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Research Article

A COMPETENT AND AN ECONOMICALLY CHEAP SYNTHESIS OF AMIDES CATALYZED BY CALCIUM CHLORIDE

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ABSTRACT

$CaCl_2$ has been found to be an efficient and economically cheap catalyst for the rapid synthesis of amides in high yields. The use of stoichiometric quantities of acetic anhydride under solvent free conditions without any additional purifications makes this etiquette a safe and sound alternative to the existing methods.

Keywords: Amide, acetylation, amine, $CaCl_2$.

1. INTRODUCTION

The protection of any functional groups in protection and deprotection techniques via environmentally compassionate trial is vastly advantageous as are the commonly encounter employ for the synthesis of complex organic materials. Hence, a group is one of the most important group present in surplus of biologically relevant compound. Many protective groups are available for the protection of amine functionality. Of which acetyl group is the most common being stable in acidic conditions and can be removed easily under alkaline conditions [1]. Different reagents used for the acetyl protection of amines are acetic acid, acetyl chloride [2] anhydride [3], acetyl acetone [4], zinc acetate [5] acetic acid [6], and thioacid [7]. Amongst, acetic anhydride is the most commonly used reagent as it is cheap, readily available and easy to handle. Besides their use as a protecting group, amides are present in various important natural products and pharmaceuticals such as lacosamide, paracetamol, zonisamide, *etc*. that are required in mass quantities. Various methods are available for the amide synthesis underacidic as well as basic conditions using acetic anhydride [8].

However, most of the methods suffer from less or more demerits such as tediuos conditions, elevated temperatures, costly catalysts and reagents, more reaction times and high toxicity. Recently, Kim [9] *et al* reported the synthesis of acetamides using sulfated choline ionic liquid as a catalyst using grindstone method, though this method is quite efficient in terms of yield and reaction times, however the catalyst is not commercially available, and require preparation. To overcome these drawbacks still there is a chance to develop a new catalyst system that can minimize these boundaries. Therefore, desirable efficient catalysts which are more economical, environmentally friendly and use stoichiometric amount of reagent in absence of volatile organic solvents. Calcium chloride ($CaCl_2$) is a readily available, cheap dehydration reagent used and recently gaining thrust as a green catalyst in various organic reactions. To exemplify, $CaCl_2$ has been used in Kabachnik-Fields [10] Mannich reaction [11], Biginelli three component reaction [12] and aldol transformations [13]. In recent times, it has been utilized as an efficient Lewis acid catalyst for the synthesis of 9-aryl-1, 8-dioxooctahydroxanthene [14].

2. MATERIAL AND METHODS

All commercially available reagents were used without purification. Acetic anhydride was distilled prior to use. Reaction was monitored by using TLC plates (Merck Silica Gel 60 F254), I_2 and anisaldehyde in ethanol as development reagents and visualization with UV light (254 and 365 nm). Mass spectra were recorded on LC-MS. Optical rotations were measured with a JASCO P 1020 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 NMR spectrometer. Spectra were obtained in $CDCl_3$. Chemical shifts are reported in δ (ppm) and coupling constants are reported in Hertz (Hz).

2.1. General procedure for the synthesis of acetamides

To a mixture of amine (0.1 mol) and acetic anhydride (0.1 mol) was added $CaCl_2$ (0.015 mol) and stirred at room temperature for appropriate time as provided in Table 3. The progress of reaction was monitored by TLC. After completion, the reaction mixture was washed with saturated aq. $NaHCO_3$ solution (20 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to obtain pure product.

2.2. Spectral characterization of the compounds

2.2.1. N-(4-Phenylazo-phenyl)-acetamide (Entry 8, Table 3)

^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.73 (s, 1H), 2.20 (s, 3H), 7.35-7.60 (m, 3H), 7.62-7.73 (m, 3H), 7.75-8.07 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 168.4, 151.6, 148.0, 142.5, 132.7, 127.0, 124.9, 123.5, 1225, 120.0, 119.8, 24.7; MS: *m/z* 240 $[M+H]^+$.

2.2.2. N-Benzothiazol-2-yl-acetamide (Entry 17, Table 3)

^{1}H NMR (200 MHz, $CDCl_3$): δ_H 2.20 (s, 3H), 7.05-7.55 (m, 2H), 7.53-7.95 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 167.0, 162.1, 146.5, 133.7, 125.4, 124.05, 121.7, 120.2, 23.4; MS: *m/z* 193 $[M+H]^+$.

