Organic LETTERS

Letter

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4-(*N*,*N*-Dimethylamino)pyridine Hydrochloride as a Recyclable Catalyst for Acylation of Inert Alcohols: Substrate Scope and Reaction Mechanism

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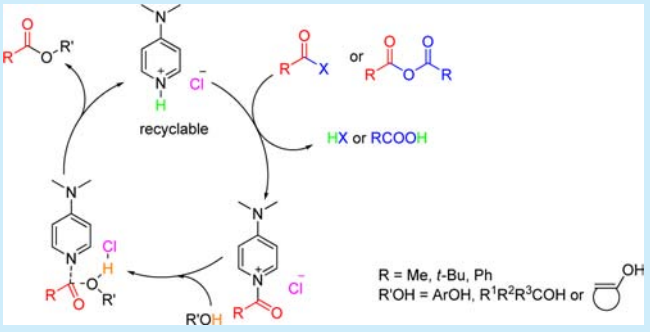
Supporting Information

ABSTRACT: 4-(*N*,*N*-Dimethylamino)pyridine hydrochloride (DMAP·HCl), a DMAP salt with the simplest structure, was used as a recyclable catalyst for the acylation of inert alcohols and phenols under base-free conditions. The reaction mechanism was investigated in detail for the first time; DMAP·HCl and the acylating reagent directly formed *N*-acyl-4-(*N*′,*N*′-dimethylamino)pyridine chloride, which was attacked by the nucleophilic substrate to form a transient intermediate that released the acylation product and regenerated the DMAP·HCl catalyst.



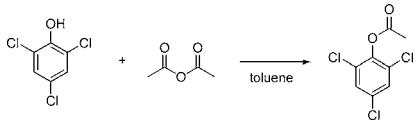
4-(*N*,*N*-Dimethylamino)pyridine (DMAP) is an effective nucleophilic base catalyst. Since its use in acylation reactions was first reported,[1,2] its applications have been extensively investigated. More active analogues have been developed,[3] and chiral versions have been used as catalysts in asymmetric synthesis,[4] for kinetic resolution of racemic alcohols[5] and amines,[6] and for applications in biological[7] and supramolecular chemistry.[8]

Unfortunately, DMAP and some of its derivatives exhibit acute dermal toxicity.[9] Several strategies have been developed to circumvent this problem, but all have been accompanied by activity loss[10] or recycling difficulty.[11] Connon et al.[12] reported that DMAP supported on magnetic nanoparticles can be reused up to 32 times without activity loss and can be recovered with an external magnet. Polymer-supported DMAP derivatives have also been extensively studied,[13] but all these derivatives are limited by inconvenient handling. Ishihara et al.[14] reported a DMAP-catalyzed acylation under base-free conditions, and Legros et al.[15] reported an acylation employing a fluorous DMAP salt as a recyclable catalyst that could be recovered by filtration. Similarly, Lu et al.[16] used a saccharin-DMAP salt to acylate alcohols. Unfortunately, when acylating reagents other than acid anhydrides are used, salts of DMAP and weak acids can be destroyed.

Here, we report the use of DMAP·HCl, the simplest salt of DMAP, as a recyclable catalyst for acylation reactions, and we describe its unique advantages and catalytic mechanism.

We chose the acylation of 2,4,6-trichlorophenol with acetic anhydride as a model reaction (Table 1). In the absence of catalyst, no reaction took place over the course of 78 h (entry 1), and 5% HCl had no obvious catalytic activity (entry 2). In contrast, both 5% DMAP and 5% DMAP·HCl exhibited excellent catalytic activity at room temperature, though the reaction catalyzed by DMAP·HCl required a longer reaction time (entries 3 and 4); but at elevated temperature (60 or 100 °C), the reaction time was markedly shortened while the conversion and yield were maintained (entries 5 and 6).

Table 1. Catalytic Activity of DMAP·HCl[a]



entry	catalyst	*t* (°C)	time (h)	conv (%)[b]	yield (%)[c]
1	none	25	78	<5	–
2	5% HCl	25	78	<20	–
3	5% DMAP	25	18	>99	98
4	5% DMAP·HCl	25	78	>99	98
5	5% DMAP·HCl	60	8	>99/<5[d]	98
6	5% DMAP·HCl	110	1	>99/<5[d]	98

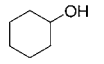
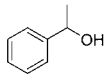
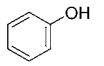
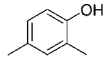
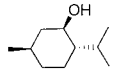
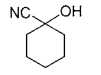
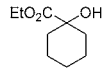
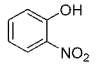
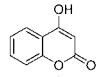
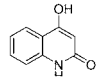
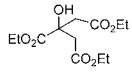
[a]The reaction of 2,4,6-trichlorophenol (10.0 mmol) and acetic anhydride (11.0 mmol) was conducted in 20 mL of toluene. [b]Conversion was calculated based on recovered substrate. [c]Isolated yield. [d]Conversion in the absence of DMAP·HCl.

