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Development of More Potent 4-Dimethylaminopyridine Analogues

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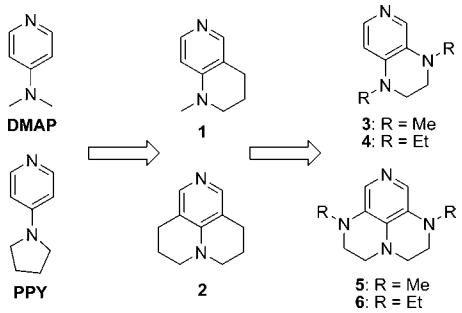
ABSTRACT



The syntheses of bicyclic diaminopyridines 3 and 4 and tricyclic triaminopyridines 5 and 6, two novel series of nucleophilic catalysts, are described. Arguments are made for predicting the superiority of these catalysts over DMAP and even 2, the best esterification catalyst reported to date. The efficiencies of DMAP, PPY, and 2–6 in catalyzing the esterification of tertiary alcohols were compared. As predicted, 5 and 6 were about 6-fold more effective than DMAP and slightly better than 2.

Catalytic amounts of 4-dimethylaminopyridine (DMAP) or 4-pyrrolidinopyridine (PPY) cause enormous rate accelerations in the acylation reactions of amines and, particularly, alcohols with carboxylic acid halides and anhydrides.[1] Such reactivity enhancements are not only confined to acylations but also occur in carbamylation, sulfonylation, phosphorylation, and silylation reactions of alcohols and amines.[2−7] DMAP and PPY are therefore the nucleophilic catalysts of choice for such reactions, especially when an alcohol or amine is less reactive, and their use in syntheses has been the subject of several reviews.[8,9] The increase in reactivity is also occasionally accompanied by improvements in regio- and stereoselectivity as well.[8] Furthermore, in recent years, chiral variants of DMAP have been developed for the successful kinetic resolution of alcohols and amines.[10−15]

The development of the even more potent DMAP/PPY analogues **1** and **2** was reported by Steglich et al.[16] Extending his line of reasoning, we hypothesized and predicted that the two novel series of catalysts, bicyclic diaminopyridines **3** and **4**, and tricyclic triaminopyridines **5** and **6**, should be even more effective. In this paper, we report the development of general protocols for the synthesis of these novel *N*-substituted bicyclic and tricyclic pyridines as well as the

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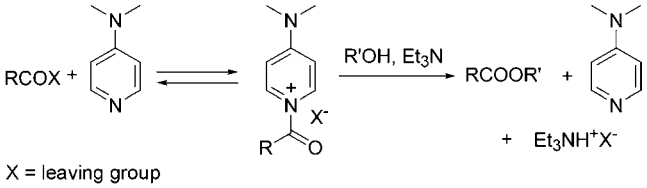
results of comparisons of their efficiencies in the esterification reactions of representative tertiary alcohols with acetic anhydride. We discovered that **5** and **6** were indeed very potent nucleophilic catalysts, being about six times more effective than DMAP and about 10% more effective than **2**, which is the best catalyst reported for the esterification reaction of alcohols.

The simplified, but well-accepted mechanism of esterification of an alcohol using DMAP, is illustrated in Scheme 1 and is believed to involve initial reaction of the acyl donor

Scheme 1. Simplified Mechanism of Catalysis of Esterification of an Alcohol by an Acyl Donor in the Presence of DMAP



(typically an acyl halide or anhydride) with DMAP to form an acylpyridinium halide/acetate ion-pair intermediate. This is followed by attack of the alcohol on this intermediate (usually in the presence of an auxiliary base like triethylamine) to yield the ester and regenerate the DMAP.[17,18] The superiority of DMAP over pyridine has been explained by the strong $+R$ effect of the 4-dimethylamino group,[19] which delocalizes the positive charge on the acylpyridinium intermediate and thus stabilizes the intermediate.[20]

