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Note

A green approach to chemoselective *N*-acetylation of amines using catalytic amount of zinc acetate in acetic acid under microwave irradiation[§]

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It has been found for the first time that zinc acetate alone can act as a selective *N*-acetylating agent without any solvent under closed vessel microwave irradiation. It is also observed that the use of a catalytic amount of this reagent in acetic acid is sufficient enough for smooth running of *N*-acetylation of a number of structurally diverse amines, and the reaction is chemoselective with respect to phenols, thiols, acids and alcohols. Herein is reported a simple, efficient, cost-effective and environmentally benign alternative method for chemoselective *N*-acetylation of amines using catalytic amount of zinc acetate in acetic acid under microwave irradiation. The reaction procedure requires no other solvent, and is rapid with good to excellent yields.

Keywords: Microwave irradiation, amines, acetic acid, zinc acetate, *N*-acetylation, chemoselectivity

In the past few years, use of microwave as energy resource to induce organic reactions has been under intense study with significant benefits in the area of organic synthesis as this protocol bears so many advantages compared to oil heating[1]. Microwave assisted organic syntheses are suited to the increased demands in industry, particularly because of short reaction time, selectivity, solvent free technique and also for the expanded reaction range[1,2]. The present report demonstrates the application of this microwave-assisted technique in the development of green methodology for C–N bond formation.

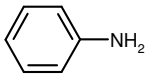
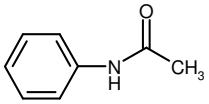
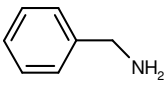
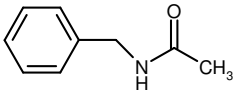
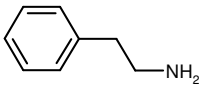
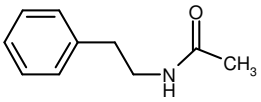
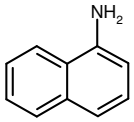
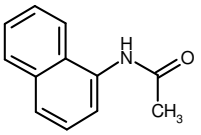
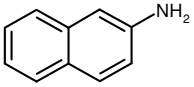
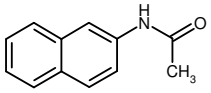
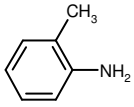
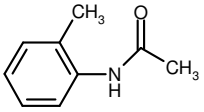
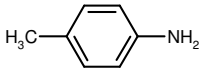
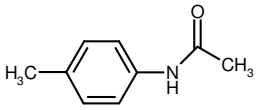
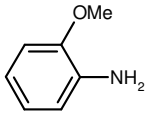
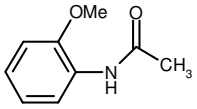
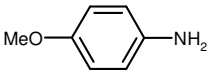
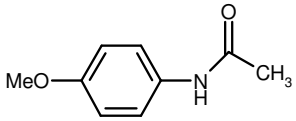
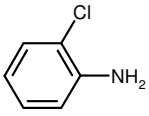
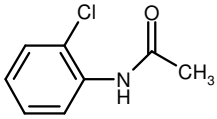
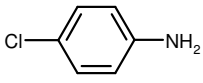
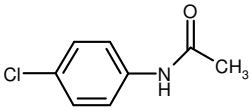
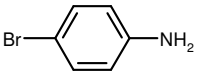
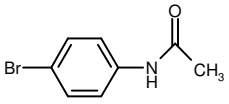
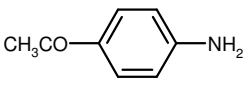
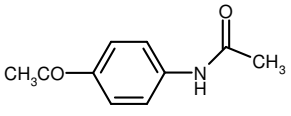
N-Acetylation reaction finds immense applications in organic syntheses[3]; the amide bond is found to be present in a large number of pharmacologically active molecules. Owing to its nucleophilic as well as reactive nature, selective protection of an amino group is usually needed during most of the multi-step organic syntheses including the synthesis of a diverse array of biological molecules such as amino acids, peptides, amino glycosides, β-lactams, nucleosides, alkaloids, *etc.*[4] *N*-Acetylation reaction is usually carried out with acetic anhydride or acetyl chloride in the presence of either acidic[5] or basic[6] catalysts in different conditions. These reactions bear certain advantages as well as a lot of disadvantages; such advantages and disadvantages were extensively described recently by Katritzky *et al.*[7]. Some 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 or acetyl chloride were used[8]. Some methods utilizing microwave irradiation have also been reported[9]. Instead of using such reagents, acetic anhydride (or acetyl chloride) is still regarded as the key *N*-acetylating agent, both in commercial as well as non-commercial sectors. However, both of these reagents, being corrosive and a lachrymator respectively are not always ideal.

