Indion resin: Efficient, environmentally friendly and reusable catalyst for acylation of amines

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Abstract- Amines are efficiently acylated with anhydrides by using Indion Resin as catalyst and acyclic anhydrides react with an amine and amines of various stereo-electronic factors react with the same rates withan anhydride. No chromatographic separation is needed for isolation of the acylated product.Method was developed for the acylation of amine, andin the presence of catalyticamount of Indion 190 resin. Short reaction time, ambient conditions, simple work-up procedure, high yield, easyavailability, reusability, and use of an eco-friendly catalyst are some of the striking features of the presentprotocol.

Index Terms- Amines, acylation, anhydrides, Indion resin;

I. Introduction

The acylation of amines is a common methodand acylated amine is often used as protecting group in organic synthesisas it provides an efficient and inexpensive means for protecting an amino functionality in amulti-step synthetic process [1,].Acetic anhydride and acetyl chloride are generally used in thepresence of acidic[2,-5] or basic[6,-8], catalysts in an organic medium. These reactions have advantagesand drawbacks too, as recently described by Katritzky [9]. Some of these reagents and catalysts lead towaste as well as some reactions involving organic solvents, often are toxic and polluting, henceunacceptable in present days. One of the major factors for a green chemical process insolution involves the choice of cheap, safe and non-toxic solvents. Water being abundant innature is the first choice. In addition to satisfying above criteria it has also special effects onreaction arising from intra- and inter-molecular non-covalent interactions leading to assemblyprocesses. After Breslow's discovery of positive effect on the reaction rates and selectivities ofDiels-Alder reaction, which is otherwise insensitive to solvent effects, special attention wasfocused on the origin of the aqueous acceleration[10]. Reaction of N-acylation are broadly applied inorganicsynthesis,biology, agriculture and pharmaceuticals[11-13]In multi step synthesis it is robust technique for protection of amino group in organic synthesis ,for their appropriate activation of the towards chemical synthesis,or as universal biologically active targets containing amide building block,pharmaceutical and natural products[14,15] In medicinal chemistry amide bond is unusually important[16,-18]. In natural compound and organic compounds amide bond give individual property also in peptide and proteins. Amide bond predominantly present in Active pharmaceutical and natural compound [19-24]Amide unit contributes in pharmaceutical market around 25%[25],and by drug candidate survey of major pharmaceutical company found in 2006 that 2/3 functional amide group present[26].Drugs are available in market of different phtherapeuticactivity such as atorvastatin(antihyperlipidemic)[27],penicillin(antibacterial),pyrazinamide(antitubercular) contains main activity due to presence of amide functional in the structure[28]

N-acylation via aceticanhydride and acid chloride has been associated with many disadvantages[29,30] but acylation strategy using acid chloride and acetic anhydride is very common in all reported strategies. Also other methodology are used for acylation of amine through different coupling reagents ,but they don't have selectivity and contains hazardous in nature so they are difficult to handle and gives hazardous waste into environment[31].

The various strategies under metal catalyzed and direct coupling of inactivated carboxylic acid are reported [32-34] acylation by using N-acyl 1,5-diazabicyclo[4.3.0]non-5ene.(DBN) tetraphenyl borate salt [35] ,those strategy will be overcome the challenges of acyl chloride and acid anhydride mediated acylation reactions on amine using acid chloride and acid anhydrides.

Use of ruthenium and mercury catalyst for acylaion reaction in Beckman rearrangement [36,37] Acyl transfer reaction via triazole and imidazole-mediator [38-40] Oxidative amidation of aldehyde using copper catalyst[41,42]. Acylation reaction and their methods in various types of reaction including synthesis of amide chemistry have been explored.

In development of green synthetic methods in organic synthsis has become an important strategy. Environmentally benign ,inexpensive Water has experienced increasing popularity due to being inexpensive, readily available, and environmentally benign. In addition, water: (i) is cheap, nonflammable, non-toxic and safe for use; (ii) eliminates additional efforts required to dry the substrates/reagents before use; (iii) offers unique physical and chemical properties that often achieve the reactivity or selectivity unattainable in organic solvents; and (iv) allows easy product isolation by filtration.

Thus development of an efficient andconvenient synthetic methodology in water is an important area of research. Considering theimportance of acylation and environmental factors as well as our interest in green chemicalprocesses[43-45], we report in this method acylation of amines using Indion resin as catalyst, which fulfils manyof the above requirements.

II. Experimental Section

Typical Experimental Procedure. To a stirred heterogeneous suspension of anhydride (1-1.5 mmol) in ethanol (15 mL) was added to the Indion resin catalyst solution. (PH cal.4.5). The resulting solution was cooled in an ice bath. To this was then added amine (1-mmol) until effervescences appeared and pH of the mixture became 5.The completion of the reaction was confirmed by TLC .The catalyst was recovered by filtration and was washed with methanol (2 × 1 mL). The filtrate was distilled out to get crude product. The crude products were crystallized from ethyl acetate to yield the pure products which were identified by comparison of their NMR, IR, ^{13}C NMR.