Encouraged by these results, we acylated additional substrates with acetic or benzoic anhydride and DMAP·HCl (Table 2). Cyclohexanol, 1-phenylethanol, phenol, and 2,4-dimethylphenol gave high yields of the desired esters at room temperature (entries 1−8). More inert alcohols and electron-deficient phenols, such as menthol, 1-cyanocyclohexanol, 1-

Received: November 9, 2013
Published: December 16, 2013

   dx.doi.org/10.1021/ol4030875 | *Org. Lett.* 2014, 16, 236−239

Table 2. DMAP·HCl-Catalyzed Acylation of Alcohols and Phenols by Acid Anhydrides under Base-Free Conditions[a]

entry	substrate	acylating agent	t (°C)	time (h)	yield (%)[b]
1		Ac_2O	rt	6	98
2		$(PhCO)_2O$	rt	8	97
3		Ac_2O	rt	6	98
4		$(PhCO)_2O$	rt	8	98
5		Ac_2O	rt	10	99
6		$(PhCO)_2O$	rt	15	99
7		Ac_2O	rt	8	99
8		$(PhCO)_2O$	rt	10	97
9		Ac_2O	60	4	98
10		$(PhCO)_2O$	60	6	98
11		Ac_2O	60	6	97
12		$(PhCO)_2O$	60	9	98
13		Ac_2O	60	8	98
14		$(PhCO)_2O$	60	12	97
15		Ac_2O	60	4	98
16		$(PhCO)_2O$	60	8	96
17		Ac_2O	60	4	99
18		$(PhCO)_2O$	60	5	98
19		Ac_2O	60	6	96
20		$(PhCO)_2O$	60	8	94
21		Ac_2O	110	8	90
22		$(PhCO)_2O$	110	28	88
23		Ac_2O	110	4	97
24		$(PhCO)_2O$	110	8	93

[a]The reaction of each alcohol or phenol (10.0 mmol) with acetic anhydride or benzoic anhydride (11.0 mmol) was conducted in the presence of DMAP·HCl (0.5 mmol) in toluene (20 mL); for liquid substrates, no solvent was used. [b]Isolated yield.

ethoxycarbonyl-cyclohexanol, 4-hydroxycoumarin, and *o*-nitrophenol (entries 9–20), as well as 2,4,6-trichlorophenol (Table 1, entry 4), gave high yields of the desired products when the temperature was raised to 60 °C. Even the most inert alcohols tested, adamantanol and triethyl citrate (entries 21–24), could be easily acylated at 110 °C under solvent-free conditions.

When benzoyl or pivaloyl chloride was used as the acylating reagent, the reaction temperature had to be increased to 110 °C (Table 3). Because acyl chlorides are highly reactive, we also performed the corresponding reactions without DMAP·HCl as control reactions, and we found that the DMAP·HCl-catalyzed reactions were always faster and higher yielding than the uncatalyzed reactions. Inert phenols (Table 3, entries 1–6), tertiary alcohols (entries 9–14), enols (entries 15–18), 2-hydroxypyridine (entries 19 and 20), a heterocyclic amine (entry 21), and even an amide (entries 7 and 8) were suitable substrates, and some of the reactions were complete within a few minutes.

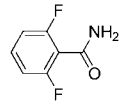
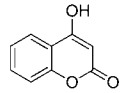
To further highlight the advantages of the DMAP·HCl-catalyzed reaction, we evaluated additional acylating reagents, as well as the recyclability of the catalyst (Table 4). DMAP·HCl worked well with all the tested substrates and acylating reagents; the isolated yields of the products exceeded 88%,