Recently, Wang *et al.*[10] reported that acetic acid alone can act as an acetylating agent under microwave irradiation; but this method is applicable only to primary amines, and is not chemoselective — both hydroxy and amino groups have been shown to be acetylated. However, a chemoselective acetylation was reported very recently by Farhadi *et al.*[11] using bismuth ferrite ($BiFeO_3$) nanopowder, but this method involves the use of acetic anhydride/acetyl chloride.

Hence, development of novel and green methodologies using heterogeneous catalysts under solvent-free condition for simple, chemoselective and truly cost-effective synthesis of amide bond is still required for its usefulness in synthetic organic chemistry as well as in medicinal chemistry. Having this background, it is felt pertinent to report herein a chemoselective as well as an environmentally benign methodology for *N*-acetylation of amines. It has been found that zinc acetate, a benign and inexpensive chemical, alone can act as a selective *N*-acetylating agent in the absence of solvent under microwave irradiation (**Table I**) with moderate yields; but it is interesting to note that the use of a catalytic amount of this reagent (zinc acetate) in acetic acid under closed

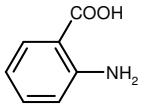
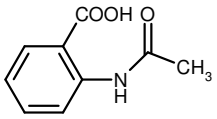
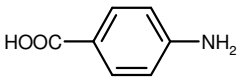
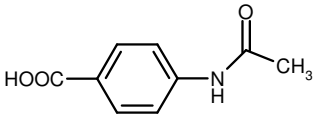
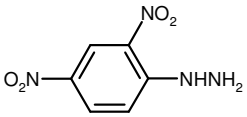
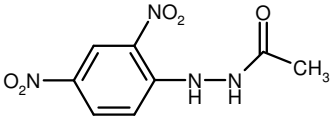
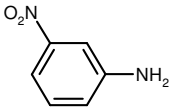
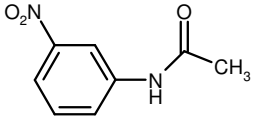
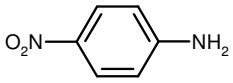
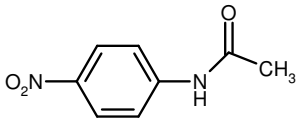
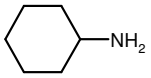
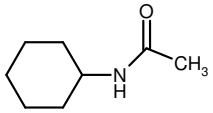
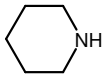
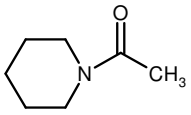
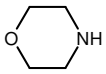
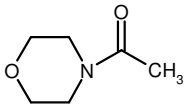
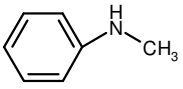
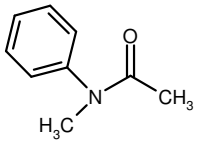
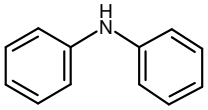
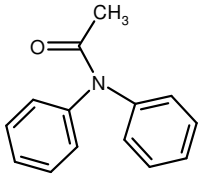
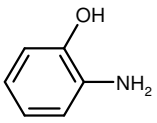
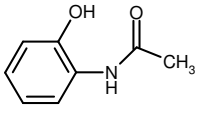
[§]A part of this work has been presented at the 11th CRSI National Symposium in Chemistry, 6-8 February 2009, National Chemical Laboratory, Pune, India.

