Metal acetate/metal oxide in acetic acid: an efficient reagent for the chemoselective *N*-acetylation of amines under green conditions

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The use of catalytic amount of metal acetate or metal oxide in acetic acid is a new and highly efficient acetylating system for chemoselective *N*-acetylation of primary and secondary amines in excellent yields under reflux condition. No other solvent is required. The noted features of this method include mild reaction conditions, use of innocuous reagents, excellent yields, convenient work-up, and reuse of catalyst.

Keywords: amines, *N*-acetylation; chemoselectivity, metal acetates, metal oxides, acetic acid

N-Acetylation of an amino group is one of the most fundamental as well as useful transformations in organic chemistry.[1,2] Because of their nucleophilic and basic character, amines must be blocked with a protecting group during a multi-step synthesis, *e.g*. in the synthesis of a diverse array of biological molecules such as amino acids, peptides, amino glycosides, β-lactams, nucleosides and alkaloids. Hence, selective protection of amino group through acetylation finds immense significance in organic synthesis. The acetylation of amines is usually performed employing acid anhydride or acetyl chloride in the presence of stoichiometric amount of an amine base, such as triethylamine or pyridine along with 4-(dimethylamino)pyridine (DMAP), which acts as a co-catalyst, or 4-pyrrolidinopyridine (PPY).[3] Sometimes tributylphosphine (Bu_3P) is also employed as a less basic catalyst for acylation reactions, particularly for the base sensitive substrates.[4,5] Exhaustive literature survey reveals the applications of a variety of other catalysts also; these include 4-dialkylaminopyridine,[3] basic alumina,[6] perchloric acid adsorbed on silica gel,[7] $In(OTf)_3$,[8] ruthenium(III)chloride,[9] montmorillonite K-10 and KSF,[10] (pyridine)(tetrahydroborato)zinc complex,[11] sodium dodecyl sulfate (SDS),[12] acetonyltriphenylphosphonium bromide,[13] and many others.[14–19] A number of alternative methods have also been reported for *N*-acetylation of primary and secondary amines, where a variety of acetylating agents other than the conventional acetic anhydride, such as ethyl trifluoroacetate,[20] *ortho*-substituted *N*,*N*-diacetylaniline,[21] dichlorotriphenylphosphorane in chloroform,[22] imidoylbenzotriazoles,[23] poly(3-acyl-2-oxazolone),[24] 2-acyl-4,5-dichloropyridazine-3-one,[25] *N*,*N*-dialkylformamide dimethyl acetal with primary amides,[26] *N*-acetyl-*N*-acyl-3-aminoquinazolinones,[27] *N*-methoxydiacetamide,[28] *N*-acyl-*N*-(2,3,4,5,6-pentafluorophenyl)methan esulphonamides,[29] and many others were used.[30–32] In spite of such developments, acetic anhydride (or acetyl chloride) is still regarded as the key *N*-acetylating agent, both in commercial and non-commercial sectors. However, both of these reagents, being corrosive and a lachrymator respectively are not always ideal.

Thorough inspection into all these reported methods reveals that although they have certain advantages, they also bear many drawbacks; such advantages and disadvantages were extensively described recently by Katritzky.[33] The major drawbacks in some of the above described methods include harsh reaction conditions, use of hazardous materials, use of excess acetylating agent and scope for possible side reactions with acid-sensitive substrates. Pyridine derivatives, such as DMAP and PPY are highly toxic, while tributylphosphine (Bu_3P) is flammable and air sensitive. Metal triflates lead to potential side reactions (rearrangement, dehydration, *etc*.) with acid-sensitive substrates requiring the use of a large excess of acetic anhydride and low temperature; the reagents are expensive and some of them are difficult to handle.[34–40] Bis(cyclopentadienyl) zirconium dichloride was found to be a good catalyst,[41] but was used with acetic anhydride and the reaction was not a chemoselective one; similarly with acetonyltriphenylphosphonium bromide (ATPB).[42] Kulkarni *et al*.[43] reported the use of zeolite catalysed acetylation with acetic acid under microwave irradiation, but this method is not also chemoselective; the reagent acetylates both alcohols and amines. However, there are two recent separate reports on the chemoselective acetylation of amines, alcohols and phenols, but both of the methods involve the use of acetic anhydride/acetyl chloride as the acetylating agent in the presence of catalysts.[44,45]

Although there are numerous methods known for the conversion of amines into *N*-acetylated products in good yields, there is to the best of our knowledge no report on a reliable methodology which is at same time environmentally benign and chemoselective in nature. Hence, there is a demand for a mild as well as an effective and environmentally benign reagent applicable for chemoselective *N*-acetylation reactions for a wide variety of amine substrates. In general, most of the acetyl transfer reagents are expensive and are obtained by acetylation with acetylating agents making them unsuitable for large-scale reactions. Some of these reagents and catalysts lead to waste and some reactions involve organic solvents, often toxic and polluting, both unacceptable in these environmentally conscious days. A crucial factor for green chemical processes involves the choice of cheap, safe, efficient and nontoxic reagents. In continuation of our work on the development of green methodologies for carbon–heteroatom bond-forming reactions,[46] we have now developed a novel and environmentally benign alternative method for chemoselective *N*-acetylation of amines; here we report that metal acetate(s) or metal oxide(s) in acetic acid act as useful reagents for chemoselective *N*-acetylation of structurally diverse amines under reflux condition (Scheme 1). Metal acetates or metal oxides used in this reaction act as precatalysts; the process is highly efficient, cost-effective and environmentally safe with excellent yields. No other solvent is required for carrying out the reaction. This alternative method for *N*-acetylation of amines avoids the use of conventional acetylating agents (acetyl chloride or acetic anhydride) and amine additives, and employs instead a catalytic (and reusable) amount of a metal acetate/metal oxide in acetic acid without the addition of any more solvent. We have also found for the first time that metal acetate (*e.g.* zinc acetate, a benign and inexpensive chemical) alone can act as a selective *N*-acetylating agent in the absence of acetic acid with moderate yields (Table 3).