Table 3. DMAP·HCl-Catalyzed Acylation of Alcohols and Phenols by Acyl Chlorides under Base-Free Conditions[a]

entry	substrate	acylating agent	time (h)	yield (%)[b]	conv (%)[c]
1		PhCOCl	8	97	20
2		tBuCOCl	6	95	30
3		PhCOCl	6	98	40
4		tBuCOCl	18	96	20
5		PhCOCl	6	98	40
6		tBuCOCl	8	99	40
7		PhCOCl	2	93	30
8		tBuCOCl	8	99	40
9		PhCOCl	4	94	67
10		tBuCOCl	2	95	56
11		PhCOCl	2	94	28
12		tBuCOCl	2	95	32
13		PhCOCl	6	96	5
14		tBuCOCl	5	97	5
15		PhCOCl	1	96	15
16		tBuCOCl	1.25	98	10
17		PhCOCl	2.5	96	5
18		tBuCOCl	4	93	5
19		PhCOCl	0.25	94	60
20		tBuCOCl	0.13	94	50
21		PhCOCl	2	94	50

[a]The reaction of each substrate (10.0 mmol) with the acylating reagent (11.0 mmol) was conducted in the presence of 5 mol % DMAP·HCl in 20 mL of toluene at 110 °C. For liquid substrates, reactions were conducted under solvent-free conditions. [b]Isolated yield. [c]Conversion of the corresponding reaction in the absence of DMAP·HCl.

Table 4. Assessment of DMAP·HCl as a Recyclable Catalyst for Acylation of Various Substrates under Base-Free Conditions[a]

entry	substrate	acylating reagent	yield (%)[b] range of each run	M[c] (mg)
1		$(i$PrCO$)_2$O	92–98	67.1
2		Ac_2O	93–99	65.5
3		$(PhCO)_2O$	89–96	62.6
4		Me_2NCOCl	90–97	70.0
5		tBuCOCl	93–98	64.8
6		PhCOCl	88–96	65.2
7		tBuCOCl	90–99	61.6
8		PhCOCl	89–94	63.7
9		Ac_2O	94–99	68.8
10		$(PhCO)_2O$	90–98	62.9
11		tBuCOCl	92–98	67.2
12		PhCOCl	89–96	66.2
13		Ac_2O	93–99	69.0
14		$(PhCO)_2O$	92–97	62.8
15		tBuCOCl	89–96	60.9
16		PhCOCl	89–94	58.9

[a]The reaction of each substrate (10.0 mmol) with the acylating reagent (11.0 mmol) was conducted in toluene (20 mL) with 5 mol % DMAP·HCl (79.0 mg). For 1-cyanocyclohexanol, no solvent was used. [b]Isolated yield. [c]Weight of DMAP·HCl recovered after 8 or 10 cycles.

and DMAP·HCl was recovered nearly quantitatively from each run. It is worth mentioning that because HCl is a stronger acid than carboxylic acid, DMAP·HCl is first formed and separated,

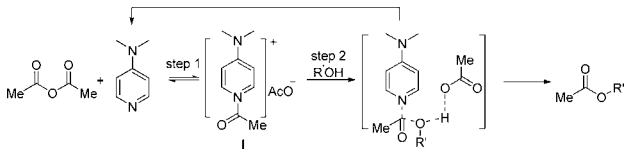
dx.doi.org/10.1021/ol4030875 | Org. Lett. 2014, 16, 236–239

which is supported by the fact that only signals for DMAP·HCl were found in the ^{1}H NMR spectrum of the recycled catalyst.

We demonstrated that DMAP·HCl had excellent catalytic activity, but the mechanism of its activity was not clear. Various investigators[14−16] have suggested that its activity is due to free DMAP in the solvent, but we are skeptical of this suggestion because we observed that the rate of the DMAP-catalyzed acetylation of cyclohexanol was slowed by the addition of tetrabutylammonium chloride (the conversion at 1.5 h was 99% in the absence of the ammonium salt but 53% in its presence (see Supporting Information)).

Zipse et al.[17] reported a two-step mechanism for DMAP-catalyzed acetylation (Scheme 1); in step 1, DMAP reacts with

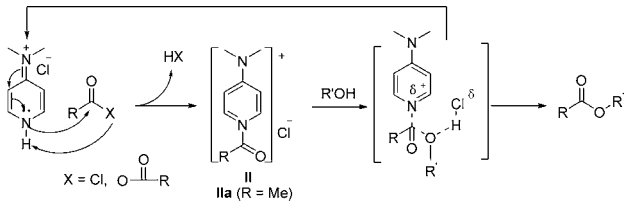
Scheme 1. Mechanism of DMAP-Catalyzed Acetylation Proposed by Zipse et al.



acetic anhydride to form *N*-acetylated DMAP acetate (**I**), and in step 2, the alcohol substrate attacks **I** to form a transient intermediate that leads to the ester product after proton transfer and simultaneous release of DMAP and acetic acid. Step 2 is thought to be the rate-determining step.