The design of improved catalysts **1** and **2** by Steglich and co-workers was based on the reasoning that the rigid scaffold of **2** would force the 4-N lone pair orbital to remain always parallel to the pyridine ring π-orbitals, the orientation for maximal overlap. This would result in an acylpyridinium intermediate with greater stability than that derived from DMAP because, in the latter, the N lone pair of the NMe_2 group can take up a nonparallel orientation with respect to the pyridine π system due to free rotation around the C−N single bond.[21] Additionally, the two alkyl groups at the meta positions of the pyridine ring would have stabilizing $+I$ effects.[19] The net result of these stabilizing interactions should be a significant increase in the concentration of the reactive intermediate and/or lower activation energy for the reaction, which might in turn lead to greater rate enhancement. Such enhanced stability of the acylpyridinium intermediates originating from **1** and **2** is supported by the results of DFT calculations of the enthalpy change associated with the isodesmic acetyl-transfer reaction shown in eq 1 at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level of theory (Table 1).

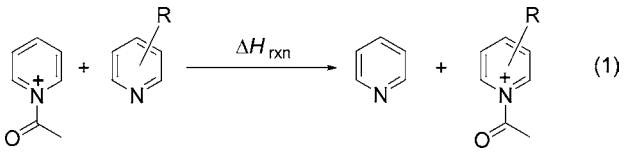


Table 1. Calculated Enthalpies $-\Delta H_{rxn}$ (kcal mol^{-1}) for Acetyl Group Transfer (eq 1)

	DMAP	PPY	**1**	**2**	**3**	**5**
$-\Delta H_{rxn}$	20.0	22.7	22.9	26.0	26.5	30.4

The results show that the acetyl derivatives of **1** and **2** are more stable than those of DMAP by 2.9 and 6 kcal, respectively. This extra stabilization energy results most probably from conformational fixation of the 4-N lone pair orbital parallel to the pyridine π system. Similar theoretical results were obtained for conformationally restricted cyclic N substituents on the stability of benzhydryl cations by Mayr et al.[22]

Based on similar reasoning, we predicted that one or two additional cyclic N-substituents on the meta positions of the pyridine ring, as in **3**−**6**, respectively, would provide an even greater stabilization of the acylpyridinium intermediate because a *m*-dimethylamino substituent [$\sigma_m(NMe_2) = -0.16$] is more electron releasing than an alkyl group [$\sigma_m(Et) = -0.07$], and the six-membered cyclic scaffold would also force the substituent N lone pair orbital to be parallel to the π-orbitals of the pyridine ring.[19] This prediction of enhanced stability was further supported by the results of DFT calculations for the acetyl transfer reactions shown in Table 1.[23] Acetyl transfer to **5** is predicted to be about 4 kcal mol^{-1} more favorable than to **2**, the best reported esterification catalyst until now.

Encouraged by the results of these calculations, we developed syntheses of bicyclic diaminopyridines **3** and **4**, and tricyclic triaminopyridines **5** and **6**.

Scheme 2 illustrates the synthesis of **3** and **4**. Reaction of 3,4-diaminopyridine (**7**) with glyoxal in refluxing aqueous ethanol gave pyrido[3,4-*b*]pyrazine (**8**),[24] which was reduced with sodium borohydride to yield 1,2,3,4-tetrahydro-pyrido-[3,4-*b*]pyrazine (**9**).[25] Use of lithium aluminum hydride in place of sodium borohydride resulted in much lower yields. Selective alkylation of the 3- and 4-NH groups of **9** necessitated the initial protection of the pyridine nitrogen, which was achieved by reaction with trityl chloride. Reaction of the trityl salt **10** with sodium hydride and methyl iodide, or ethyl bromide in anhydrous tetrahydrofuran, resulted in the formation of **11** and **12** respectively. Finally, detritylation

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(18) The role of the auxiliary base is to scavenge the acid generated and prevent it from protonating DMAP.

(19) $\sigma_p(NMe_2) = -0.83$; $\sigma_m(Alkyl) = -0.06$; Hansch, C.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

(20) The acylpyridinium salt derived from DMAP has a higher solubility than the pyridinium salt, and this could also contribute to its greater effectiveness. Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436−5441.