For this present protocol, six metal acetates CH_3COONa, $Ca(CH_3COO)_2$, $Mg(CH_3COO)_2.4H_2O$, $Mn(CH_3COO)_2.4H_2O$,

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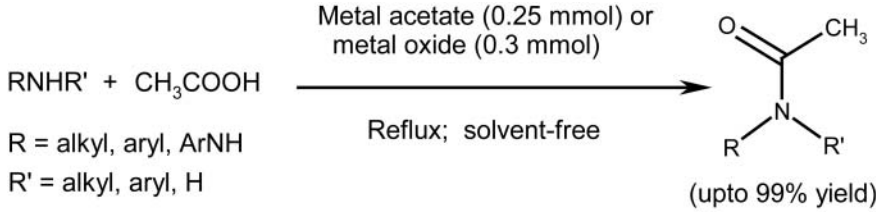


Scheme 1 Chemoselective *N*-acetylation of amines.

$Cu(CH_3COO)_2.H_2O$ and $Zn(CH_3COO)_2.2H_2O$, and five metal oxides such as MgO, CaO, Al_2O_3, Cr_2O_3 and ZnO were used as precatalysts; all these chemicals are cheap, readily available and environmentally safe [$Pd(CH_3COO)_2$ was also found as a useful precatalyst for this reaction but was studied in two cases only because it is a costly chemical]. A variety of structurally diverse amines (as shown in Table 1) were screened for the present type of reaction; treatment of the substrates with acetic acid separately in the presence of catalytic amount of each of the metal acetates, and each of the metal oxides at reflux temperature afforded the corresponding *N*-acetyl derivatives in excellent yields. No other solvent was required for smooth running of the reaction. The results of the selective *N*-acetylation of amines using a catalytic amount of metal acetates and also of metal oxides in acetic acid (Scheme 1) are shown in Table 1 and Table 2, respectively; the overall observations amply demonstrate the generality and scope of the reaction with regard to structurally diverse amines. The reaction course was monitored by thin layer chromatography (TLC) and IR spectra. The work-up and isolation of the acetylated products were easy; in most of the cases a chromatographic technique for isolation of the products was not required. All the acetylated products were characterised on the basis of elemental analyses and physical as well as spectroscopic properties; the observed melting points/boiling points, IR and ^{1}H NMR spectral data were in full agreement with the values reported for authentic samples, and also with those reported in the literature (as referred to in Table 1).

The present method is very simple in nature involving no drastic reaction conditions; the reagents used are also not hazardous and toxic. As shown in Table 1, the process affords excellent yields within a reasonable reaction time-frame; the newly developed methodology is not only efficient and environmentally benign, but also offers a cheap as well as a readily available acetylating agent. Hence, our present methodology is anticipated to draw attention for its immense application in large scale production as well. In most of the cases, the reaction was completed within 0.25–4.5 h with more than 90% of yield. The reaction is applicable to both aromatic and aliphatic amines; the most fascinating feature of this present reaction scheme is its chemoselectivity — the process is selective for amines in the presence of alcohols (both aliphatic and aromatic), thiols, and also tolerant of some other functionality as evidenced from the experimental results shown in Table 1. The aminoalcohols and aminophenols (entries 17,18,38–40) underwent smooth acetylation under the reaction procedure only at the amino group. Like hydroxy groups, thiols did not get acetylated under the reaction condition (entries 14–16). Amino-acetic acid (glycine), a natural aminoacid, was also found to be acylated effectively at the amino group following this procedure (entry 19). In one case (entry 30), this reaction was also applied to a hydrazine substrate successfully with *N*-acetylation only at the primary amino group; thus for hydrazine derivatives where both 1^0- and 2^0-amino groups are present, it appears that it is only the 1^0- amino group that will undergo acetylation under this reaction. This is also a notable feature of this present procedure.

For better understanding of the role of metal acetate in this present reaction, we studied whether such acetylation of amines could be carried out using a metal acetate only, in the absence of acetic acid or any other solvent; we have chosen zinc acetate for this purpose. A mixture of amine and zinc acetate (1:1 mol ratio) in finely ground form was placed in a properly sealed container, and heated in an oil-bath (see Experimental). The experimental results revealed that zinc acetate alone is capable of carrying out the desired transformation; a number of amino compounds were converted into the corresponding *N*-acetyl derivatives retaining the chemoselectivity intact with moderate yields. The reaction course and yields of the products are summarised in Table 3.

Thus, zinc acetate can act as an acetylating agent for selective *N*-acetylation of amines. From the reaction course, we assume that the relatively more nucleophilic amino group within the substrate molecules makes a nucleophilic attack at the metal-bound carbonyl carbon (Scheme 2) resulting the corresponding *N*-acetyl derivative and zinc oxide. This mechanism was supported by the isolation of zinc oxide from the resulting reaction mixture.