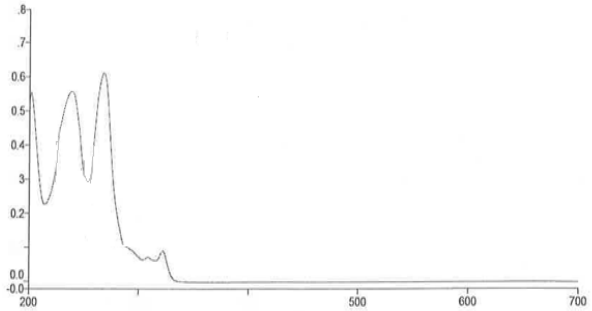
Spectral Data:

Selected spectroscopic data:

10. Selected spectroscopic data: **N-(2-fluoro-phenyl)-acetamide (5a):** 1H NMR (400 MHz, CDCl3) δ 2.2 (s, 3H), 7.02 (m, 1H), 7.28 (s, 1H), 7.3 (s, 1H), 7.42 (s, 1H), 8.2 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 24.45, 114.64, 114.89, 122.17, 124.35, 124.38, 124.43, 126.17, 126.31, 150.91, 154.13, 168.63. **N-(2,4-Difluoro-phenyl)-acetamide (6a**): 1H NMR (400 MHz, CDCl3) δ 2.20 (s, 3H), 6.86 (m, 2H), 7.27 (brs, 1H), 8.22 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 24.50, 103.25, 103.48, 103.52, 103.76, 111.10, 111.14, 111.32, 111.35, 122.52, 122.91, 123.00, 153.56, 157.36, 159.81, 168.28. **N-(2,4-Dimethoxy-phenyl)-acetamide (9a):** 1H NMR (400 MHz, CDCl3) δ 2.15 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 6.44 (m, 2H), 7.52 (brs, 1H), 8.18 (d, 1H, J = 9.5 Hz); 13C NMR (100 MHz, CDCl3) δ 24.66, 55.47, 55.60, 98.49, 103.65, 120.74, 121.18, 149.10, 156.27, 167.86. **(R)-N-Phenyl-ethylacetamide (10a):** 1H NMR (200 MHz, DMSO-d6) δ 1.30 (d, 3H, J = 7.0 Hz), 1.82 (s, 3H), 4.87 (m, 1H), 7.23 (m, 5H), 8.4 (brs, 1H); 13C NMR (50 MHz, DMSO-d6) δ 22.78, 22.96, 48.15, 126.29, 126.92, 128.57, 145.09, 168.82. **N-(2-Mercapto-phenyl)-acetamide (12a**): 1H NMR (300 MHz, CDCl3) δ 1.27 (s, 1H), 1.98 (s, 3H), 7.02 (m, 1H), 7.40 (m, 2H) 7.93(brs, 1H), 8.31 (m, 1H); 13C NMR (75 MHz, CDCl3) δ 24.97, 121.75, 123.47, 124.40, 124.88, 132.48, 136.69, 140.19,168.91. **Thioacetic acid S-(2-acetylamino-phenyl)ester (12aa):** 1H NMR (200 MHz, CDCl3) δ 2.14 (s, 3H), 2.42 (s, 3H), 7.13 (m, 1H), 7.42(m, 2H), 7.69 (brs, 1H), 8.25 (brs, 1H); 13C NMR (50 MHz, CDCl3) δ 25.02, 30.70, 117.73, 122.86, 125.20, 131.91, 136.46, 140.02, 168.67, 193.82. **2-Methyl-benzothiazole (12ab):** 1H NMR (300 MHz, CDCl3) δ 2.81 (s, 3H), 7.29 (m, 1H), 7.43 (m, 1H), 7.78 (m, 1H), 7.93 (m, 1H); 13C NMR (75 MHz, CDCl3) δ 20.07, 121.35, 122.34, 124.66, 125.87, 135.60, 153.31, 166.92. **N- (2-Amino-phenyl)-acetamide (13a):** 1H NMR (200 MHz, CDCl3) δ 2.10 (s, 3H), 3.65 (brs, 2H), 6.75 (m, 2H), 7.01 (m, 2H), 7.64 (brs, 1H); 13C NMR (50 MHz, CDCl3) δ 23.94, 118.41, 119.81, 126.04, 127.72, 129.42, 141.37, 169.69**. N-(2-Acetylamino-phenyl)-acetamide** (13aa): 1H NMR (300 MHz, DMSO-d6) δ 2.07 (s, 6H), 7.11 (m, 2H), 7.52 (m, 2H), 9.37 (s, 2H); 13C NMR (75 MHz, DMSO-d6) δ 23.63, 124.51, 124.67, 130.40, 168.57. **N-(4- Acetylamino-phenyl)-acetamide** (14a): 1H NMR (300 MHz, DMSO-d6) δ 2.06 (s, 6H), 7.10 (m, 2H), 7.53 (m, 2H), 9.43 (s, 2H); 13C NMR (75 MHz, DMSO-d6) δ 23.7, 124.8, 130.5, 168.8. **N-(4-Hydroxy-phenyl)-propionamide (11b):** 1H NMR (400 MHz, DMSO-d6) δ 1.04 (t, 3H), 2.26 (q, 2H), 7.47 (s, 4H), 9.76 (s, 2H); 13C NMR (100 MHz, DMSO-d6) δ 9.86, 18.57, 114.99, 120.80, 131.08, 153.05, 171.24**. N-(2-Mercapto-phenyl)-propionamide** (12b): 1H NMR (400 MHz, CDCl3) δ 1.10 (t, 3H), 2.14 (q, 2H), 6.96 (t, 1H), 7.36 (m, 3H), 7.95 (s, 1H), 8.33 (d, 1H); 13C NMR (100 MHz, CDCl3) δ 9.49, 30.62, 120.85, 124.10, 132.03, 136.35, 139.79, 171.94. **2-Ethyl-benzothiazole (12bb):** 1H NMR (400 MHz, CDCl3) δ 1.47 (t, 3H), 3.15 (q, 2H), 7.25 (t, 1H), 7.35 (t, 1H), 7.75 (d, 1H), 7.88 (d, 1H); 13C NMR (100 MHz, CDCl3) δ 13.76, 27.65, 121.45, 122.34, 124.61, 125.87, 134.90, 152.99, 173.72. **N- (4-Hydroxy-phenyl)-benzamide (11c):** 1H NMR (400 MHz, DMSO-d6) δ 6.75 (m, 2H), 7.38-7.61(m, 6H), 7.93 (m, 2H), 10.04 (s, 1H); 13C NMR (100 MHz, DMSO-d6) δ 115.05, 122.35, 127.56, 127.74, 128.34, 131.31, 135.23, 153.86, 165.03. **N-p-Tolyl-succinamic acid (7d):** 1H NMR (400 MHz, DMSO-d6) δ 2.19 (s, 3H), 2.49 (s, 4H), 7.04 (d, 2H, J = 8.4Hz), 7.42 (d, 2H, J = 8.4Hz), 9.82 (s, 1H), 12.08 (brs, 1H); 13C NMR (100 MHz, DMSO-d6) δ 20.44, 28.84, 30.71, 118.92, 129.06, 131.77, 136.84, 169.83, 173.91. **N- (4- ydroxyphenyl)- succinamic acid (11d**): 1H NMR (300 MHz, DMSO-d6) δ 2.56 (s, 4H), 6.74 (d, 2H, J = 8.7 Hz), 6.90 (m, 1H), 7.20 (m, 1H), 7.41 (d, 2H, J = 8.4 Hz), 9.74 (s, 1H); 13C NMR (75 MHz, DMSO-d6) δ 29.2, 31.1, 116.1,121.1, 131.2, 153.3, 169.8, 174.2. **N-p-Tolylphthalamic acid (7f):** 1H NMR (300 MHz, DMSO-d6) δ 2.26 (s, 3H), 7.13 (d, 2H), 7.50- 7.67 (m, 5H), 7.87 (d, 1H), 10.25 (s, 1H), 13.02 (s, 1H); 13C NMR (75 MHz, DMSO-d6) δ 20.68, 119.14, 127.31, 128.50, 128.83, 129.02, 129.56, 131.14, 131.73, 136.56, 138.41, 166.48, 166.86**. N-(4-Methoxy-phenyl)-phthalamic acid (8f)** : 1H NMR (300 MHz, DMSO-d6) δ 3.75 (s, 3H), 6.92 (d, 2H), 7.55-7.67 (m, 5H), 7.87 (d, 1H), 10.32 (s, 1H). 13.10 (s, 1H); 13C NMR (75 MHz, DMSO-d6) δ 55.22, 113.46, 120.78, 127.39, 128.88, 129.10, 129.74, 131.19, 132.35, 138.51, 154.81, 166.36, 167.02. **N-(4-Hydroxy-phenyl)-phthalamic acid (11f):** 1H NMR (300 MHz, DMSO-d6) δ 6.72 (d, 2H), 7.44-7.66 (m, 5H), 7.84 (d, 1H), 9.20 (s, 1H), 10.07 (s, 1H), 13.14 (s, 1H); 13C NMR (75 MHz, DMSO-d6) δ 114.49, 120.79, 127.24, 128.64, 128.86, 129.69, 130.69, 130.93, 138.37, 152.70, 165.91, 166.88.

