mg, 25%) of sufficient purity for further experiments. λ_{max} (MeOH) 331 nm; mp 126−132 °C dec; ^{1}H NMR ($CDCl_3$ + drop of D_2O, 300 MHz) δ 3.19 (br s, 2H, NCH_2), 3.03 (br s, 3H, N-Me), 2.62 (br s, 2H, Ar-CH_2), 2.33 (br s, 3H, 6-Me), 2.06 (br s, 3H, 4-Me), 1.96 (s, 2H, CH_2); after standing overnight in $CDCl_3$ and D_2O under argon, the peaks sharpened; ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 3.19 (t, 2H, NCH_2, J = 5.6 Hz), 3.03 (s, 3H, N-Me), 2.62 (t, 2H, Ar-CH_2, J = 6.6 Hz), 2.33 (s, 3H, 6-Me), 2.06 (s, 3H, 4-Me), 1.96 (p, 2H, CH_2, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$ + D_2O, 75 MHz) δ 151.3, 140.1, 138.5, 132.4, 114.6, 50.1, 37.4, 24.9, 22.1, 18.9, 11.5; HRMS for $C_{11}H_{16}N_2O$ [M + H] 193.1335, found 193.1345. The material was recrystallized from hot hexanes to give a light brown solid, although the following elemental analysis of this material actually suggested that the purity was diminished after this. Anal. Calcd for $C_{11}H_{16}N_2O$: C 68.72, H 8.39, N 14.57. Found: C 67.78, H 8.41, N 13.92.

Hex-4-ynoic Acid (16). This compound was prepared according to the literature from hex-5-ynoic acid, mp 100 °C. NMR data have been reported.[40]

***tert*-Butyl Pent-3-ynylcarbamate (17).** Acid **16** (7.7 g, 6.9 mmol) was dissolved in *t*-BuOH (100 mL). Diphenylphosphoryl azide (16.3 mL, 7.6 mmol) and Et_3N (9.57 mL, 6.9 mmol) were added and the reaction mixture was heated at reflux for 30 h. The solvent was evaporated and the residue dissolved in EtOAc. This solution was extracted with 1 N aq HCl, water, saturated aq $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. This afforded 9.97 g (79%) of a crude yellow oil that was sufficiently pure for the next step. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.82 (br s, 1H, NH), 3.20 (m, 2H, NCH_2), 2.30 (m, 2H, C≡CCH_2), 1.76 (t, 3H, C≡CMe, J = 2.5 Hz), 1.45 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8, 79.3, 77.2, 76.3, 39.7, 28.4, 20.2, 3.5. HRMS for $C_{10}H_{17}NO_2$ [M + Na] 206.1151, found 206.1154.

Pent-3-ynylamine Hydrochloride (18). Crude BOC-protected amine **17** (16.34 g, 8.9 mmol) was dissolved in ethereal 2 M HCl (50 mL). The solution was stirred for 24 h, during which a precipitate was formed. The crystals were filtered off, washed with ether, and dried. This afforded the ammonium salt (7.46 g, 70%) as white crystals. ^{1}H NMR (D_2O, 300 MHz) δ 3.07 (t, 2H, NCH_2, J = 6.5 Hz), 2.51 (m, 2H, CH_2≡C), 1.73 (t, 3H, Me, J = 2.1 Hz); ^{13}C NMR (D_2O, 75 MHz) δ 80.8, 74.1, 38.9, 17.3, 2.8. NMR data were in agreement with a literature report.[26]

4,6-Dimethylpyrimidin-2-yl Trifluoromethanesulfonate (25). This compound was prepared according to the literature procedure[31] from 4,6-dimethylpyrimidin-2-ol. It was obtained as a brown oil that was >95% pure. NMR data have been reported.[31]