2.2.3. N,N-Dibenzyl-acetamide (Entry 22, Table 3)

^{1}H NMR (200 MHz, $CDCl_3$): δ_H 2.24 (s, 3H), 4.45 (s, 2H), 4.65 (s, 2H), 7.04-7.62 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 171.4, 135.2, 1353, 126.5, 126.5, 128.6, 127.8, 127.8, 126.8, 50.6, 47.9, 21.6; MS: *m/z* 240 $[M+H]^+$.

2.2.4. N-(2-Hydroxy-1-phenyl-ethyl)-acetamide (Entry 26, Table 3)

^{1}H NMR (200 MHz, $CDCl_3$): δ_H 2.02-2.05 (m, 3H), 3.85 (d, J = 4.9 Hz, 2H), 5.06 (dt, J = 7.1, 5.0 Hz, 1H), 6.26(brs, 1H), 7.30-7.37 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 170.7, 138.6, 128.6, 127.6, 126.5, 66.4, 56.6, 23.3; MS: *m/z* 180 $[M+H]^+$.

2.2.5. N-Benzyl-acetamide (Entry 27, Table 3)

^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.95 (s, 3H), 4.35 (d, J = 5.7 Hz, 2H), 6.13 (brs, 1H), 7.05-7.46 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 170.06, 138.3, 128.7, 127.9, 127.8, 43.7, 23.3; MS: *m/z* 150 $[M+H]^+$.

2.2.6. N-(3-Benzyloxy-1-methyl-propyl)-acetamide (Entry 30, Table 3)

^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.06 (d, J = 6.7 Hz, 3H), 1.51-1.77 (m, 2H), 1.75 (s, 3H), 2.04 (brs, 1H), 3.41-3.67(m, 3H), 3.95-4.15 (m, 1H), 4.35-4.45 (m, 2H), 6.01 (brs, 1H), 7.21-7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 169.5, 138.4, 132.4, 131.6, 128.4 128.4, 127.7, 127.8, 73.3, 67.5, 43.8, 35.5, 235, 20.4; MS: *m/z* 222 $[M+H]^+$.

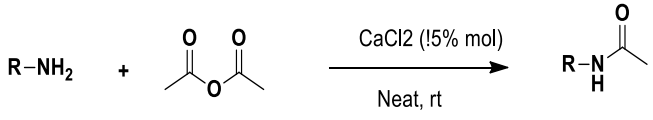
3. RESULTS AND DISCUSSION

The findings encouraged to extend the use of $CaCl_2$ in simplistic organic transformations, here I report the first time an efficient, environmentally benign, low cost and clean protocol for acetamide synthesis using $CaCl_2$. Initially, the reaction was performed with equimolar quantities of aniline and acetic anhydride in presence of 15mol% $CaCl_2$ using acetonitrile as a solvent, the reaction was completed in 30 min with 95% yield (Scheme I). Next, we evaluated different solvents like acetone, chloroform and they also produced excellent results in short time (Table I). Polar solvents (Table I, entry 3,5) shows slight decrease in yields as compared to other less polar solvents. But the best results were obtained when the reaction was carried out in solvent free conditions, the desired product was obtained in 97% yield in 20 min. Comparison of our result with few of the reported procedures is presented in Table II which clearly indicates the efficiency of $CaCl_2$ in the synthesis of acetamides.

Table I: Effect of various solvents on the yield of the model reaction[a]

Entry			
1	Acetonitrile	20 min	94
2	Acetone	15 min	92
3	THF	15 min	92
4	Ethanol	25 min	90
5	Ethyl acetate	25 min	90
6	Methanol	30 min	88
7	Solvent free	10 min	97

[a] *Aniline (1mmol), $(Ac)_2O$ (1 mmol), $CaCl_2$ (0.1mmol), Solvent (1mL), RT.*