III. Results and Discussion

Acetylation of aromatic amines has been carried out in aqueous media but with a limited number of substrates[46-53]. The same has been achieved using amine, acetic anhydride and Indion resin as catalyst. We thought to add Indion resin protonate the anhydride and react it with aceticanhydride and convert the liberated acetic acid. To test ourhypothesis and to optimise the reaction conditions, aniline **4** wasconverted to acetanilide using acetic anhydride and Indion resin. Thus,when acetic anhydride was added to solution of amine no acetylationisoccurred. However, upon addition of Indion resin to the above medium, freeamines formswhich reacted immediately with protonated acetic anhydride, precipitating theacetylated product with the evolution of carbon dioxide. The reaction works best when the finalpH of the medium is 5.5, approximately one pKa unit higher compared to that of acetic acid(pKa 4.8). Protonation of amine in an acidic medium has been confirmed by hypochromic shiftsat 226 nm and 276 nm for (π- π*) and (n- π*) respectively, by titrating a dilute solution of 2-fluoroaniline **5** with a dilute solution of HCl using UV spectrophotometer. A hyperchromic shiftof these transitions upon addition of a dilute solution of sodium bicarbonate confirms theregeneration of free amines.



To choose the best catalyst among various catalysts available for the reaction using a criteria of maximum product yield and time requirement for the completion of reaction, we carried out screening test of catalysts. To achieve the goal we set up reactions namely A1, A2, A3, A4, A5, A6, A7, A8, A9 and A10. All the substrates were added as described in the procedure but we varied the catalyst for each reaction. We had added the catalysts as follows B1- RuCl3, B2- La(NO3)3.6H2O6, B3- NbCl5, B4- NaHSO4.SiO2 , B5- ammonium acetate in acetic acid, B6- ZrOCl2·8H2O, B7- zinc dust , B8-18-Crown-6, B9- iodine, B10- Indioin 190 resin, respectively. We then allowed the reactions to complete while noting the time required for the same. Upon recovery of products we observed that, Indioin 190 resin successfully fulfilled both the criteria applied. So it was selected for further analysis.

