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Conformationally restricted 4-dimethylaminopyridine (DMAP) analogs: synthesis and evaluation of catalytic effectiveness

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Abstract—The syntheses of a series of conformationally restricted 4-dimethylaminopyridine (DMAP) analogs **1**–**3** are described. Evaluations of catalyst effectiveness demonstrated that **1** was the best catalyst for the acetylation reaction of a tertiary alcohol, while **2** and **3** were roughly comparable to DMAP. The order of effectiveness of these catalysts roughly parallels their acetylation enthalpies estimated from ab initio calculations.

The reaction between an alcohol/amine and an acyl donor, typically acid chloride or anhydride, is often sluggish if the alcohol/amine is sterically hindered and/or less reactive. The facilitation of such difficult acylations by pyridine was recognized early on and the mechanism of catalysis was first proposed by von Doering and McEwen.[1] Since then Steglich and Hofle reported that 4-dimethylaminopyridine (DMAP), facilitated acylations to a far greater extent than pyridine.[2–4] Over the years, DMAP has been shown to catalyze a wide variety of reactions like carbamylation, silylation, sulfonylation and phosphorylation of amino and hydroxyl groups.[5–10] Its widespread use in syntheses has been extensively reviewed.[11,12] Chiral DMAP analogs have been developed and successfully used in asymmetric syntheses involving alcohols and amines.[13–21]

In a prior communication, Steglich et al. reported that bis-six-membered DMAP analog **1** (Fig. 1) was about sixfold more effective than DMAP in catalyzing the esterification reaction of a tertiary alcohol.[22] This result was rationalized by the greater stability of the acylpyridinium intermediate resulting from **1** compared to that from DMAP due to conformational fixation of the 4-N lone pair orbital parallel to the π orbitals of the pyridine ring in **1**. This observation suggested the possibility

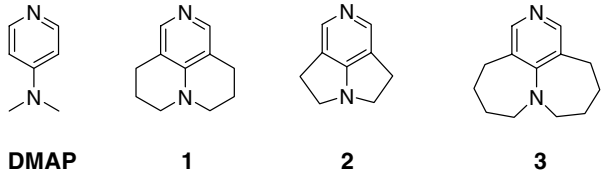

Figure 1. DMAP and conformationally restricted analogs.

that the five-membered analog **2** with even greater rigidity and overall planarity might be an even more potent catalyst. It was also of interest how the ring size in such DMAP analogs affects catalyst effectiveness. Steglich utilized Yamanaka et al.'s method for the synthesis of **1**.[23] However, this protocol only provides the six-membered analog **1** and cannot be modified for the synthesis of other cyclic variants like **2** and **3**. We therefore embarked upon the development of a general protocol for the preparation of these conformationally restricted DMAP analogs. In this Letter, we describe our synthetic strategy and present the results of comparisons of effectiveness of the nucleophilic catalysts **1**–**3** in catalyzing the acetylation reaction of a tertiary alcohol.

As illustrated in Scheme 1, the generally accepted mechanism of catalysis of acylation by DMAP and other nucleophilic catalysts involves initial reaction of DMAP with an acyl donor to generate an acylpyridinium-anion ion-pair intermediate. This is followed by essentially irreversible attack of an alcohol/amine to the intermediate to generate an ester/amide product and to regenerate

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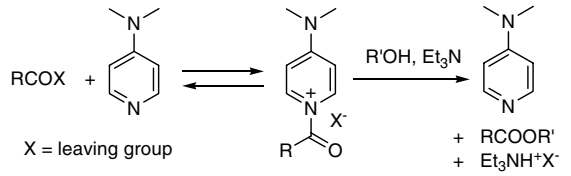
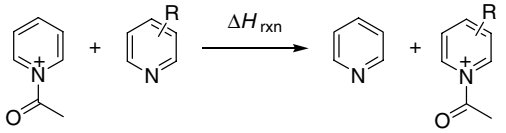


Scheme 1. Simplified mechanism of catalysis of the esterification reaction of an alcohol by an acyl donor in the presence of DMAP.

DMAP.[24] The reaction is generally conducted in the presence of one or more equivalents of an auxiliary base like triethylamine to scavenge an acid generated and thus to prevent DMAP from being protonated. The higher potency of DMAP compared to pyridine arises as a result of improved delocalization of the positive charge on the acylpyridinium intermediate via the $+R$ effect of the 4-NMe_2 group.[25,26]

The design of **1** by Steglich et al. was based on the reasoning that the cyclic framework of **1** would position the 4-N lone pair orbital parallel to the pyridine π orbitals for the maximum orbital overlap. Additionally, the $+I$ effect of the two alkyl groups in the *m*-positions would also have a stabilizing influence. The net result of these interactions should be a significant increase in the concentration of the acylpyridinium intermediate derived from **1** which should in turn result in a greater rate enhancement. Such stability enhancements are supported by the results from ab initio calculations of the enthalpy change arising from the isodesmic acetyl-transfer reactions as shown in Eq. 1 at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level of theory (Table 1).[22,27]



(1)