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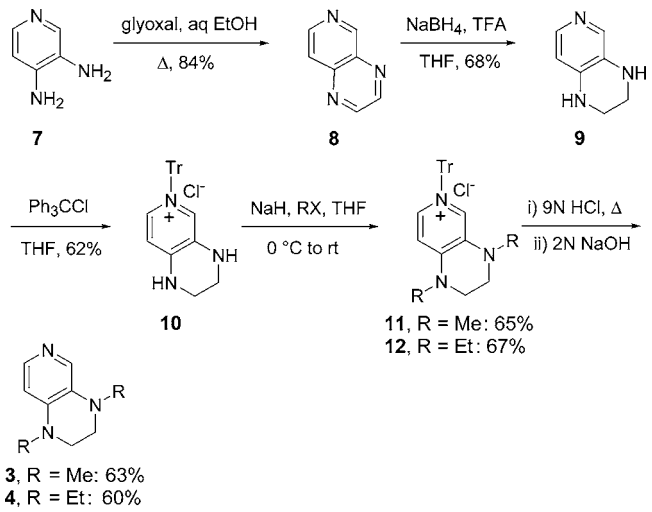
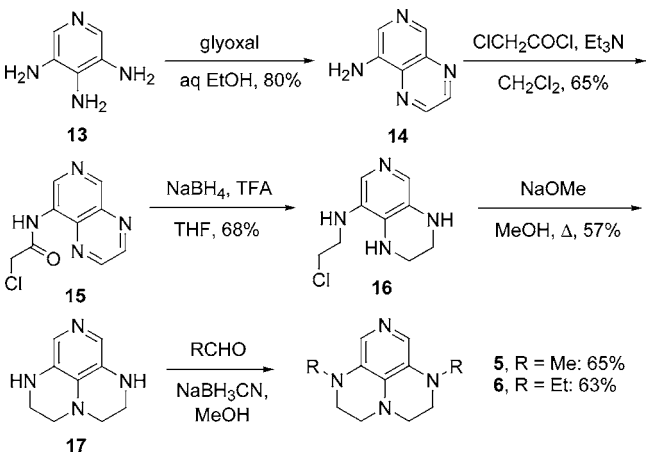
Scheme 2. Synthesis of Bicyclic Diaminopyridines **3** and **4**



Scheme 3. Synthesis of Tricyclic Triaminopyridines **5** and **6**



by hydrolysis of **11** and **12** in aqueous HCl followed by neutralization with aqueous NaOH gave compounds **3** and **4**, respectively.

The synthesis of **5** and **6,** shown in Scheme 3, begins with 3,4,5-triaminopyridine (**13**), which was prepared by a literature procedure.[26] Reaction of **13** with refluxing aqueous ethanolic glyoxal in the presence of sodium hydroxide yielded **14**.[27] Reaction of **14** with chloroacetyl chloride and triethylamine gave the chloroacetyl amide **15**.[28] Reduction of **15** with sodium borohydride in the presence of trifluoroacetic acid gave **16**,[29] which underwent intramolecular *N*-alkylation upon refluxing with sodium methoxide in methanol to yield **17**. Finally, reductive alkylation of **17** with formaldehyde or acetaldehyde and sodium cyanoborohydride in methanol furnished **5** and **6**, respectively.[30]

The effectiveness of DMAP, PPY, and catalysts **2**−**6** was evaluated by following the esterification of 1-ethynylcyclohexanol (1.0 equiv) with acetic anhydride (2.0 equiv) in the presence of triethylamine (3.0 equiv) and each of the catalysts (0.1 equiv) in 5 mL of dichloromethane at 25 °C. The reaction progress was monitored by ^{1}H NMR spectroscopy and the percent conversion of the alcohol to its acetate was plotted as a function of time. The results are summarized in Figure 1.