Table 1. Acylation of the Amine using various catalysts

Entry	Catalyst	Time	Yield
1	RuCl3	9	65
2	La(NO3)3.6H2O6	10	72
3	NbCl5	8	66
4	NaHSO4.SiO2	7	69
5	ammonium acetate in acetic acid	12	70
6	ZrOCl2·8H2O	10	59
7	zinc dust	13	65
8	18-Crown-6	14	55
9	Iodine	11	65
10	Indioin 190 resin	5	90

After selection of a good catalyst we then decided to check the effect of solvent system being used during reaction on the yield of product as well on the rate of reaction. A series of ten reactions was set up as 1,2, 3-----, 10. Each of the reaction set up consisted of all the reagents with Indioin 190 resin as a catalyst. The reactions were run using Methanol in 1st set, Dichloromethane in 2nd, Ethanol in 3rd, Butanol in 4th , Isopropanol in 5th , Acetonitrile in 6th , DMF in7th,Ethyl acetate in 8th,Acetone in 9th and Ethylene dichloride in 10th set correspondingly. While reactions were proceeding time required for the completion of the reaction in presence of each solvent was being monitored. Completion of reaction was being examined using TLC. After completion of reactions products were obtained and quantified. The results for the time requirement for the completion of reaction and the product yield revealed ethanol as the best solvent.

Table2: Screening of solvent

Entry	Solvent	Time	Yield
1	Methanol	7	65
2	Dichloromethane	9	55
3	Ethanol	5	90
4	Butanol	7	60
5	Isopropanol	7.5	62
6	Acetonitrile	12	58
7	DMF	14	57
8	Ethyl acetate	10	45
9	Acetone	14	40
10	Ethylene dichloride	13	48

We then decided to check the efficiency of the catalyst Indioin 190 resin in terms of maximum product yield at its lowest possible quantity used. (by using the lowest possible amount of it). We had now set up the series of reaction with all the substrates along with ethanol as a solvent but we varied the catalyst loading in the range of 1% to 10% progressively. We monitored the progress of reaction by using chromatography techniques. After completion of the reaction the harvested products were measured to know the yield with each loading of the catalyst. Upon observation it was found that 10% catalyst loading has given 90% product yield.

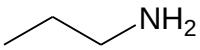
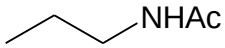
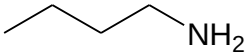
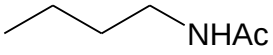
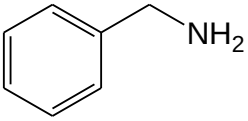
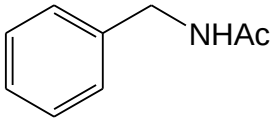
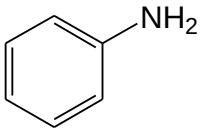
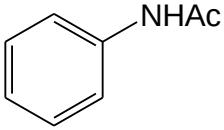
After all of these screening tests we optimized our reaction conditions based on the results. We used Indioin 190 resin at 10% loading as our catalyst along with ethanol as a solvent.

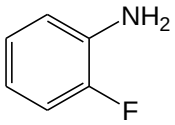
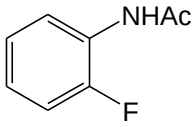
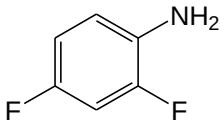
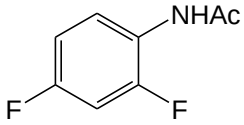
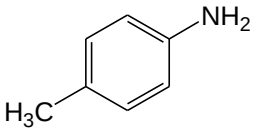
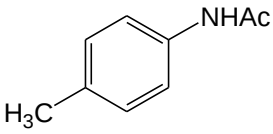
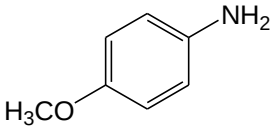
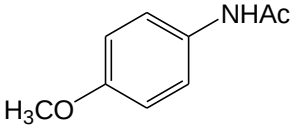
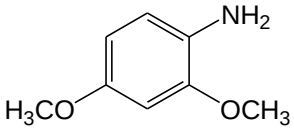
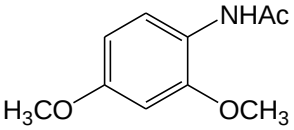
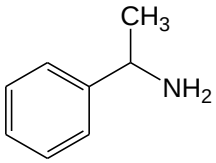
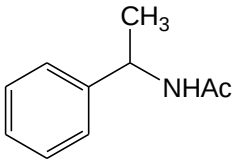
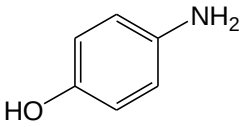
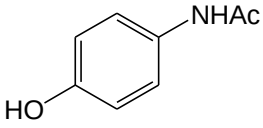
Table 3: Catalyst loading

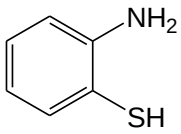
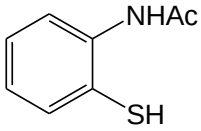
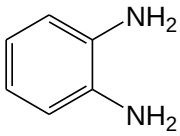
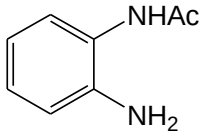
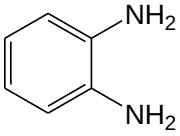
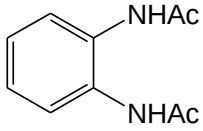
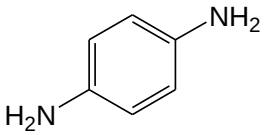
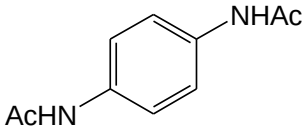
Entry	Indioin 190 Resin	Cat.% loading	Yield%
1	Indioin 190 Resin	1	25
2	Indioin 190 Resin	2	36
3	Indioin 190 Resin	3	40
4	Indioin 190 Resin	4	45
5	Indioin 190 Resin	5	50
6	Indioin 190 Resin	6	56
7	Indioin 190 Resin	7	60
8	Indioin 190 Resin	8	64
9	Indioin 190 Resin	9	75
10	Indioin 190 Resin	10	90

