JOURNAL OF CRITICAL REVIEWS

ISSN- 2394-5125 VOL 07, ISSUE 06, 2020

N-acetyl-4-dimethylaminopyridinium chloride: An in situ formed Lewis Base adduct for Direct Base Free Acetylation in water.

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Abstract: A new base free direct acetylation reagent $[DMAPAc]^+Cl^-$ was identified, prepared in grams scale and unambiguously characterised. Several amines, phenols and alcohols were successfully acetylated employing this reagent in water as a solvent at ambient temperature in almost quantitative yields. Water as a solvent, Chromatography free purification, recovery of DMAP and operation simplicity of the methodology rates as environmentally benign strategy.

Key words: $[DMAPAc]^+Cl^-$, acetylation, Lewis base adducts, DMAP

Introduction:

Electrophilic acetyl transfer reaction is one of the fundamental organic transformation which serves as an excellent masking group for various classes of compounds viz. alcohols, amines, phenols, thiols, carboxylic acids etc.

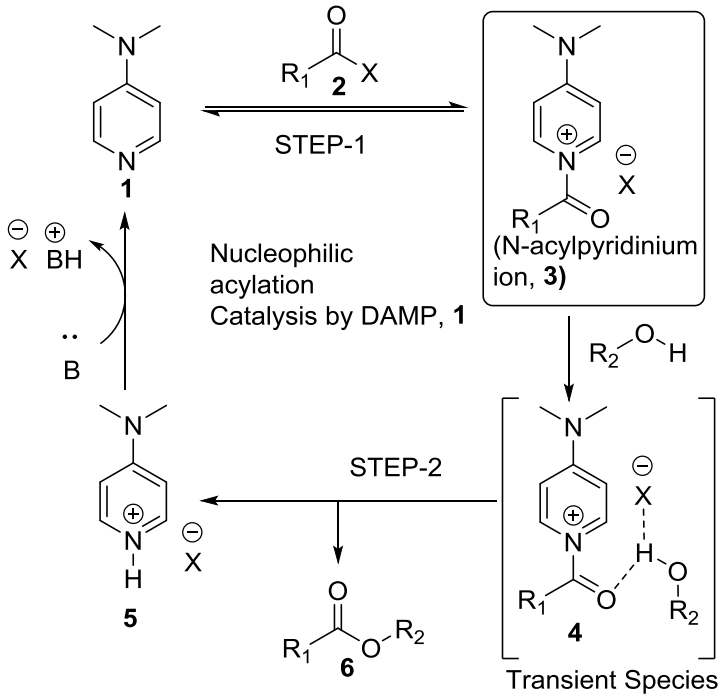
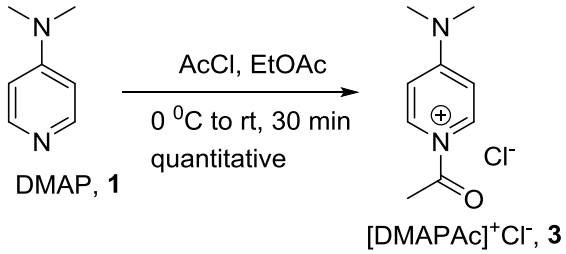


Figure 1: A typical mechanism of DMAP catalysed acylation

ISSN- 2394-5125 VOL 07, ISSUE 06, 2020

Tertiary amine catalysed acetylation has gained the attention of many research groups over a period of time. 4-(N,N-dimethylamniopyridine) is the choice of organocatalyst for various types of acyl transfer reactions.[1] Subsequently several modifications were evolved including asymmetric versions for chiral synthesis[2] and also for use in biological and other branches of chemistry.[3] Mechanistically DMAP catalysed acetylation reactions involves a two step process[4] involving formation of Lewis base adduct N-acetyldimethylaminopyridinium salts, **3** in step 1 which is the active acetylation reagent while in the second step alcohol reacts with **3** to produce the product **6** through the formation of transient product **4**. Several other modifications of DMAP as an effective catalyst were developed by various groups to overcome its toxicity effects and also to improve its catalytic activity.[5] In this communication we wish to report our results by employing these in situ formed Lewis base adducts as direct reagents, which is our present interest,[6] for acetylation of phenols, amines and alcohols because such studies were unprecedented.

Results and discussion:



Scheme 1: Preparation of $[DMAPAc]^+Cl^-$, **3**

Our journey began with the preparation of reagent **3** by treatment of DAMP with acetyl chloride in ethyl acetate (Scheme 1)

Table 1: Acetylation studies on aniline, **7** employing $[DMAPAc]^+Cl^-$, **3**

SN	Quantity of 3	*t* (^{0}C)	Solvent	Base	Time (In min.)	Yield (%)
1	1.1 eq.	rt	DCM	NEt_3	30	65
2	1.1 eq.	rt	DCM	-	45	50
3	1.1 eq.	rt	$CHCl_3$	NEt_3	35	60
4	1.1 eq.	rt	$CHCl_3$	-	50	57
5	1.1 eq.	rt	THF	NEt_3	60	55
6	1.1 eq.	rt	THF	-	90	35
7	**1.1 eq.**	**rt**	**H_2O**	**NEt_3**	**20**	**97**
8	**1.1 eq.**	**rt**	**H_2O**	**-**	**25**	**95**
9	1.1 eq.	60	DMF	NEt_3	40	55
10	1.1 eq.	60	DMF	-	60	35
11	1.1 eq.	rt	CH_3CN	NEt_3	45	50
12	1.1 eq.	rt	CH_3CN	-	60	30
13	1.1 eq.	rt	EtOH	NEt_3	120	15
14	1.1 eq.	rt	EtOH	-	150	05