Table I — *N*-Acetylation of amines using zinc acetate–acetic acid under microwave irradiation (300 W)

Entry	Substrate	Product	Time (min)	[a]Yield (%)	Melting point (°C)	
					Found	Literature
1			6	90	112-14	114 (Ref 12)
2			4	96	58-59	60 (Ref 12)
3			2	92	49-50	51 (Ref 12)
4			10	71	158-60	160 (Ref 12)
5[c]			10	82	132-33	134 [c](Ref 12)
6			11	91	112	112 (Ref 12)
7			1	98	152-53	154 (Ref 12)
8			5	90	86-87	88 (Ref 12)
9			1	98	128-30	130 (Ref 12)
10			13	81	88	88 (Ref 12)
11			3	90	178	179 (Ref 12)
12			10	80	166-67	167 (Ref 12)
13			26	91	165-66	167 (Ref 12)

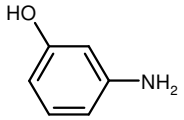
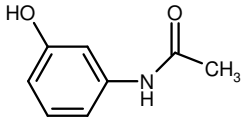
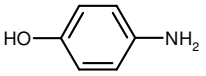
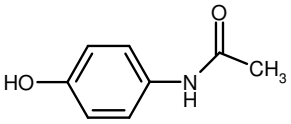
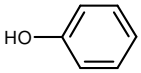
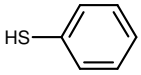
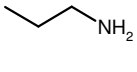
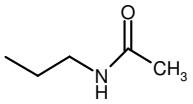
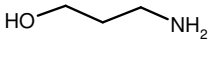
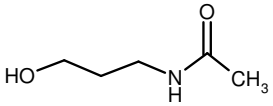
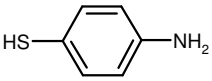
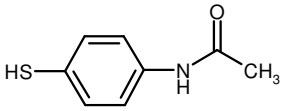
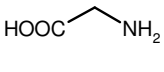
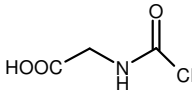
— Contd

Table I — *N*-Acetylation of amines using zinc acetate–acetic acid under microwave irradiation (300 W) — *Contd*

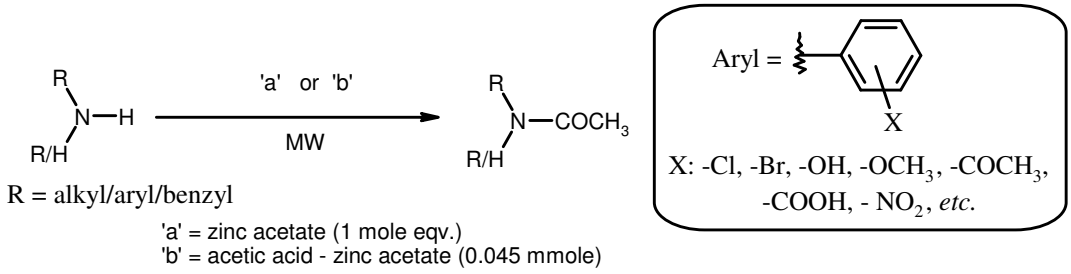
Entry	Substrate	Product	Time (min)	[a]Yield (%)	Melting point (°C)	
					Found	Literature
14			7	80	184	185 (Ref 12)
15			6	81	250-52	251 (Ref 12)
16			5	95	196-98	198 (Ref 12)
17			15	86	154	155 (Ref 12)
18			19	80	215-16	216 (Ref 12)
19			2	96	101-03	104 (Ref 12)
20			2	85	224-26[b]	226-27[b] (Ref 13)
21			2	87	Oil	14 (Ref 18)
22			7	62	102-04	103 (Ref 12)
23			15	40	100-02	103 (Ref 12)
24			16	95	207-09	209 (Ref 13)

— *Contdf*

Table I — *N*-Acetylation of amines using zinc acetate–acetic acid under microwave irradiation (300 W) — *Contd*