As shown in Table 4 several amines underwent acetylation very smoothly gives good yields.The optimized acetylation reaction was performed by adding acetic anhydride (1.5 equiv) to thedissolved in methanol followed by addition of Indion resinone lot to obtain a final pH ca. 5.5. The methodology works well for aliphatic, **1-2**andaromatic, **3-9**amines, as reported in Table 1[49]. Primary amines of varying electronic and stericfactors, substrate **3-9** were examined. It is interesting to note that in most of these cases theproduct precipitates in less than 5 minutes. It has been observed that the acetylation of arylamines performed in an organic reaction mediumsubstrate containing electron-donating groupsin the aromatic ring facilitate the reaction, whereas electron-withdrawing groups slow down thereaction. No such effect was observed by the present methodology and all the substrates reactwith equal rates. However, aryl amines gave better yields as compared to alkyl amines. Chiralamines **10** can be easilyacetylated with complete retention of optical activity. Phenol andthiophenol reacted slowly under the identical conditions giving poor yields of products. Thus, by takingadvantage of the differential reactivity among nucleophiles, we were able to carry outchemoselective acetylation of amines over phenols and thiols. Similarly, in a competitive acetylationreaction with an equimolar mixture of aniline **4** and phenol by this procedure, the amine isacetylated selectively leaving the phenol unaffected.

Table-4 Acylation of amines with acetic anhydride

Substrate		Anhydride	Product		Yield
	1	Acetic		1a	85
	2	Acetic		2a	75
	3	Acetic		3a	95
	4	Acetic		4a	97

Subtrate		Anhydride	Product		Yield
	5	Acetic		5a	84
	6	Acetic		6a	87
	7	Acetic		7a	97
	8	Acetic		8a	95
	9	Acetic		9a	86
	10	Acetic		10a	80
	11	Acetic		11a	95

	12	Acetic		12a	35[c]
	13	Acetic		13a	95
	13	Acetic		13aa	85
	14	Acetic		14a	85

a Confirmed by comparison with IR, 1H and 13C NMR of the authentic sample. b Isolated yields' Rest of the products being diacetylated product **12aa** and 2-methyl-benzothiazole **12ab**. d Basedon the recovery of starting material. e 3 equivalent of Ac2O was used.

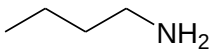
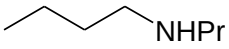
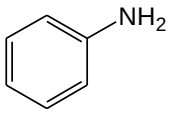
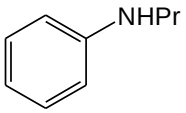
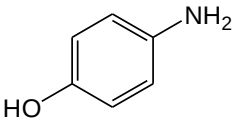
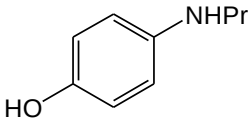
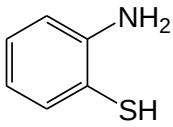
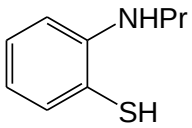
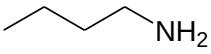
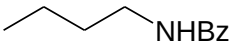
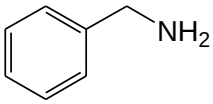
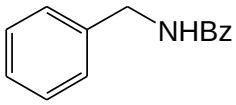
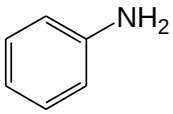
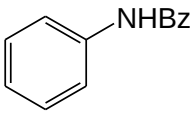
In an analogous reaction between aniline **4** and thiophenol, the thiophenol is unaffected. Similar selectivity was observed for intramolecular reaction as well. Thus,acetylation of 4-aminophenol **11** and 2-aminothiophenol **12** produced the correspondingacetamides; the phenolic and thiophenolic moiety remained untouched with one equivalent of thereagent. The selective acetylation is of significant interest for the preparation of antipyretic andanalgesic drugs,likeparacetamol **11a**. Monoacetylation of 1,2-phenylenediamine **13** demonstrates theefficacy of the method.However, no chemoselectivity was observed for symmetrical diamine1,4-phenylenediamine **14** even with one equivalent of the acetic anhydride.