ISSN- 2394-5125 VOL 07, ISSUE 06, 2020

The product 3 was quantitatively produced and was thoroughly characterised by ^{1}H NMR, ^{13}C NMR, IR and Mass spectral data. Aniline, **7** was chosen as a model substrate for acetylation. In this direction several studies were done as per the table given below. **Table 1** clearly suggested that H_2O is the solvent of choice and the reaction went smoothly at room temperature even with or without base. The reaction involves almost quantitative conversion with short reaction times (20 min). After establishing the optimal reaction conditions for monoacetyltion we wished for testing substrate scope of acetylation using **3**.

Table 2: acetylation of various amines

SN	Substrate	Time (in min)	Yield (%)
1	Aniline, **7**	20	95
2	*p*-toluidine, **9**	25	96
3	*o*-toluidine, **11**	25	92
4	p-anisidine, **13**	20	94
5	p-chloroaniline, **15**	20	96
6	N-methylaniline, **17**	20	90
7	o-nitroaniline, **19**	25	95
8	Piperidine, **21**	30	89
9	Benzyl amine, **23**	25	92
10	p-aminophenol, **25**	20	93
Reaction conditions: substrate (5.0 mmol), reagent **3** (5.5 mmol), H_2O (3 mL), rt			

A total of 10 different amines were tested on 5.0 mmol scale using 1.1 eq. of acetylation reagent 3 in H_2O ar rt for an average time of 25 min to produce mono N-acetylated products in excellent yields (89-96%). The advantage of our methodology is total elimination of base and also chromatographic purification as the only by product DMAP.HCl is water soluble.

Table 3: acetylation of various phenols and alcohols

SN	Substrate	Time (in min)	Yield (%)
1	Phenol, 2**7**	20	95
2	*p*-cresol, 2**9**	25	93
3	β-napthol, **31**	25	95
4	p-chlorophenol, **33**	20	88
5	3,5-dimethylphenol, **35**	20	90
6	8-hydoyquinoline, **37**	20	90
7	Vanillyl alcohol, **39**	25	80
8	Benzyl alcohol, **41**	30	86
9	Salicilic acid, **43**	25	98

ISSN– 2394–5125 VOL 07, ISSUE 06, 2020

Reaction conditions: substrate (5.0 mmol), reagent **3** (5.5 mmol), H_2O (3 mL), rt.

phenols and alcohols also underwent smooth acetylation (table 2) to furnish monoacetylated phenols in good yields. The reagent **3** serves as a good chemoselective acetylating reagent (table 1; entriy 10 and table 2; entries 7 & 9). One of the additional advantage of our methodology is recovery of DAMP after the reaction by simply neutralizing the aqueous layer with aq. NaOH and extracting into ethylacetate which upon evaporation yields DMAP which is again used for the preparation of reagent **3**.

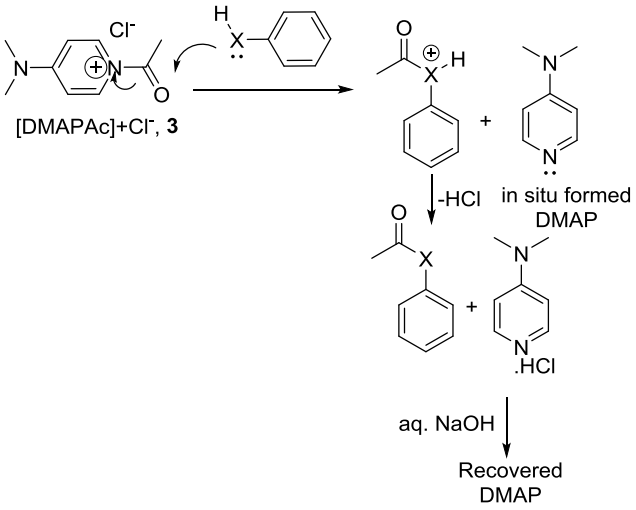


Figure 3: Plausible mechanism of acetylation by **1**

Figure 3 explains about the possible mechanism of acetylation employing 3. In the rate determining step anilne reacts with 3 to form protonated acetyl product and by product DMAP which serves as in situ formed base for the second step. This explains why the reaction does not require a base. Recovery of DMAP was done by saponification of DMAP.HCl .

Conclusions:

In conclusion the acetyl transfer reagent [DMAPAc]+Cl- was prepared in grams scale and thoroughly characterised by spectral studies. This reagent was successfully applied for acetylation of various amines, phenols and alcohols in excellent yields. performing the reactions in water and recovery of DMAp rates This methodology is an Eco-friendly one.

Acknowledgements:

Dr NCK and Swathi thank Palamuru University for provding the infrastructural facilitis and Indian Institute of Chemical Technology, University of Hyderabad and Osmania University for spectral data assistance.

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