Entry	Substrate	Product	Time (min)	[a]Yield (%)	Melting point (°C) Found	Literature
25			10	93	146-48	148-49 (Ref 13)
26			14	80	166-67	168 (Ref 13)
27		No reaction	30	–	–	–
28		No reaction	30	–	–	–
29			4	81	223-25[b]	222-25[b] (Ref 14)
30			5	92	165-67[b]	166-67[b] (Ref 15)
31			6	89	150-52	151-53 (Ref 16)
32			4	88	203-05	206 (Ref 17)

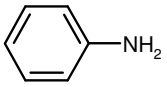
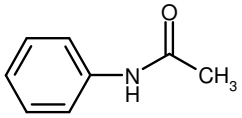
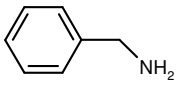
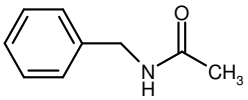
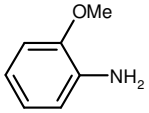
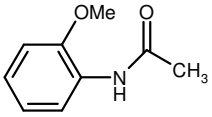
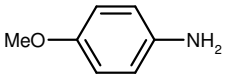
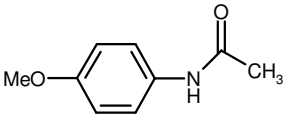
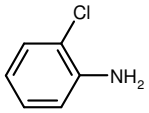
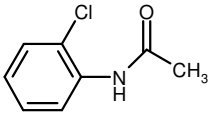
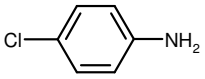
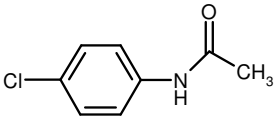
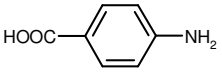
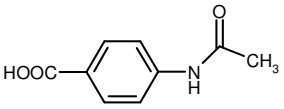
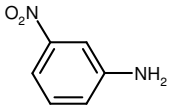
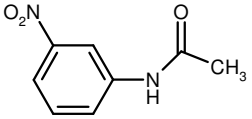
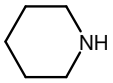
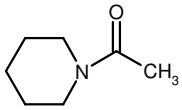
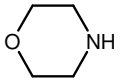
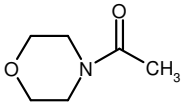
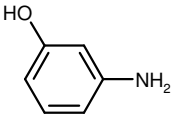
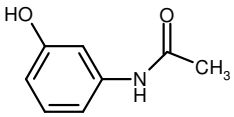
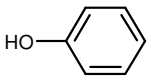
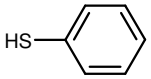
[a]Yields are of pure isolated products characterized by their physical constants, spectral characteristics (FT-IR, ^{1}H NMR) and comparison with authentic samples; [b]boiling point; [c]known to be a potent carcinogen and care must be taken in handling.



Scheme I

vessel microwave irradiation in a solvent free condition is sufficient enough for achieving chemoselective *N*-acetylation of amines (**Table I**). The present communication is aimed to highlight this modification in using zinc acetate because this modified method is more efficient with regard to chemoselectivity as well as reaction time and quantitative yield; the reaction completes within time-frames of minutes with good to excellent yields. No other solvent is required. Reagents used are non-toxic, cheap and readily available. Moreover, the present method is applicable to all types of amines and is completely *N*-selective (**Scheme I**) in

Table II — *N*-Acetylation of amines using zinc acetate under microwave irradiation (300 W)

Entry	Substrate	Product	Time (min)	[a]Yield (%)
1			20	91
2			5	94
3			8	60
4			15	62
5			16	63
6			18	66
7			24	51
8			11	48
9			12	79
10			12	86
11			15	49
12		No reaction	30	–
13		No reaction	30	–

[a]Yields are of pure isolated products characterized by their physical constants, spectral characteristics (FT-IR, ^{1}H NMR) and comparison with authentic samples

contrast to the reported method of Wang *et al.*, which involves the use of acetic acid only[10].