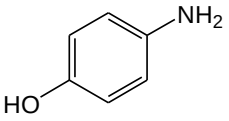
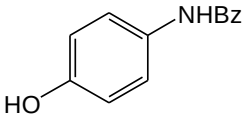
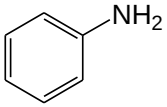
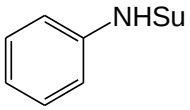
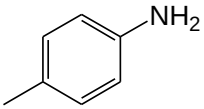
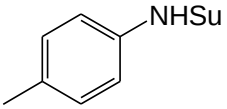
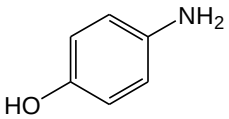
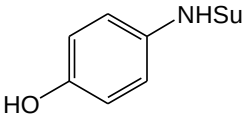
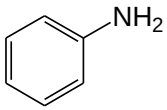
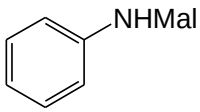
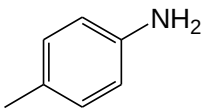
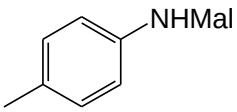
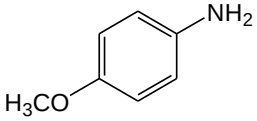
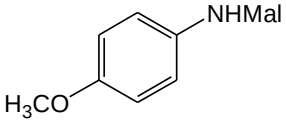
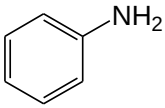
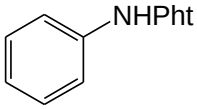
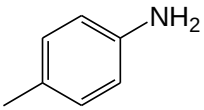
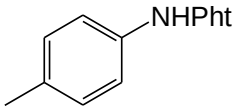
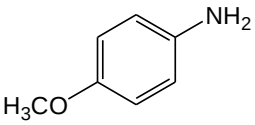
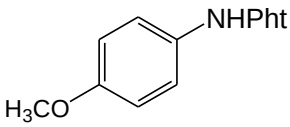
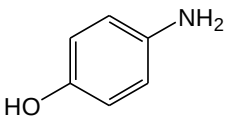
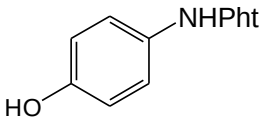
When 2-aminothiophenol **12** was treated with one equivalent of acetic anhydride under theidentical conditions; along with a trace amount of diacetylated product **12aa** (<5 %) andmonoacetylated product **12a** (>28%) and an interesting heterocyclic product 2-methylbenzothiazole**12ab** was obtained (*ca.*40%). The formation of 2-methyl-benzothiazole **12ab** isvia acetylation of amine isfollowed by a nucleophilic attack of thiophenolic group on the carbonylcarbon of the amide and subsequent water elimination. Formation of 2-methyl-benzothiazole**12ab** hasconfirmed the chemoselective acetylation of amines over thiols. In most of these cases theacetylated product precipitated out from the aqueous reaction medium and in few cases it wasextracted with ethyl acetate to obtain the pure product, except for substrates **1**and **2** wheretheproductsneeded extraction and in the case of substrates **13** and **14** the products requiredextraction as well as chromatographic separation. It was found that primary amines underwentsmooth acetylation while secondary amines such as diphenylamine remained inert under thepresent experimental conditions. The by-product, sodium acetate is a useful buffering agent andit can be recovered from the aqueous effluent upon concentration of the aqueous medium, if desired.

The novel aspect of the present methodology was applied to cyclic anhydride such assuccinic and maleic anhydride. In this case the anhydride 1.2 equivalent was used per equivalentof amine. All these substrates reacted easily as shown in Table 2, giving good yields. The reactiontook place readily with simultaneous precipitation of white coloured solid product. Finally themethodology was tested with an aromatic cyclic anhydride, the phthalic anhydride. Finely powderedphthalic anhydride, 1 equivalent, was added to amine solution followed byIndion resin. This methodology has been tested with a number of aromatic amines and the resultsaresummarized in Table 2.

Table 2. Acylation of amines with different anhydrides

Substrate	Anhydride	Product Yield

	2	Propaonic		2b	85
	4	Propaonic		4b	94
	11	Propaonic		11b	92
	12	Propaonic		12b	87
	2	Benzoic		2c	85
	3	Benzoic		3c	90
	4	Benzoic		4c	90

	11	Benzoic		11c	92
	4	Succinic		4d	85
	7	Succinic		7d	80
	11	Succinic		11d	90
	4	Maleic		4e	75
	7	Maleic		7e	82
	8	Maleic		8e	85
	4	Phthalic		4f	90
	7	Phthalic		7f	85
	8	Phthalic		8f	80
	11	Phthalic		11f	88

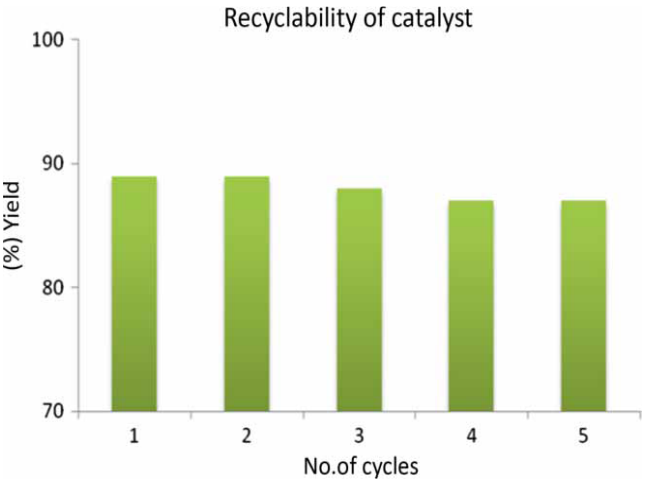
Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample, b Isolated yields.

Besides, acetic anhydride this procedure is amenable also to acyclic, cyclic, aliphatic andaromatic anhydrides, Table 2.10 Propionylation of aliphatic **2** and aromatic amine **4**usingpropionic anhydride was carried out under the identical conditions as described for aceticanhydride. Here again the amino functionality has been chemoselectively propionylated in thepresence of phenols and thiols as demonstrated for 4-aminophenol **11** and 2-aminothiol **12**correspondingly. Substrate 2-aminothiol **12** gave heterocyclic product, 2-ethylbenzothiazole **12bb** asthe exclusive product and N-(2-mercapto-phenyl)-propionamide **12b** as the

minor producttthereby supporting the chemoselective propionylation of amines over thiols. Benzoylation ofaliphatic amine **2**, benzylamine **3**, aromatic amine **4** and chemoselective benzoylation of 4-aminophenol **11** further proves the efficacy. The product precipitated into lumps, canthen be recrystallised either from acetone or from ethyl acetate. The catalyst can be recovered from the reaction mass.