It has earlier been mentioned that a catalytic amount of metal acetate in acetic acid is sufficient enough to bring out the conversion. Now, we are interested to look into the exact role of metal acetate in the presence of acetic acid under the reaction condition. For this purpose also, zinc acetate was selected. Interestingly, on completion of the reaction (with aniline) we isolated the product along with zinc acetate derivative from the reaction mixture, and this recovered metal acetate derivative can successfully be reused for carrying out the transformation (for three times; Table 4). As per Scheme 2, metal acetate (*e.g.* zinc acetate) is converted into a metal oxide (*e.g.* zinc oxide) during reaction; but in the presence of acetic acid, it is the metal acetate that is isolated. Hence, we may assume that the metal oxide, formed initially, is converted into a metal acetate derivative in the presence of excess acetic acid under the reaction conditions; consequently, a minute amount of metal acetate is sufficient enough to carry on the reaction following a catalytic cycle. If this assumption is correct, then a metal oxide in the presence of acetic acid can also act as an acetylating system. Such presumption motivated us to carry out the reaction with amines in the presence of a catalytic amount of zinc oxide in acetic acid; the experimental observations (Table 2) revealed that the reaction course is almost comparable to that with zinc acetate in the acetic acid system (Table 1). Successful chemoselective *N*-acetylation of amines was also achieved under this metal oxide/acetic acid system (Table 2). During isolation of the acetylated products, we also recovered zinc acetate instead of zinc oxide from the resulting reaction mixture, which can be reused. Thus, it may be concluded that the metal oxide is definitely converted to the metal acetate in the presence of acetic acid under the reaction condition as per our mechanistic assumption. To establish the generality of the reaction, we used six metal acetates as well as five metal oxides as pre-catalysts (Tables 1 and 2). We also carried out control experiments with a variety of amines by refluxing them in acetic acid in the absence of any metal salt – in all these cases

Table 1 *N*-Acetylation of amines with catalytic amount of metal acetate(s) in acetic acid; melting points of the *N*-acetylated products along with their literature values

Entry	Amines	Products	Metal acetates												Melting points of *N*-acetylated products	
			Sodium acetate		Calcium acetate		Magnesium acetate		Manganese acetate		Copper acetate		Zinc acetate		Found /°C	Lit. /°C
			Time /h	% Yield[a]	Time /h	% Yield[a]	Time /h	% Yield[a]	Time /h	% Yield[a]	Time /h	% Yield[a]	Time /h	% Yield[a]		
1	*n*-Propylamine	*N*-Propylacetamide	2.66	94	2.75	95	2.75	92	2.75	90	2.66	91	2.66	96	222–225[b]	222–225[b,47,48]
2	*n*-Butylamine	*N*-Butylacetamide	2.66	92	2.75	93	2.75	90	2.75	92	2.66	90	2.66	94	227–229[b]	229[b,49,50]
3	Aniline	*N*-Phenylacetamide	2.75	98	2.5	97	2.5	98	2.33	98	2.5	99	2.5	99	112–114	114[51]
4	Benzylamine	*N*-Benzylacetamide	3.15	85	3.0	87	2.8	88	3.0	87	3.0	88	3.0	88	58–59	60[51]
5	3-Methoxy-benzylamine	*N*-(3-Methoxybenzyl)-acetamide	3.15	91	3.25	91	3.25	90	3.15	94	3.25	92	3.15	95	59–61	58–59[52,53]
6	4-Methoxy-benzylamine	*N*-(4-Methoxybenzyl)-acetamide	3.0	93	3.10	92	3.10	89	3.0	93	3.10	93	3.0	96	86–88	87–89[54]
7	1-Phenyl-ethylamine	*N*-(1-Phenylethyl)-acetamide	2.75	95	2.75	90	2.66	92	2.66	94	2.75	93	2.75	92	78–79	79–80[12,55]
8	Phenethylamine	*N*-(Phenethyl)-acetamide	3.10	70	3.0	72	3.0	71	3.0	73	3.0	70	3.0	74	49–50	51[45,51]
9	Naphthalen-1-ylamine	*N*-Naphthalen-1-yl-acetamide	3.5	90	3.15	91	3.25	92	3.15	93	3.25	94	3.25	90	158–160	160[45,51]
10	Naphthalen-2-ylamine[c]	*N*-Naphthalen-2-yl-acetamide	3.15	95	2.5	95	2.5	98	2.5	97	2.75	99	2.25	95	132–133	134[51]
11	Phenol	–	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction	–	–
12	4-Methylphenol	–	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction	–	–
13	Naphthalen-2-ol	–	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction	–	–
14	Benzenethiol	–	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction	–	–
15	Mercaptoacetic acid	–	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction	–	–
16	4-Aminobenze-nethiol	*N*-(4-Mercaptophenyl)-acetamide	3.15	91	3.15	92	3.5	89	3.15	87	3.15	89	3.0	92	156–158	157–159[56,57]
17	2-Aminoethanol	*N*-(2-Hydroxyethyl)-acetamide	3.0	92	3.15	93	3.15	92	3.0	90	3.0	91	2.75	94	194–196[b]	195–196[58]
18	1-(4-Amino-phenyl)-ethanol	*N*-[4-(1-Hydroxyethyl)-phenyl]-acetamide	3.25	92	3.25	91	3.15	90	3.25	94	3.25	92	3.15	93	68–70	68–71[59–62]
19	Aminoacetic acid (glycine)	Acetylaminoacetic acid	3.15	90	3.15	92	3.0	91	3.15	90	3.0	93	3.0	95	203–205	206[63,64]
20	*o*-Tolylamine	*N*-*o*-Tolylacetamide	2.66	90	2.75	92	3.0	93	2.75	92	2.5	95	3.0	90	112	112[51,65]
21	*p*-Tolylamine	*N*-*p*-Tolylacetamide	0.75	94	0.66	99	0.5	99	0.50	95	0.33	99	0.25	98	152–153	154[12,51]
22	2-Methoxy-phenylamine	*N*-(2-Methoxypheny)-acetamide	4.0	85	3.75	80	4.0	82	4.0	85	3.5	90	2.75	95	86–87	88[51,66]
23	4-Methoxy-phenylamine	*N*-(4-Methoxypheny)-acetamide	2.0	98	2.0	95	2.0	97	2.0	98	2.25	98	2.75	96	128–130	130[12,51]
24	2-Chlorophenyl-amine	*N*-(2-Chloro-pheny)-acetamide	2.5	95	2.5	97	2.5	95	2.5	96	2.25	95	2.25	95	88	88[51,67]
25	4-Chlorophenyl-amine	*N*-(4-Chloropheny)-acetamide	2.15	95	2.0	96	2.5	95	2.25	94	2.0	98	2.25	97	178	179[43,51]
26	4-Bromophenyl-amine	*N*-(4-Bromopheny)-acetamide	3.0	99	3.0	98	3.0	97	3.0	98	2.75	98	2.75	96	166–167	168[51,68,69]
27	1-(4-Amino-phenyl)-ethanone	*N*-(4-Acetylphenyl)-acetamide	4.66	99	4.75	92	4.0	86	4.5	93	4.0	88	4.5	98	165–166	167[43,51]
28	2-Aminobenzoic acid	2-Acetylaminobenzoic acid	6.0	70	6.0	72	6.0	71	6.0	72	5.5	74	5.0	71	184	185[12,51]