Results and Discussion

Catalytic amount of zinc acetate (0.045 mmole) in acetic acid acts as a highly effective acetylating reagent for selective *N*-acetylation of amines under closed-vessel microwave (CVMW) irradiation at 300 W; the reaction completes within short time-frames of minutes (monitored by TLC) with good to excellent yields. This simple and straightforward strategy of *N*-acetylation of amines is applicable to a wide variety of aliphatic, aromatic, primary and secondary amines with high yields. 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, catalytic amount of zinc acetate in acetic acid. The present methodology, thus, offers an efficient and environmentally safe protocol for chemoselective *N*-acetylation of amines using a cheap and readily available acetylating agent.

During development of the present method, aniline was first screened (**Table I**, entry 1) as the target substrate that afforded a good yield of acetanilide when treated with zinc acetate in acetic acid at 300 W in the micro-oven; this result prompted the screening of a number of structurally diverse amines shown in **Table I**. All types of amines (1°/2° and aliphatic/aromatic) were efficiently acetylated with more than 90% yield in most of the cases. The work up and isolation of the acetylated products was easy. Both aqueous and non aqueous work up can be adopted for the isolation of the products by this method. The products were characterized by comparison of their TLC, IR spectra, ^{1}H NMR spectra, and melting points with authentic samples. Aminophenols (**Table I**, entries 24-26) were easily acetylated selectively at the amino group with 80–90% yields. Now, the challenge was to establish the chemoselectivity of this method with respect to alcohols and thiols. Ethanolamine (**Table I**, entry 30) on treatment with catalytic amount of zinc acetate and acetic acid under MW furnished only the *N*-acetylated product leaving the alcoholic group free in the substrate molecule. Similar result was obtained with aminothiolphenol (**Table I**, entry 31); exclusive *N*-acetylation was achieved with good yield. This method was applied for the formation of amide bond in naturally available essential amino acids which is a demanding need of the medicinal chemists; a natural amino acid glycine (**Table I**, entry 32) was successfully *N*-acetylated with good yield in a short time. Hence, the newly developed methodology is not only efficient and environmentally safe, but also offers a cheap and readily available acetylating agent that would find immense application in synthetic organic chemistry.

The generality of the methodology was verified by using a variety of amino compounds containing different functionalities like $-OCH_3$, $-Cl$, $-Br$, $-OH$, $-SH$, $-COCH_3$, $-COOH$, $-NO_2$ *etc.*, and in each and every case these functionalities remained intact under the reaction condition. The present reagent (zinc acetate/acetic acid) selectively acetylates the amino group as evidenced from the experimental results (**Table I**). In one case (**Table I**, entry 16) this reaction was also applied to a hydrazine substrate successfully with *N*-acetylation only at the primary amino group; thus it appears that in hydrazine type substrates where both 1°- and 2°-amino groups are present, it is only the 1°-amino group that will undergo acetylation under this reaction. This is also a notable feature of the present procedure. It is observed that the deactivating groups (*viz.* $-NO_2$, $-COOH$) do not have much influence on the rate and the yield of the reactions. Quite lower yield was obtained in case of diphenyl amine (**Table I**, entry 23) due to steric factors as could be expected.

It has already been mentioned in the earlier section that zinc acetate alone can act as a selective *N*-acetylating agent without solvent under microwave irradiation, and this has been demonstrated in **Table II**; however, zinc acetate alone (at 1 mole eqv.) requires relatively higher reaction time and also gives poorer yields in comparison to the newly developed acetylating system, *i.e.* zinc acetate in acetic acid. To investigate the solvent effect on this reaction, the experiment has been carried out using zinc acetate in the presence of various solvents (such as 1,4-dioxane, PEG-400, acetonitrile and THF) with *p*-toluidine as the substrate (**Table III**). The experimental results revealed that the solvents have very little or no influence on the reaction yield. From the selective *N*-acetylating nature (which is not observed when only acetic acid was used)[10] of the present protocols (*i.e.* use of zinc acetate alone as well as zinc acetate in acetic acid as acetylating agents), it is assumed that amino group (being more nucleophilic than hydroxy as well as thiol) in the substrate molecules makes a nucleophilic attack at the carbonyl carbon of metal-bound acetoxy function. Investigation on detailed

Table III — Effect of solvent on the reaction of zinc acetate with *p*-toluidine

Entry	Solvent	Time (min)	Yield (%)
1	No solvent	14	79
2	1,4-Dioxane	14	<40
3	PEG-400	14	<40
4	Acetonitrile	14	>65
5	THF	14	50

mechanism of this reaction is currently in progress and will be reported in due course.