Recycle study:

With the increasing interest in human health and environmental protection more attention is being paid to green chemistry.With the view we studied the recyclability and reusability of the catalyst,after completion of the reaction the catalyst was separated by filtration, washed with hexane and dried.The activated catalyst was used for two more subsequent cycles.To our surprise consistentperformance of the catalyst is observed in all the cycles



Conclusions

In conclusion, this method represents a tremendous opportunity for the practice of green chemistry. The notable advantages of the method are: (i) operational simplicity, (ii) moderate to good yield of products, (iii) no chromatographic separation, (iv)excellentselectivity for aryl amines over phenols and thiols and (v) general applicability. The method is environment friendly with respect to the by-products and the effluents are innocuous. We believe this will present a better and more practical alternative to the existing methodologies for selective acylation of primary amines and thus will find useful application in the synthesis of complex natural products where selective protection of hydroxy, thio and amino groups is required.

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REFERENCES

[1] 1. T.W.Greene,P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Edn; Wiley &Sons, New York(1999).

[2] 2. C.-T.Chen,J.-H.Kuo, Li, C.-H. Barhate, N. B. Hon, S.W. Li, T.W.; Chao, S. D.Liu C.-C. Li, Y.-C. Chang, I.H. Lin, J.-S. Liu, C.-J. Chou, Y.C. Org. Lett., 3, 3729(2001).

[3] 3. P. A Procopiou,S. P. D Baugh,S. S Flack,G. G. A Inglis, J. Org. Chem., 63, 342 (1998).

[4] 4. P. Saravanan,V. K.Singh. Tetrahedron Lett. 40, 2611 (1999).

[5] 5. K. K Chauhan, C. G Frost.I. Love,D.Waite, Synlett., 1743(1999).

[6] 6. E.Vedejs,S. T.Diver, J. Am. Chem. Soc., 115, 3358(1993).

[7] 7.E.Vedejs,O.Daugulis, J. Org. Chem.,61, 5702(1996).

[8] 8.B. A.D'Sa,J. G.Verkade, J. Org. Chem., 61, 2963(1996).

[9] 9. A. R.Katritzky, He, H. Y.,K Suzuki, J. Org. Chem., 65, 8210(2000).

[10] 10. D. C. Rideout,R.Breslow, J. Am. Chem. Soc., 102, 7816(1980).

[11] 11.H.M.Savanur,S.S.Malunavar,P.Prabhala,S.M.Sutar,R.G.Kalkhambkar,K. K.Laali., Tetrahedron Lett., 60, 151159(2019).

[12] 12. J.M.Humphrey, A.R.Chamberlin, Chemical Synthesis of Natural Product Peptides: Coupling Methods for the Incorporation of Noncoded Amino Acids into Peptides. Chem. Rev. 97, 2243–2266 (1997).

[13] 13.A.Scozzafava,T.Owa,A.Mastrolorenzo,C.T.Supuran,Anticancerandantiviral,sulfonamides.Curr. Med. Chem., 10, 925–953(2003).

[14] 14.V.Pace,W.Holzer, B.Olofsson. Increasing the Reactivity of Amides towards Organometallic Reagents: An Overview. Adv. Synth. Catal., 356, 3697–3736(2014).

[15] 15. A. Greenberg, C.M.Breneman, J.F.Liebman, The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Material Science; Wiley-Interscience: NewYork,N.Y, USA, (2000).

[16] 16.S.S.Panda, A.S.Girgis, B.B.Mishra, M.Elagawany, V.Devarapalli, W.F Littlefield, A.Samir, W.Fayad, Fawzy, N.G., Srour, A.M.etal, Synthesis, computational studies, antimycobacterial and antibacterial properties of pyrazinoic acid–isoniazid hybrid conjugates. RSC Adv., 9, 20450–20462(2019).

[17] 17. B.Alcaide, P.Almendros, C.Aragoncillo, β-Lactams: Versatile building blocks for the stereoselective synthesis of non-β-Lactam products. Chem. Rev., 107, 4437–4492(2007).

[18] 18. S.D.Roughley, A.M.Jordan, The medicinal chemist's toolbox: An analysis of reactions used in the pursuit of drug candidates. J. Med. Chem., 54, 3451–3479 (2011).

[19] 19. K.Ishihara, Dehydrative condensation catalyses. Tetrahedron , 65, 1085–1109(2009).

[20] 20. R.M.Lanigan, T.D.Sheppard, Recent developments in amide synthesis: Direct amidation of carboxylic acids and transamidation reactions. Eur. J. Org. Chem., 2013, 7453–7465(2013).

[21] 21. H.Lundberg, F.Tinnis, N.Selander, H.Adolfsson, Catalytic amide formation from non-activated carboxylic acids and amines. Chem. Soc. Rev., 43, 2714–2742 (2014).

[22] 22. M.T.Sabatini, L.T.Boulton, H.F Sneddon, T.D.Sheppard, A green chemistry perspective on catalytic amide bond formation. Nat. Catal., 2, 10–17 (2019).

[23] 23. X.Wang, Challenges and outlook for catalytic direct amidation reactions. Nat. Catal., 2, 98–102(2019).