Table 1 *Continued*

Entry	Amines	Products	Metal acetates												Melting points of *N*-acetylated products	
			Sodium acetate		Calcium acetate		Magnesium acetate		Manganese acetate		Copper acetate		Zinc acetate		Found /°C	Lit. /°C
			Time /h	% Yield[a]	Time /h	% Yield[a]	Time /h	% Yield[a]	Time /h	% Yield[a]	Time /h	% Yield[a]	Time /h	% Yield[a]		
29	4-Aminobenzoic acid	4-Acetylaminobenzoic acid	3.0	70	2.5	65	2.5	76	2.75	74	3.0	98	2.25	98	250–252	251[51]
30	(2,4-Dinitrophenyl)-hydrazine	Acetic acid *N*-(2,4-dinitrophenyl)-hydrazide	0.5	98	0.5	98	0.5	99	0.5	97	0.5	98	0.5	98	196–198	198[51]
31	3-Nitrophenylamine	*N*-(3-Nitrophenyl)-acetamide	3.5	90	3.5	91	3.5	90	3.5	90	3.5	93	3.5	91	154	155[45,51]
32	4-Nitrophenylamine	*N*-(4-Nitro-phenyl)-acetamide	4.5	80	4.5	79	5.0	70	5.5	75	4.5	85	5.5	82	215–216	216[12,51]
33	Cyclohexylamine	*N*-Cyclohexylacetamide	3.0	80	3.0	80	3.0	81	3.0	82	3.0	85	3.0	79	101–103	104[43,51]
34	Piperidine	1-Piperidin-1-yl-ethanone	3.5	82	4.15	84	3.5	81	3.15	79	3.0	82	3.0	87	224–226	226–227[66,70]
35	Morpholine	1-Morpholin-4-yl-ethanone	0.75	91	0.75	92	0.75	92	0.75	93	0.55	92	0.5	92	Oil	14[7,66]
36	Methylphenylamine	*N*-Methyl-*N*-phenyl-acetamide	4.0	62	4.15	60	3.5	62	3.25	60	3.15	61	3.5	65	101–104	103[51,71]
37	Diphenylamine	*N,N*-Dipheylacetamide	10.0	40	8.5	41	8.5	43	8.5	41	8.15	40	8.0	45	100–102	103[51]
38	2-Aminophenol	*N*-(2-Hydroxyphenyl)-acetamide	6.0	92	5.5	91	5.5	92	5.5	90	5.15	92	5.0	94	207–209	209[70]
39	3-Aminophenol	*N*-(3-Hydroxyphenyl)-acetamide	3.0	97	3.0	94	3.0	92	3.0	90	3.0	96	3.0	95	146–148	149[70,72]
40	4-Aminophenol	*N*-(4-Hydroxyphenyl)-acetamide	2.5	77	2.5	72	2.5	75	2.5	77	2.5	78	2.5	80	166–167	168[12,70,73–75]

[a]Yields are of pure isolated products characterised by their physical constants, spectroscopic characteristics (FT-IR, ^{1}H NMR) as compared with those of authentic samples (commercially available or prepared as per reported methods) as well as with reported values in the literature.
[b]Boiling point.
[c]2-Naphthylamine (β-naphthylamine, naphthalene-2-amine) is a known potent human carcinogen (see Caution). In the UK it appears in Schedule 2 of the Control of Substances Hazardous to Health Regulations (COSSH) 1999 which prohibits its "manufacture and use for all purposes".