4,6-Dimethyl-2-(1-pent-3-ynylamino)pyrimidine (19). Triflate **25** (19.18 g, 74.9 mmol), hydrochloride **18** (7.46 g, 62.4 mmol), and Et_3N (34.7 mL, 250 mmol) were stirred in freshly distilled DMF (150 mL) at room temperature for 1 d. Water was added to decompose the remaining triflate and the mixture was extracted with ether (3×) and water. To the organic layers were added $MgSO_4$ and activated charcoal and the mixture was stirred for 10 min. After filtration, the filtrate was concentrated and dried under high vacuum to afford a light brown solid of good purity (10.98 g, 93%). The product was recrystallized from water/acetone to afford white crystals (6.78 g, 57%). Mp 64 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (s, 1H, ArH), 5.35 (br s, 1H, NH), 3.58 (q, 2H, NCH_2, J = 6.5 Hz), 2.42 (m, 2H, CH_2C≡C), 2.27 (s, 6H, Ar-CH_3), 1.77 (t, 3H, C≡CCH_3, J = 2.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.8, 162.5, 110.2, 77.6, 77.2, 40.9, 24.3, 20.1, 3.9; HRMS for $C_{11}H_{15}N_3$ [M + Na] 212.1158, found 212.1177. Anal. Calcd for $C_{11}H_{15}N_3$: C 69.81, H 7.99, N 22.20. Found: C 69.92, H 8.10, N 22.38.

2-[*N*-Acetyl-*N*-(1-pent-3-ynyl)amino]-4,6-dimethylpyrimidine (20). Amine **19** (3.0 g, 15.87 mmol) and DMAP (387 mg, 3.2 mmol) were heated overnight in Ac_2O (30 mL) at ca. 100 °C. The reaction mixture was cooled and the solvent was removed in vacuo. The residue was dissolved in EtOAc and washed with saturated aq $NaHCO_3$ solution and brine to remove the bulk of DMAP. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and dried under high vacuum to yield a brown-orange solid (3.33 g, 91%) of sufficient purity for further experiments. An analytical sample was obtained by column chromatography (2:1 hexanes:EtOAc) followed by recrystallization from hexanes to afford white crystals. Mp 63 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.78 (s, 1H, ArH), 4.12 (t, 2H, NCH_2, J = 7.6 Hz), 2.44 (m, 2H, CH_2C≡C), 2.42 (s, 6H, Ar-CH_3), 2.31 (s, 3H, $COCH_3$), 1.65 (t, 3H, C≡CCH_3, J = 2.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 168.5, 161.5, 116.7, 77.6, 77.2, 46.3, 25.9, 24.6, 19.3, 4.1; HRMS for $C_{13}H_{17}N_3O$ [M + Na] 254.1264, found 254.1274. Anal. Calcd for $C_{13}H_{17}N_3O$: C 67.51, H 7.41, N 18.17. Found: C 67.13, H 7.35, N 18.06.

1-Acetyl-4,6-dimethyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (21). Acetamide **20** (4.0 g, 17.3 mmol) was heated at reflux in diphenyl ether (50 mL) for 10 h. The solution was cooled and ether (25 mL) was added. The resulting solution was extracted with aq 1 M HCl (3 × 25 mL). The aqueous layers were combined and carefully neutralized with solid $NaHCO_3$ until the pH was slightly basic. The suspension was extracted 3× with CH_2Cl_2. $MgSO_4$ and activated charcoal were added to the combined organic layers and the mixture was stirred for 10 min. After filtration, the filtrate was concentrated under reduced pressure and dried under high vacuum. The residue was recrystallized from hexanes/EtOAc to afford orange crystals (2.69 g, 82%). Mp 105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.53 (s, 1H, Ar-H), 4.07 (t, 2H, NCH_2, J = 8.7 Hz), 2.86 (t, 2H, CH_2, J = 8.7 Hz), 2.65 (s, 3H, COMe), 2.36 (s, 3H, 6-Me), 2.15 (s, 3H, 4-Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 155.7 (two overlapping C), 144.5, 121.7, 118.8, 45.9, 25.1, 24.4, 23.1, 18.6. HRMS for $C_{11}H_{14}N_2O$ [M + H] 191.1179, found 191.1176. Anal. Calcd for $C_{11}H_{14}N_2O$: C 69.45, H 7.42, N 14.73. Found: C 69.43, H 7.45, N 14.80.