However, the slowing of the DMAP-catalyzed acylation when tetrabutylammonium chloride was added suggests that the rate-determining step of the DMAP-catalyzed reaction differs from that of the DMAP·HCl-catalyzed reaction. That is, it is not **I** but some other *N*-acetylated DMAP salt that is attacked by the alcohol substrate. We isolated the intermediate, and ^{1}H NMR spectroscopy (see Supporting Information) indicated it to be *N*-acetylated DMAP chloride (**IIa**, Scheme 2). Therefore, we are sure that the DMAP·HCl-catalyzed acylation proceeds through the same intermediate (Scheme 2).

Scheme 2. Proposed Mechanism of DMAP·HCl-Catalyzed Acylation Reaction



To determine whether **IIa** formed from DMAP·HCl or from free DMAP, we performed some additional experiments (Table 5). We found that when DMAP and acetyl chloride were mixed in a $CHCl_3$ solution, **IIa** formed immediately[18] (entry 1), suggesting that if free DMAP is present in DMAP·HCl solution, **IIa** should form after the acylating reagent is added. However, we found that this was not the case; when acetyl chloride was mixed with DMAP·HCl at room temperature, no reaction occurred even after 7 days (entry 2), whereas when acetic anhydride was used as the acylating reagent at room temperature, **IIa** formed within 24 h, even when 10 equiv of HCl were added in advance (entry 3). These results rule out the possibility that **IIa** formed from the acylating reagent and

Table 5. Reaction of DMAP·HCl with Acetyl Chloride or Acetic Anhydride

entry	catalyst	acylating reagent	t (°C)	result
1[a]	DMAP	AcCl or Ac_2O	rt	**IIa** formed immediately
2[a]	DMAP·HCl	AcCl	rt	no reaction happened even after 7 days
3[a]	DMAP·HCl + 10 equiv of HCl	Ac_2O	rt	**IIa** formed within 24 h
4[b]	DMAP·HCl	AcCl	110	**IIa** formed within 30 min

[a]Acylating reagent was added to a $CHCl_3$ solution of DMAP or DMAP·HCl, and the solution was kept at rt. [b]Acetyl chloride was added to a toluene solution of DMAP·HCl, and the solution was refluxed.

free DMAP derived from dissociation of DMAP·HCl. Therefore, we believe that *N*-acetylated DMAP chloride (**IIa**) formed directly from DMAP·HCl (Scheme 2). The difference in activity between acetyl chloride and acetic anhydride could be explained by the fact that Cl^- is a weaker conjugate base than AcO^-, which means that it is more difficult for Cl^- to capture a proton from DMAP·HCl to form the transient intermediate leading to **IIa**. When we repeated the reaction of acetyl chloride with DMAP·HCl in refluxing toluene (entry 4), **IIa** formed within 30 min. From entries 1 and 4 we also know when acid chloride is used as an acylating agent under reflux conditions; both DMAP and DMAP·HCl work through DMAP·HCl, so they theoretically have the same catalytic activity.

On the basis of these results, we propose the following mechanism (Scheme 2): first, DMAP·HCl and the acylating reagent form *N*-acylated DMAP chloride (**II**), and second, the nucleophilic substrate attacks **II** to form a transient intermediate that releases the acylation product and regenerates DMAP·HCl. This mechanism suggests the possibility of using this reaction as a novel method for kinetic resolution of alcohols by means of an acylation catalyzed by a salt of DMAP and a chiral acid. The chiral anion may facilitate stereoselective dehydrogenation.

In summary, we demonstrated that DMAP·HCl is an effective, recyclable organocatalyst for acylation under base-free conditions (liquid substrates could also be acylated under solvent-free conditions). The catalyst can be reused more than eight times without loss in activity, and it works with multiple acylating reagents. Therefore, it might be practical for industrial applications. We also investigated the catalytic mechanism and found that *N*-acyl-4-(*N*′,*N*′-dimethylamino)pyridine chloride formed directly from DMAP·HCl and the acylating reagent, suggesting that this reaction could be used for kinetic resolution of alcohols.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures (preparation of DMAP·HCl, general procedure for DMAP·HCl-catalyzed acylation, and procedure for catalyst recycling) and compound characterization data are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Key Project for Basic Research (2010CB126100), the National Natural Science Foundation of China (21132003, 21121002, 21372131), Tianjin Natural Science Foundation (11JCZDJC20500), and the Specialized Research Fund for the Doctoral Program of Higher Education (20120031110010) for generous financial support for our research.

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