Table 2 *N*-Acetylation of amines with catalytic amount of metal oxide(s) in acetic acid

Entry	Amines	Products	Metal oxides									
			MgO		CaO		Al_2O_3		Cr_2O_3		ZnO	
			Time/h	% Yield[a]	Time/h	% Yield[a]	Time/h	% Yield[a]	Time/h	% Yield[a]	Time/h	% Yield[a]
1	*n*-Propylamine	*N*-Propylacetamide	2.5	91	2.75	96	2.5	97	2.66	92	2.75	95
2	Aniline	*N*-Phenylacetamide	2.5	98	2.5	97	2.33	98	2.5	98	2.33	99
3	Naphthalen-2-ol	–	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction
4	4-Aminobenzenethiol	*N*-(4-Mercaptophenyl)-acetamide	3.5	90	3.5	93	3.15	92	3.5	91	3.0	94
5	2-Aminoethanol	*N*-(2-Hydroxyethyl)-acetamide	3.15	91	3.25	93	3.25	93	3.15	89	3.0	95
6	1-(4-Aminophenyl)-ethanol	*N*-[4-(1-Hydroxyethyl)-phenyl]-acetamide	3.25	90	3.15	88	3.15	89	3.0	90	3.15	91
7	Aminoacetic acid	Acetylaminoacetic acid	3.25	91	3.15	89	3.0	91	3.25	89	3.15	92
8	*p*-Tolylamine	*N*-*p*-Tolylacetamide	0.33	90	0.33	92	0.33	91	0.33	93	0.33	95
9	4-Methoxyphenylamine	*N*-(4-Methoxypheny)-acetamide	2.25	96	2.33	92	2.25	95	2.25	93	2.0	98
10	4-Chlorophenylamine	*N*-(4-Chloropheny)-acetamide	2.33	95	2.25	94	2.25	93	2.15	91	2.0	96
11	1-(4-Aminophenyl)-ethanone	*N*-(4-Acetylphenyl)-acetamide	4.75	94	5.0	86	4.5	95	4.5	91	4.25	90
12	4-Aminobenzoic acid	4-Acetylaminobenzoic acid	2.15	85	2.15	81	2.15	84	2.15	85	2.15	88
13	(2,4-Dinitrophenyl)-hydrazine	Acetic acid *N*-(2,4-dinitrophenyl)-hydrazide	0.5	98	0.5	97	0.5	96	0.5	92	0.5	98
14	4-Nitrophenylamine	*N*-(4-Nitrophenyl)-acetamide	4.25	80	4.25	80	5.15	72	5.25	70	4.25	78
15	Cyclohexylamine	*N*-Cyclohexylacetamide	2.75	80	2.75	78	2.5	83	3.0	82	2.75	85
16	Methylphenylamine	*N*-Methyl-*N*-phenyl-acetamide	4.15	61	4.15	60	3.75	62	3.5	60	3.25	61
17	4-Aminophenol	*N*-(4-Hydroxyphenyl)-acetamide	3.0	75	2.75	72	2.5	75	2.75	71	2.5	76
18	Benzenethiol	–	20	No reaction	20	No reaction	20	No reaction	20	No reaction	20	No reaction

[a] Yields are of pure isolated products characterised by their physical constants, spectroscopic characteristics (FT-IR, ^{1}H NMR). as compared with those of authentic samples (commercially available or prepared as per reported methods) as well as with reported values in the literature.

Table 3 *N*-Acetylation of amines with zinc acetate without acetic acid

Entry	Amines	Time/h	% Yield[a]
1	*n*-Propylamine	2.75	58
2	Aniline	3.0	60
3	1-Phenylethylamine	3.0	60
4	4-Aminobenzenethiol	3.15	60
5	2-Aminoethanol	3.0	66
6	1-(4-Aminophenyl)ethanol	3.5	62
7	Aminoacetic acid	3.5	68
8	*p*-Tolylamine	3	64
9	2-Chlorophenylamine	3.5	54
10	4-Chlorophenylamine	1.5	53
11	4-Bromophenylamine	3	61
12	1-(4-Aminophenyl)-ethanone	4	63
13	4-Aminobenzoic acid	4	62
14	3-Nitrophenylamine	4	69

[a]Yields are of pure isolated products characterised by their physical constants, spectroscopic characteristics (FT-IR, ^{1}H NMR) as compared with those of authentic samples (commercially available or prepared as per reported methods) as well as with reported values in the literature.

the reactions were found to be unsatisfactory; minor amounts of conversion are observed only after prolonged heating (see Experimental).

In conclusion, we have demonstrated metal acetate or metal oxide in acetic acid as a novel and highly efficient acetylating system for the chemoselective *N*-acetylation of primary and secondary amines in excellent yields at reflux temperature; it has also been shown that metal acetate alone can act as a selective *N*-acetylating agent in the absence of acetic acid. To the best of our knowledge, this is the first report on chemoselective *N*-acetylation of all types of amines under green conditions. This newly developed chemoselective procedure for the *N*-acetylation of a wide variety of structurally diverse amines by the use of a catalytic amount of metal acetate or metal oxide (as pre-catalyst) in acetic acid represents a tremendous opportunity for the practice of green chemistry. The major advantages of this environmentally benign and safe protocol include a simple reaction setup, mild reaction condition, high efficiency, moderate reaction times, the possibility for reusing the catalyst, chemoselectivity, and obviously use of innocuous, cost-effective and readily available reagents. Hence, we are optimistic that this present methodology as a whole would find itself as a useful alternative for large scale production in the future.