4,6-Dimethyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (22). Acetamide **21** (2.69 g, 14.1 mmol) was dissolved in MeOH (100 mL). Solid NaOH (2.27 g, 56.6 mmol) was added and the mixture was heated at reflux overnight. Solid NH_4Cl (3.03 g, 56.5 mmol) was added to neutralize the solution and then MeOH was removed by evaporation. The resulting solids were extracted with CH_2Cl_2 (3×). The combined organic extracts were concentrated in vacuo and dried under high vacuum. The product was obtained as an orange solid in quantitative yield with satisfactory purity. Further purification could be achieved by recrystallization from EtOAc, although the resulting orange crystals retained traces of CH_3COOH. Mp 150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.05 (s, 1H, Ar-H), 4.56 (br s, 1H, NH), 3.54 (t, 2H, NCH_2, J = 8.4 Hz), 2.91 (t, 2H, CH_2, J = 8.3 Hz), 2.28 (s, 3H, 6-Me), 2.09 (s, 3H, 4-Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4, 154.3, 142.4, 117.2, 114.2, 44.2, 26.2, 23.6, 18.2; HRMS for $C_9H_{12}N_2$ [M + H] 149.1073, found 149.1077. Anal. Calcd for $C_9H_{12}N_2$: C 72.94, H 8.16, N 18.90. Found: C 72.37, H 8.13, N 18.81.

5-Bromo-4,6-dimethyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (23). This compound was prepared from amine **22** (0.92 g, 6.2 mmol), CH_2Cl_2 (25 mL), and 1,3-dibromo-5,5-dimethylhydantoin (0.86 g, 3.1 mmol) following the same procedure as for **13**. After being quenched with $Na_2S_2O_3$ and KOH, the mixture was extracted with CH_2Cl_2 (3×). The organic layers were dried ($MgSO_4$), concentrated in vacuo, and dried under high vacuum to yield a yellow solid. This solid consisted of ~90% product and ~10% remaining starting material (by NMR, 83% corrected yield). This compound proved difficult to purify due to its extremely low solubility in any

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solvent. Therefore, it was used in the next step as the 90% pure product. ^{1}H NMR (d_6-DMSO, 300 MHz) δ 4.60 (br s, 1H, NH), 3.61 (t, 2H, NCH_2, J = 6.3 Hz), 2.97 (t, 2H, CH_2, J = 6.3 Hz), 2.42 (s, 3H, 6-Me), 2.19 (s, 3H, 4-Me); ^{13}C NMR (d_6-DMSO, 75 MHz) δ 164.1, 153.0, 141.9 121.4, 111.0, 45.0, 27.7, 26.3, 20.5; HRMS for $C_9H_{11}BrN_2$ [M + H] 227.0178, found 227.0178.

5-Bromo-1,4,6-trimethyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (24). This compound was prepared from bromide **23** (1.8 g, 7.9 mmol) and a mixture of formic acid (40 mL), 37% formaline (40 mL), and *i*-PrOH (40 mL) following the same procedure as for **14**. The crude product was purified by column chromatography (CH_2Cl_2) to afford the product (1.7 g, 84%) as a light-brown solid. Recrystallization from hexanes gave analytically pure product as beige crystals. Mp = 64 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.42 (t, 2H, NCH_2, J = 7.9 Hz), 2.86 (s + t, 5H, NCH_3 + $ArCH_2$), 2.48 (s, 3H, 6-Me), 2.22 (s, 3H, 4-Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.0, 153.5, 141.6, 120.9, 111.8, 53.0, 33.6, 25.7, 19.8; HRMS for $C_{10}H_{13}BrN_2$ [M + H] 241.0334, found 241.0336.