The results in Table 1 indicate that acetyl transfer from pyridine to **1** is 6 kcal mol^{-1} more exothermic than the corresponding acetyl transfer to DMAP. This additional stabilization energy may result partly from conformational fixation of the 4-N lone pair orbital parallel to the pyridine π orbitals, and partly from the $+I$ effect of the alkyl groups at the *m*-positions. Similar theoretical results have been obtained for the effects of conformationally restricted cyclic N substituents on the stability of cyclic benzhydryl cations by Mayr et al.[28]

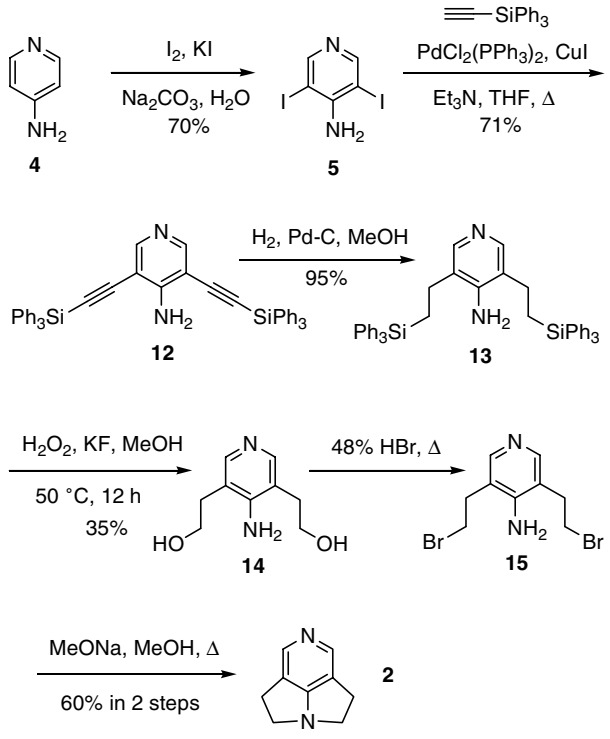
Based on the similar reasoning, we predicted that **2** might be more effective than (or as effective as) **1** because it is more rigid and planar with the 4-N substituent 'conformationally locked' so that its lone pair orbital can be parallel to the pyridine π system. We were also aware that **2** had a lower calculated enthalpy for the acetyl transfer compared to **1**, even though these enthalpies did not always translate to catalytic effectiveness.[27a] The conformationally more flexible seven-membered analog **3** has an enthalpy change for the acetyl transfer similar to **1**, but greater than **2**. So it would be interesting if some conformational flexibility would aid in catalyst effectiveness.[29]

Table 1. Calculated enthalpies $-\Delta H$ (kcal mol^{-1}) for acetyl group transfer (Eq. 1)

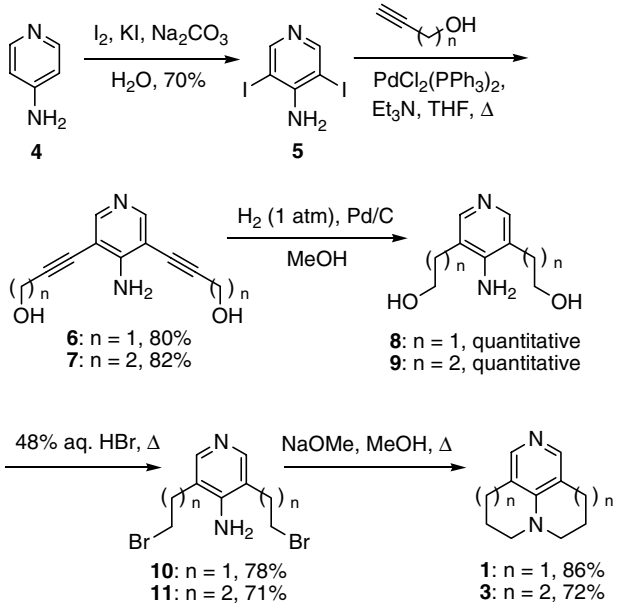
	DMAP	1	2	3
$-\Delta H_{rxn}$	19.5	25.9	21.8	24.5[a]

[a] Ref. 27b.

The synthesis of **2** is illustrated in Scheme 2. 4-Aminopyridine (**4**) was iodinated with iodine in refluxing aqueous potassium iodide solution to give 3,5-diiodo-4-aminopyridine (**5**). Sonogashira coupling of **5** with triphenylsilylacetylene using palladium dichloride bis(triphenylphosphine) complex, copper(I) iodide and triethylamine in refluxing tetrahydrofuran yielded the 3,5-dialkynyl-4-aminopyridine **12**.[30,31] Catalytic hydrogenation of **12** using hydrogen at atmospheric pressure over palladium on activated charcoal in methanol provided **13**. Fleming–Tamao–Kumada oxidation of **13** using hydrogen peroxide in the presence of potassium fluoride in warm methanol resulted in the conversion of the terminal triphenylsilyl groups to the hydroxyl groups to furnish **14**.[32] The low yield was probably due to the concomitant oxidation of **13** and **14** to their *N*-oxides under the reaction conditions. Diol **14** on refluxing with aqueous hydrobromic acid provided the corresponding dibromide as the dihydrobromide salt, which after neutralization yielded **15**.[33] Finally, refluxing **15** with sodium methoxide in methanol effected double intramolecular cyclizations to yield **2**.[34,35]



Scheme 2. Synthesis of doubly annelated five-membered pyridine **2**.