Experimental

General remarks

All the reagents and the solvents (analytical grade) as used were purchased from reputed commercial suppliers. All the solvents were dried before use. IR spectra were recorded in KBr discs on a Shimadzu 8201 PC–IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DRX-400 NMR spectrometer in $CDCl_3$/acetone-d_6 with TMS as internal reference. Melting points were recorded on a Vego melting point apparatus and were uncorrected. Column chromatographic separations were carried out on SRL silica gel (60–120 mesh) using EtOAc/petroleum ether as eluent. Organic extracts were dried with anhydrous sodium sulfate and the solvents were removed in a rotary evaporator under reduced pressure. Reactions were monitored by TLC on silica-gel 60 F_{254} (Merck). A water condenser having a $CaCl_2$ guard-tube was used for refluxing the reaction mixture. A sealed tube (15 mL) from Tensil Pvt. Ltd was used in solid phase reactions.

Caution: 2-Naphthylamine (β-naphthylamine, naphthalene-2-amine) is a known potent human carcinogen. In the United Kingdom it appears in Schedule 2 of the Control of Substances Hazardous to Health Regulations (COSSH) 1999 which prohibits its "manufacture and use for all purposes".

Acetylation of amines using metal acetates as precatalysts; general procedure

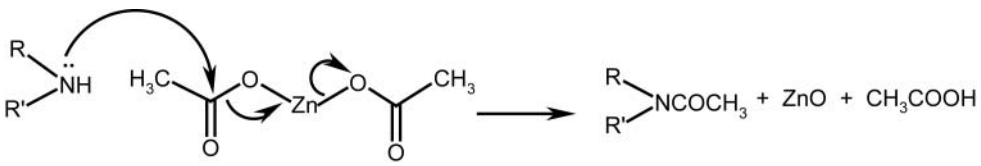
To a mixture of CH_3COOH (1.2 mL) and metal acetate (0.25 mmol), an amine (1 mmol) was added and then the reaction mixture was refluxed with gentle heating for a length of time as indicated in Table 1. The progress of the reaction was monitored by TLC. After the reaction was complete, CH_2Cl_2 or EtOAc was added to the reaction mixture, and the metal acetate was removed by filtration. The organic solution was then washed with a saturated solution of $NaHCO_3$ and also with H_2O (2 × 10 mL), and then dried over anhydrous Na_2SO_4. After removal of the solvent (in a rotary evaporator under reduced pressure), the product was obtained; it was then purified by recrystallisation with a suitable solvent. Column chromatographic techniques were used to purify the product whenever required. The structure of the products was confirmed by physical and spectral studies (IR and ^{1}H NMR) in addition to comparison with authentic samples obtained commercially or prepared by reported methods.

Alternative procedure

To a mixture of CH_3COOH (1.2 mL) and metal acetate (0.25 mmol) was added an amine (1 mmol) and then the reaction mixture was refluxed with gentle heating for the length of time indicated in Table 1. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was added in 20 mL ice cold water with vigorous stirring. The acetylated product precipitated within 5-10 min. The precipitated product was filtered, washed with water (2 × 10 mL), dried by pressing between folds of filter paper and finally dried in a vacuum desiccator. In cases where the product did not precipitate, the reaction mixture was extracted with ethyl acetate (2 × 25 mL). The organic solvent was then washed with a saturated solution of $NaHCO_3$ and also with H_2O (2 × 10 mL), and after then dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the product was obtained with almost identical yields as recorded for the earlier procedure; it was then purified by recrystallisation with a suitable solvent. A column chromatographic technique was used to purify the product whenever required. The structure of the products was confirmed by physical and spectral studies (IR and ^{1}H NMR) in addition to comparison with authentic samples obtained commercially or prepared by reported methods.

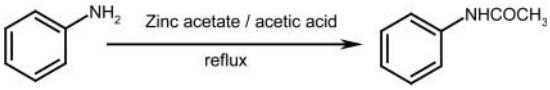
Acetylation of amines using metal oxides as precatalysts; general procedure

To a mixture of CH_3COOH (1.2 mL) and metal oxide (0.3 mmol) was added an amine (1 mmol), and then the reaction mixture was refluxed with gentle heating for a length of time indicated in Table 2. On completion of the reaction as monitored by TLC, CH_2Cl_2 or EtOAc was added to the reaction mixture and metal acetate was removed by filtration. The organic solvent was then washed with a saturated solution of $NaHCO_3$ and also with H_2O (2 × 10 mL), and after then dried over anhydrous Na_2SO_4. After removal of the solvent (with the help of rotary evaporator under reduced pressure), the product was obtained;



Scheme 2 Nucleophilic attack of amino group at the metal-bound carbonyl carbon.

Table 4 Reuse of zinc acetate



No. of uses	Product yield /%	Recovery of zinc acetate /%
1	96	98
2	92	93
3	89	91

it was then purified by recrystallisation with a suitable solvent. A column chromatographic technique was used to purify the product whenever required. The structure of the products was confirmed by physical and spectral studies (IR and ^{1}H NMR) in addition to comparison with authentic samples obtained commercially or prepared by reported methods

Acetylation of amines with zinc acetate without using acetic acid; general procedure

Finely ground amine (1 mmol) and zinc acetate dihydrate (1 mmol) was placed in a 25 mL tube which was then sealed. This was heated in an oil bath at 150 °C and stirred with a magnetic stirrer for 3–4 h (Table 3). On completion of reaction, the sealed tube was cooled and then the reaction mixture was extracted with EtOAc (2 × 25 mL). The organic solvent (separated by filtration) was then washed with a saturated solution of $NaHCO_3$ and also with H_2O (2 × 10 mL) and then dried over anhydrous Na_2SO_4. After removal of the solvent, the product was obtained which was purified by recrystallisation with a suitable solvent. A column chromatographic technique was used to purify the product. The structure of each of the products was confirmed by IR and ^{1}H NMR spectra as well as by TLC comparison with authenticated samples.