1,4,6-Trimethyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-ol (3). This compound was prepared from bromide **24** (1000 mg, 4.15 mmol), THF (30 mL), *n*-BuLi (2.5 M in hexanes, 3.8 mL, 9.5 mmol), and 2,6-dimethylnitrobenzene (2.26 mL, 16.6 mmol) following the same procedure as for **2**. The crude product was purified by careful column chromatography (5% MeOH in CH_2Cl_2) under N_2 to afford an orange solid (200 mg, 27%) with a purity >96% as judged from NMR. λ_{max} (MeOH) 330 nm; mp 115 °C dec; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (br s, 1H, OH), 3.30 (t, NCH_2-ring, J = 7.1 Hz), 2.80 (s + t, 5H, NCH_3 + $ArCH_2$), 2.17 (s, 3H, 6-Me), 2.03 (s, 3H, 4-Me), D_2O shake removed the signal at 7.26 ppm but did not sharpen signals much; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.1, 142.1, 140.8, 134.0, 121.1, 54.0, 34.8, 25.3, 18.9, 13.2; HRMS for $C_{10}H_{14}N_2O$ [M + H] 179.1179, found 179.1183. Anal. Calcd for $C_{10}H_{14}N_2O$: C 67.39, H 7.92, N 15.72. Found: C 66.46, H 7.81, N 15.28.

Autoxidation Measurements. Autoxidation experiments were performed in a two-channel oxygen uptake apparatus, based on a Validyne DP 15 differential pressure transducer that has already been described elsewere.[41] The entire apparatus was immersed in a thermostated bath that ensured a constant temperature within ±0.1 °C. In a typical experiment, an air-saturated chlorobenzene solution of styrene (4.3−8.6 M) containing the pyridinol (1.1×10^{-6} to 1.0×10^{-4} M) was equilibrated with the reference solution containing only an excess of α-tocopherol (1×10^{-3} to 1×10^{-2} M) in the same solvent at 30 °C. After equilibration, a concentrated chlorobenzene solution of radical initiator 2,2′-azobis(2,4-dimethylvaleronitrile) (AMVN, final concentration $0.5-5 \times 10^{-3}$ M) was injected in both the reference and sample flasks and, following calibration of the apparatus, the oxygen consumption in the sample was measured from the differential pressure recorded with time between the two channels. This instrumental setting allowed us to have the N_2 production and the oxygen consumption derived from the azo-initiator decomposition already subtracted from the measured reaction rates. Initiation rates, R_i, were determined for each condition in preliminary experiments by the inhibitor method with α-tocopherol as reference antioxidant: $R_i = 2[\alpha\text{-tocopherol}]/\tau$. For pyridinols **1c**, **1d**, **2**, and **3** giving a neat inhibition period in oxygen consumption plots, the rate constant for reaction with peroxyl radicals was obtained from the slope of the inhibition period itself, whose length provided instead the stoichiometric factor n.[3a,8] For compounds **1a** and **1b**, the retarded oxygen consumption plots were analyzed according to literature[42] to obtain the value of k_{inh}, using the stoichiometric factor $n = 2$ by analogy with the faster pyridinols. Values for k_{inh} values were averaged over 3 to 12 measurements with different experimental conditions (e.g. concentration of the pyridinol).

Methyl Linoleate Autoxidation. A benzene solution that contained methyl linoleate (0.2 M) and the antioxidant in varying concentrations (0.001−0.1 M) was treated with radical initiator 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (MeO-AMVN, final concentration = 10 mM). The oxidation was run at 37 °C for 4 h and then quenched by addition of BHT. The major oxidation products 9-, 11-, and 13-hydroperoxide were then quantified by normal-phase HPLC (0.5% *i*-PrOH in hexanes) with UV detection (207 and 235 nm). Autoxidations in the presence of **1d** gave about four times less oxidation products than identical oxidations in the presence of α-tocopherol. In the case of reactive pyridinols **2** and **3**, no clear peaks could be detected.

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Supporting Information Available: General experimental methods, procedure for pH titration, and ^{1}H and ^{13}C spectra of final products and selected intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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