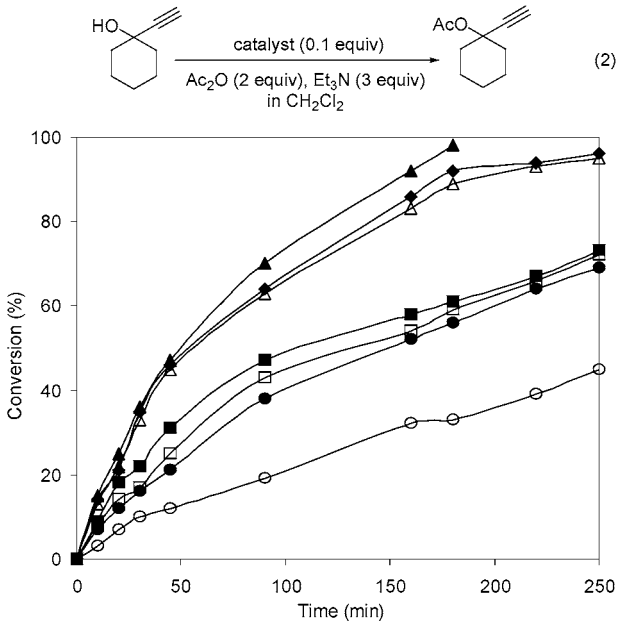


Figure 1. Graph showing the percent conversion of 1-ethynylcyclohexan-1-ol to its acetate by catalysts: DMAP (○), PPY (●), **2** (◆), **3** (□), **4** (■), **5** (△), and **6** (▲) at 25 °C at specified times under the conditions of eq 2.

The graph shows that the bicyclic diaminopyridines **3** and **4** are more effective than DMAP and even slightly more effective than PPY. The tricyclic triaminopyridines **5** and **6** are substantially more effective than DMAP. They are even

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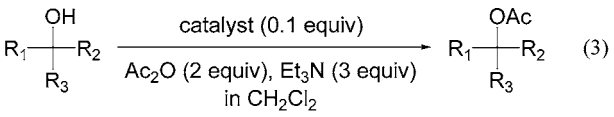
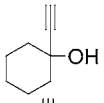
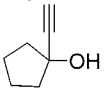
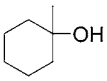
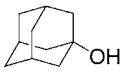
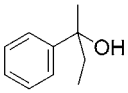
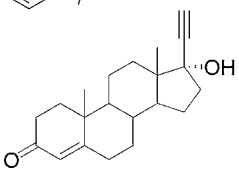
Table 2. Acetylation of Tertiary Alcohols in the Presence of DMAP, **2**, or **6** in CH_2Cl_2 at 25 °C



(3)

alcohol	time (h)	DMAP	2	6
		% conversion to acetate		
	3	33	92	98
	2.8	56	95	98
	3.2	51	96	>99
	5.2	45	95	>99
	6.5	45	94	95
	96	35	89	90

slightly more effective than **2**, which until now was the best catalyst reported for this reaction.[16] In all cases studied, the ethyl derivatives **4** and **6** were slightly better than the methyl analogues **3** and **5**.

In addition, we have also conducted studies to compare the relative effectiveness of our most potent catalyst **6**, DMAP, and **2** in the esterification of other tertiary alcohols (which are difficult to esterify) under identical conditions. The results are summarized in Table 2.

The results demonstrate that catalyst **6** is considerably more effective than DMAP with all of the alcohols studied. For example, in the acetylation of 1-methylcyclohexanol, the reaction is essentially complete in 3 h with **6**, whereas with DMAP it is only 50% complete. In the case of adamantanol, the use of DMAP results in less than 45% conversion and only after 40 h is the reaction nearly complete, while **6** gives 99% conversion in 5 h. Also, in every case we have studied, **6** is consistently better than **2**, although the reactivity difference is marginal.

In conclusion, we have designed and developed syntheses for bicyclic diaminopyridines and tricyclic triaminopyridines, and demonstrated that these compounds are highly potent nucleophilic catalysts for esterification of sterically hindered tertiary alcohols. Such catalysts should be valuable in the acylation reactions of highly hindered and/or less reactive alcohols and amines. Studies to understand the relative potency order of the nucleophilic catalysts **1**−**6** as well as development of the chiral versions of these catalysts are in progress and will be reported in due course.

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Note Added after ASAP Publication: The PPY structure was incorrect in the Abstract/TOC graphic in the version published ASAP on January 3, 2007; the corrected version was published ASAP on January 5, 2007.

Supporting Information Available: Complete experimental procedures for all new compounds and copies of ^1H and ^{13}C spectra of compounds **3**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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