Control experiment with amines

A mixture of an amine (1 mmol) and CH_3COOH (1.2 mL) in the absence of any metal salt (metal acetate/metal oxide) was refluxed for a prolonged length of time (14–16 h), and then worked-up following the same procedure as discussed in earlier sections. The percentage of isolated yields (obtained after column chromatographic resolution) of the corresponding *N*-acetylated products were found to be very poor in comparison to those obtained in the newly developed method (Tables 1 and 2). *Representative entries* : *n*-propylamine (yield, 16%; refluxing period, 12 h); *N*-methylaniline (yield, 19%; refluxing period, 14 h); *p*-methoxylaniline (yield, 24%; refluxing period, 12 h); 4-nitroaniline (yield, 21%; refluxing period, 16 h).

Reuse of metal acetate

On completion of the reaction with aniline, the reaction mixture was extracted with ethyl acetate; the metal acetate was filtered off, washed with dichloromethane, dried for 1 h at 110 °C, and then reused in another reaction (Table 4).

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References

1 T.W. Greene and P.G.M. Wuts, *Protective groups in organic synthesis*, 3rd edn, Wiley, New York, 1999, pp.150.
2 L. Pearson, W.J. Roush, *Handbook of reagents for organic synthesis: activating agents and protecting groups*, John Wiley and Sons, Chichester, UK, 1999, pp 9–16.
3 G. Hofle, W. Steglich and H. Vorbruggen, *Angew. Chem. Int. Ed.*, 1978, **17**, 569.
4 E. Vedejs and S.T. Diver, *J. Am. Chem. Soc.*, 1993, **115**, 3358.
5 E. Vedejs, N.S. Bennet, L.M. Conn, S. T. Diver, M. Gingras, S. Lin, P. A. Oliver and M.J. Peterson, *J. Org. Chem.*, 1993, **58**, 7286.
6 S. Paul, P. Nanda, R. Gutpa and A. Loupy, *Tetrahedron Lett.*, 2002, **43**, 4261.
7 A.K.Chakraborti and R. Gulhane, *Chem. Commun.*, 2003, 1896.
8 K.K. Chauhan and C.G. Frost, *J. Chem. Soc. Perkin Trans.*, 2000, 3015.
9 S.K. De, *Tetrahedron Lett.*, 2004, **45**, 2919.
10 A. Li, T. Li and T. Ding, *Chem. Commun.*, 1997, 1389.
11 B. Zeynizadeh and K. Zahmatkesh, *J. Chin. Chem. Soc.*, 2004, **51**, 801.
12 S. Naik, G. Bhattacharjya, B. Talukdar and B.K. Patel, *Euro. J. Org. Chem.*, 2004, 1254.
13 A.T. Khan, L.H. Choudry and S. Ghosh, *Eur. J. Org. Chem.*, 2005, 2782.
14 P. Saravanan and V.K. Singh, *Tetrahedron Lett.*, 1999, **40**, 2611.
15 E.F.V. Scriven, *Chem. Soc. Rev.*, 1983, **12**, 129.
16 S.P. Chavan, R. Anand, K. Pasupathy and B.S. Rao, *Green Chem.*, 2001, **3**, 320.
17 P. Lidstrom, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, 2001, **57**, 9225.
18 A.K. Chakraborti, R. Gulhane and Shivani, *Synthesis*, 2004, 111.
19 A.T. Khan, S. Islam, A. Majee, T. Chattopadhyay and S. Ghosh, *J. Mol. Cat. A*, 2005, **239**, 158.
20 D. Xu, K. Prasad, O. Repic and T.J. Blacklock, *Tetrahedron Lett.*, 1995, **36**, 7357.
21 Y. Murakami, K. Kondo, K. Miki, Y. Akiyama, T. Watanabe and Y. Yokoyama, *Tetrahedron Lett.*, 1997, **38**, 3751.
22 I. Azumaya, T. Okamoto, F. Imabeppu and H. Takayanagi, *Tetrahedron*, 2003, **59**, 2325.
23 A.R. Katrizky, C. Cai and S.K. Singh, *J. Org. Chem.*, 2006, **71**, 3375.
24 T. Kunieda, T. Higuchi, Y. Abe and M. Hirobe, *Tetrahedron Lett.*, 1982, **23**, 1159.
25 Y.-J. Kang, H.-A. Chung, J.-J. Kim and Y.-J. Yoon, *Synthesis*, 2002, 733.
26 T.A. Dineen, M.A. Zajac and A.G. Myers, *J. Am. Chem. Soc.*, 2006, **128**, 16406.
27 R.S. Atkinson, E. Barker and M.J. Sutcliffe, *Chem. Commun.*, 1996, 1051.
28 Y. Kikugawa, K. Mitsui, T. Sakamoto, M. Kawase and H. Tamiya, *Tetrahedron Lett.*, 1990, **31**, 243.
29 K. Kondo, E. Sekimoto, J. Nakao and Y. Murakami, *Tetrahedron*, 2000, **56**, 5843.
30 M.-J. Kim, W.-H. Kim, K. Han, Y.K. Choi and J. Park, *Org. Lett.*, 2007, **9**, 1157.
31 W.-J. Yoo and C.-J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 13064.
32 L. Kisfaludy, T. Mohacsi, M. Low and F. Drexler, *J. Org. Chem.*, 1979, **44**, 654.
33 A.R. Katritzky, H.-Y. He and K. Suzuki, *J. Org. Chem.*, 2000, **65**, 8210.
34 K. Ishihara, M. Kubota, H. Kurihara and H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4560.
35 P.A. Procopiou, S.P.D. Baugh, S.S. Flack and G.G.A. Inglis, *J. Org. Chem.*, 1998, **63**, 2342.
36 K.K. Chauhan, C.G. Frost, I. Love and D. Waite, *Synlett.*, 1999, 1743.
37 P. Saravanan and V.K. Singh, *Tetrahedron Lett.*, 1999, **40**, 2611.
38 K.L.Chandra, P. Saravanan, R.K. Singh and V.K. Singh, *Tetrahedron*, 2002, **58**, 1369.
39 R. Dalpozzo, A.D. Nino, L. Maiuolo, A. Procopio, M. Nardi, G.I. Bartol and R. Romeo, *Tetrahedron Lett.*, 2003, **44**, 5621.
40 A. Orita, C. Tanahashi, A. Kakuda and J. Otera, *Angew. Chem. Int. Ed.*, 2000, **39**, 2877.
41 M.L. Kantam, K. Aziz and P.R. Likhar, *Catal. Commun.*, 2006, **7**, 484.
42 A.T. Khan, L.H. Choudhury and S. Ghosh, *Eur. J. Org. Chem.*, 2005, 2782.
43 K.V.V. Krishna Mohan, N. Narender and S.J. Kulkarni, *Green Chem.*, 2006, **8**, 368.
44 S. Farhadi and M. Zaidi, *J. Mol. Catal. A*, 2009, **299**, 18.
45 B. Das, P. Thirupathi, R.A. Kumar and K. Laxminarayana, *Adv. Synth. Catal.*, 2007, **349**, 2677.
46 G. Brahmachari and S. Laskar, *Tetrahedron Lett.*, 2010, **51**, 2319.
47 *Dictionary of organic compounds*, 4th edn, Chapmann and Hall, London, 1965, Vol. 5, p 2790.
48 B. Das and P. Thirupathi, *J. Mol Cat. A.*, 2007, **269**, 12.
49 J.R. Salim, *Synth. Commun.*, 1989, **19**, 1181.
50 H. Eshghi, *J. Chem. Res.*, 2004, **No. 12**, 802.
51 B.S. Furniss, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell, *Vogel's textbook of practical organic chemistry*, 5th edn, Longman: ELBS, 1991, pp. 1370.
52 P.J. Garratt, S. Travard, S. Vonhoff, A. Tsotinis and D. Sugden, *J. Med. Chem.*, 1996, **39**, 1797.
53 F. Tamaddon, M. Khoobi and E. Keshavarz, *Tetrahedron Lett.*, 2007, **48**, 3643.
54 P. Salehi and A.R. Motlagh, *Syn. Commun.*, 2000, **30**, 671.
55 K. Kondo, E. Sekimoto, J. Nakao and Y. Murakami, *Tetrahedron*, 2000, **56**, 5843.
56 Y. Jiang, *Org. Lett.*, 2009, **11**, 5250.
57 R.S. Sengar, *New J. Chem.*, 2003, **27**, 1115.
58 H. Wenker, *J. Am. Chem Soc.*, 1935, **57**, 1079.
59 S. Nagamine, T. Otawa, H. Nakae and S. Asada, *Chem. Pharm. Bull.*, 1988, **36**, 4612.
60 S. Inui and S. Asada, *Yakugawa Zasshi*, 1987, **107**, 904.
61 R. Taylor, G.G. Smith and W.H. Wetzell, J. *Am. Chem. Soc.*, 1962, **84**, 4817.