[24] 24. J.O.Rathi, G.S.Shankarling, Concentrated solar radiation aided energy efficient and chemoselective protocol for N-acylation and N-formylation reactions in aqueous medium. Sol. Energy , 189, 471–479(2019).

[25] 25. A.K.Ghose, V.N.Viswanadhan, J.J.Wendoloski, Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases. Comb. Chem., 1, 55–68(1999).

[26] 26. J.S.Carey, D.Laffan, C.Thomson, M.T.Williams, Analysis of the reactions used for the preparation of drug candidate molecules. Org. Biomol. Chem., 4, 2337–2347 (2006).

[27] 27. R Wolf, S.Brenner, An active amide group in the molecule of drugs that induce pemphigus: A casual or causal relationship? Dermatology, 189, 1–4(1994).

[28] 28. P.Rajput, A.Sharma, Synthesis and biological importance of amide analogues. J. Pharmacol. Med. Chem., 2, 22–31(2018).

[29] 29. A.R Katritzky, H.-Y.He, K Suzuki, N-Acylbenzotriazoles: Neutral Acylating Reagents for the Preparation of Primary, Secondary, and TertiaryAmides. J.Org.Chem., 65,8210–8213 (2000).

[30] 30. S.M.Mali, R.D.Bhaisare, H.N.Gopi, Thioacids Mediated Selective and Mild N-Acylation of Amines. J. Org. Chem., 78, 5550–5555 (2013).

[31] 31. S.S Panda, C.Dennis Hall, E.Scriven, A.R.Katritzky, Aminoacyl benzotriazolides: Versatile reagents for the preparation of peptides, their mimetics and conjugates. Aldrichimica Acta., 46, 43–55(2013).

[32] 32. C.L Allen, J.M.J.Williams, Metal-catalyzed approaches to amide bond formation. Chem. Soc. Rev., 40, 3405–3415(2011).

[33] 33. J.Cossy, C Palegrosdemange, Convenient synthesis of amides from carboxylic acids and primary amines. Tetrahedron Lett. , 30, 2771–2774(1989).

[34] 34. A.C.Spivey, S Arseniyadis, Nucleophilic catalysis by 4-(dialkylamino)pyridines revisited - The search for optimal reactivity and selectivity. Chem. Int. Ed., 43, 5436–5441 (2004).

[35] 35. J.E Taylor, M.D.Jones, J.M.J.Williams, S.D.Bull, N-Acyl DBN tetraphenylborate salts as N-acylating agents. J. Org. Chem., 77, 2808–2818(2012).

[36] 36. N.A.Owston, A.J.Parker, J.M.J.Williams, Highly efficient ruthenium-catalyzed oxime to amide rearrangement. Org. Lett., 9, 3599–3601(2007).

[37] 37. C.Ramalingan, Y.T.Park, Mercury-Catalyzed Rearrangement of Ketoximes into Amides and Lactams in Acetonitrile. J. Org. Chem., 72, 4536–4538 (2007).

[38] 38. W.J.Yoo, C.J.Li, Highly Efficient Oxidative Amidation of Aldehydes with Amine Hydrochloride Salts. J. Am. Chem. Soc. , 128, 13064–13065(2006).

[39] 39. K.Ekoue-Kovi, C.Wolf, One-pot oxidative esterification and amidation of aldehydes. Chem. Eur. J. 2008, 14, 6302–6315.

[40] 40.Yang, X.Birman, V.B. Acyl Transfer Catalysis with1,2,4-Triazole Anion. Org. Lett. 2009, 11, 1499–1502.

[41] 41. S.J.Miller, In Search of Peptide-Based Catalysts for Asymmetric Organic Synthesis. Acc. Chem. Res., 37, 601–610(2004).

[42] 42. K.Ishihara, Y.Kosugi, M.Akakura, Rational design of an L-histidine-derived minimal artificial acylase for the kinetic resolution of racemic alcohols. J. Am. Chem. Soc., 126, 12212–12213(2004).

[43] 43.S.S Panda, A.S Girgis, B.B.Mishra, M.Elagawany, V Devarapalli, W.F Littlefield,. A Samir, N.G Fawzy, A.M Srour, Novel pyrazinoic acid-isoniazid conjugates with amino acid linker: Microwave assisted synthesis, anti-infective properties, and molecular modeling studies. RSC Adv., 9, 20450–20462(2019).

[44] 44. R.Breslow, Acc Chem. Res., 24, 159(1991).

[45] 45.Li, C. -J. Chem. Rev., 93, 2023(1993).

[46] 46. W. A.Herrmann,C. W.Kohlpaintner, Angew. Chem., Int. Ed.,32, 1524(1993).

[47] 47.R.Gopinath,B.Barkakaty,B.Talukdar,B. K.Patel, J. Org. Chem., 68, 2944(2003).

[48] 48.R.Gopinath,Sk. J Haque,B. K. Patel, J. Org. Chem., 67, 5842(2002).

[49] 49. R.Gopinath, A. R.Paital,B. K.Patel, Tetrahedron Lett., 43, 5123 (2002).

[50] 50. DeWitt, H. D., Indersoll, A.W. J. Am. Chem. Soc., 73, 3359 (1951).

[51] 51. S.Roseman, J.Ludowieg, J. Am. Chem. Soc., 76, 301(1954).

[52] 52. A. C.Richardson, K. A McLauchlan, J.Chem. Soc., 2499(1962).

[53] 53. B. S.Furniss,A. J Hannaford,; P. W. G Smith,A. R Tatchell,Vogel's Textbook ofPractical Organic Chemistry. 5th Edn., Longman: Singapore,(1989).

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