In conclusion, zinc acetate has been demonstrated for the first time as a new *N*-selective acetylating agent under microwave irradiation, and a novel and eco-friendly modified method has been developed for chemoselective *N*-acetylation of amines under closed vessel microwave irradiation using catalytic amount of zinc acetate in acetic acid; the high efficiency, short reaction time (in minutes), high selectivity, easy handling, easy product separation, safe reaction medium, cost-effective and readily available reagents as a whole make this newly developed method as a promising alternative to the other common existing methods. It is earnestly hoped that this new approach to *N*-acetylation of amines will be found useful to the synthetic organic chemists at large.

Experimental Section

All the amino compounds were purchased from Sigma-Aldrich Chemical Company (USA). Zinc acetate (dihydrate) and glacial acetic acid were purchased from Qualigens Fine Chemicals, Mumbai (India). All the solvents (analytical grade) used were obtained from Merck (India). Thin layer chromatography was carried out on commercial silica-gel plate (Whatman Inc.). All m.p.s are uncorrected. TMS was used as internal standard for recording ^{1}H NMR spectra on a Bruker DRX-400 NMR spectrometer using $CDCl_3$/acetone-d_6 as solvents. IR spectra (KBr discs) spectra were recorded on a Shimadzu 8201 PC-IR spectrophotometer. A Samsung domestic microwave oven with a turn-table and operating at 2450 MHz was used at 300 W, for all the experiments. An alumina batch (aluminium oxide 60 G neutral, type E, Merck: 50g; batch 4.0 cm diameter) was used as a sink inside the MW oven during irradiation of the reaction mixtures. Reactions were conducted in heavy-walled sealed tubes (25 mL; made from Tensil Glass Works, Bangalore).

General procedure. Starting amino compound (5 mmole) taken in 25 mL sealed tube was dissolved with minimum amount of glacial acetic acid (5 mL). Catalytic amount of zinc acetate dihydrate (0.045 mmole) was then added to it. The temperature of the reaction mixture at the end of microwave irradiation was found to be 90-120°C (heating and cooling at the interval of 1 min). After completion of the reaction (monitored by TLC), the reaction mixture was poured into 20 mL ice cold water with vigorous stirring. On standing, solid mass separated out, which was then filtered off and washed with cold water followed by purification by recrystallization from an appropriate solvent (ethanol-water). Column chromatographic technique was also used for isolation and purification of the acetylated products whenever required. The purified *N*-acetyl derivatives were then characterized by recording their m.p.s, IR and ^{1}H NMR spectra. In the case of non-aqueous work up: after completion of the reaction CH_2Cl_2 or EtOAc was added to the reaction mixture and metal acetate was removed by filtration. The organic extract was then washed with a saturated solution of $NaHCO_3$ and also with H_2O (2×10 mL), and thereafter dried over anhydrous Na_2SO_4. After removal of the solvent (with the help of rotary evaporator under reduced pressure), the crude product was obtained. It was then purified by recrystallization from a suitable solvent.

Reaction of amines with only zinc acetate. Finely ground 1 mmole of the amino compound along with 1 mmole of the zinc acetate was taken in a 15 mL sealed tube followed by microwave irradiation at 300 W for a length of time indicated in **Table II**. After the completion of reaction, ethyl acetate was added to the reaction mixture and the metallic waste was removed by filtration. The organic layer was washed with water (2 × 10 mL) and dried over anhydrous Na_2SO_4. Then the solvent was removed under reduced pressure and the desired product obtained. The product was purified by column chromatography.

Acknowledgements

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2 Galema S A, *Chem Soc Rev*, 26, **1997**, 233.
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