Scheme 3. Synthesis of doubly annelated six and seven-membered pyridines **1** and **3**.

The synthesis of **1** and **3** is illustrated in Scheme 3. Sonogashira coupling of **5** with prop-2-yn-1-ol and but-3-yn-1-ol yielded diols **6** and **7**, respectively. Catalytic hydrogenation of **6** and **7** under atmospheric H_2 on Pd/C provided the corresponding reduced alcohols **8** and **9**. Treatment of diols **8** and **9** with refluxing aqueous hydrobromic acid gave the dibromides as the dihydrobromide salts, which upon neutralization yielded dibromides **10** and **11**, respectively. Final double intramolecular cyclizations to yield the annelated pyridines **1** and **3** were achieved by refluxing the coresponding **10** and **11** with sodium methoxide in methanol.[35]

Evaluations of effectiveness of DMAP and catalysts **1**–**3** were conducted by following the acetylation reaction of 1-ethynylcyclohexanol (1.0 mmol) with acetic anhydride (2.0 mmol) in the presence of triethylamine (3.0 mmol) and each of the four catalysts (0.1 mmol) in 5 mL anhydrous dichloromethane at 25 °C (Eq. 2). The reactions were monitored by ^{1}H NMR spectroscopy and the percent conversion of the alcohol to its ester was plotted versus time. The results are summarized in the graph in Figure 2.

The graph shows that **1** is the best catalyst, a result that was suggested by having the highest acetyl transfer enthalpy among all the catalysts (Table 1). Surprisingly, in spite of having two *m*-alkyl substituents and the 4-N lone pair locked parallel to the pyridine π system, **2** is not better than **1** but comparable to DMAP. These results are more consistent with the calculated enthalpy data for the acetyl transfers, but are contrary to the scale of stability of cyclic benzhydryl cations proposed by Mayr et al.[28] Also, additional flexibility afforded by the seven-membered rings is not beneficial to catalytic activity, although the enthalpy data for the acetyl transfers indicate that **3** should have greater potency than **2** and DMAP (Table 1).

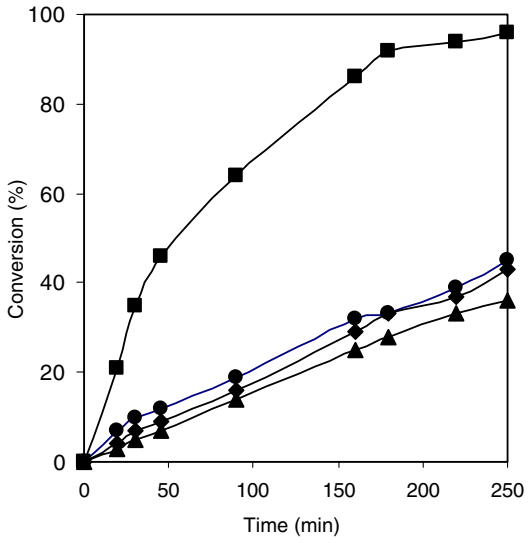
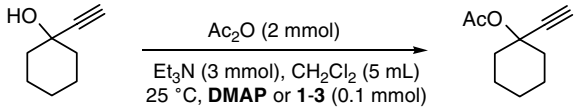


Figure 2. Graph illustrating the percent conversion of 1-ethynylcyclohexanol to its acetate ester by catalysts: DMAP (●), **1** (■), **2** (▲) and **3** (◆) at specified times under conditions described in Eq. 2.



(2)

In conclusion, we have developed a general strategy for the synthesis of conformationally restricted DMAP analogs, and further have demonstrated that their catalytic effectiveness in the esterification reaction of 1-ethynylcyclohexanol roughly parallels their estimated acetylation enthalpy data. The synthetic protocols are amenable to modification to provide non-symmetric analogs as well as chiral variants. Studies along these lines are under progress, and will be reported in due course.

Acknowledgments

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35. Characterization data. Compound **1**: mp = 270 °C (charring); ^{1}H NMR (500 MHz, CD_3OD) δ: 7.78 (s, 2H), 3.19 (t, 4H, $J = 5.9$ Hz), 2.60 (t, 4H, $J = 6.6$ Hz), 1.89 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD) δ: 147.37, 146.53, 115.04, 48.99, 24.13, 20.96. Compound **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.04 (s, 2H), 3.68 (t, 4H, $J = 5.7$ Hz), 2.85 (t, 4H, $J = 5.7$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 151.82, 146.62, 120.86, 45.04, 31.75. Compound **3**: ^{1}H NMR (500 MHz, CD_3OD) δ: 8.04 (s, 2H), 3.22 (t, 4H, $J = 5.1$ Hz), 2.66 (t, 4H, $J = 5.9$ Hz), 1.78 (m, 4H), 1.66 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD) δ: 157.39, 148.73, 129.37, 52.17, 30.61, 26.95, 25.29.