62 J. Wettergren, A. Bogevig, M. Portier and H. Adolfsson, *Adv. Synth. Catal.*, 2006, **348**, 1277.
63 *Dictionary of organic compounds*, 4th edn, Chapmann and Hall, London, 1965, Vol.1, p 21.
64 H. Dakin, *J. Biol. Chem.*, 1929, **82**, 439.
65 S.J. Tremont and H.U. Rahman, *J. Am. Chem. Soc.*, 1984, **106**, 5759.
66 R. Gupta, V. Kumar, M. Gupta, S. Paul and R. Gupta, *Indian J. Chem.*, 2008, **47B**, 1739.
67 B.T. Gowda, I. Svoboda and H. Fuess, *Acta Crystallogr.*, 2007, **E63**, 3267 (doi:10.1107/S1600536807028991).
68 G.K. Chip and J.S. Grossert, *Can. J. Chem.*, 1972, **50**, 1233.
69 S.C. Bisarya and R. Rao, *Synth. Commun.*, 1993, **23**, 779.
70 *Dictionary of organic compounds*, 5th edn, Chapmann and Hall, London, 1982, Vol. 1, pp 304-305.
71 W.S. Fones, *J. Org. Chem.*, 1949, **14**, 1099.
72 M.M. Heravi, F.K. Behbahani, R.H. Shoar and H.A. Oskooie, *Cat. Commun.*, 2006, **7**, 136.
73 B.P. Bandgar, S.P. Kasture and V.T. Kamble, *Synth. Commun.*, 2001, **31**, 2255.
74 T. Higuchi and M. Hirobe, *Tetrahedron Lett.*, 1981, **22**, 1257.
75 M. Freifelder, *J. Org. Chem.*, 1962, **27**, 1092.