Scheme I: $CaCl_2$ catalyzed synthesis of acetamides

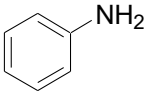
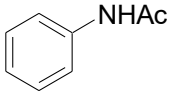
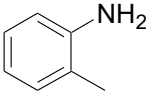
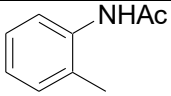
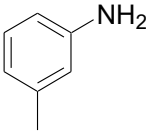
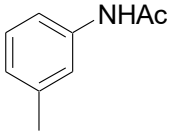
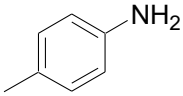
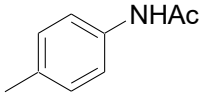
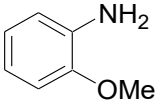
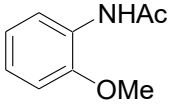
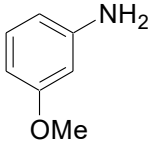
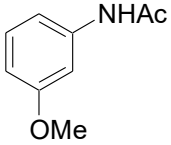
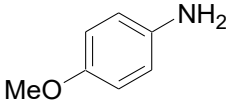
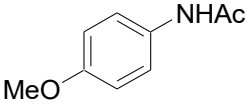
With the optimized reaction conditions in hand, we evaluated the scope of the reaction with various aromatic, aliphatic and heteroaromatic amines. Several amines were treated with 1 eq. of freshly distilled acetic anhydride in presence of 15 mol% of $CaCl_2$ under solvent free conditions to obtain pure products without purification (Table 3). Aniline having electron donating groups on the phenyl ring (methyl or methoxy) results in higher yields with rapid product formation. In contrast anilines possessing electron withdrawing groups on the phenyl ring (such aschloro ornitro group) shows decrease in product yields with slight longer reaction time.Position of substituents on aniline ring does not affect much on the yields of the product but, the effect can be seen on the reaction time. For example, substituent on *ortho* position of aniline requires more time for the completion of reaction as compared to *meta* and *para* positions due to the *ortho* effect. Exceptional chemoselectivity was observed in case of alcohols amines (entry 23-26) and phenylene diamine (entry 9) to provide the required product without formation of any side products. Sterically hindered amine(entry 19, 20, 21) was conveniently transformed into its corresponding product with moderate to good yield. Heterocyclic (entry 15-17) and aliphatic amines (entry 27-30) also worked well using this protocol in high yields and shorter reaction times.

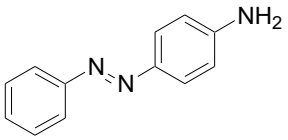
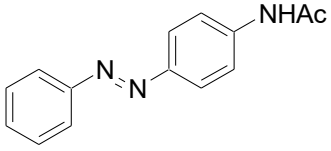
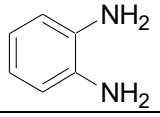
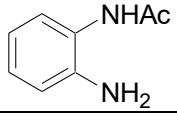
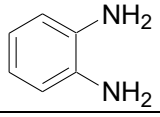
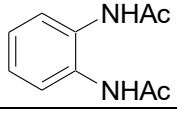
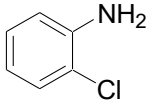
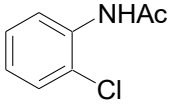
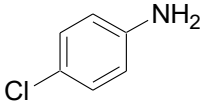
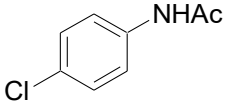
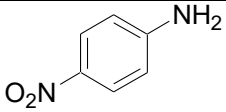
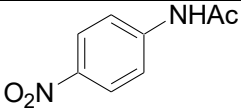
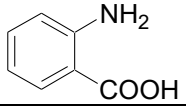
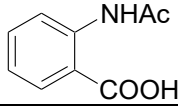
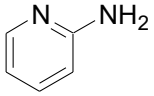
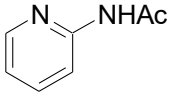
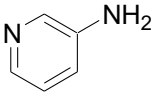
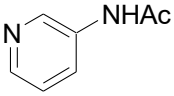
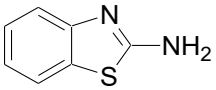
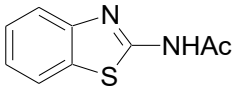
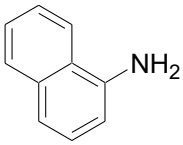
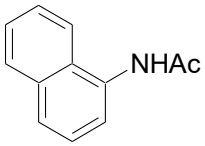
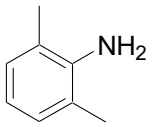
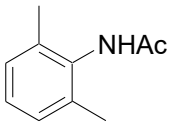
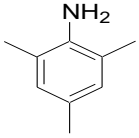
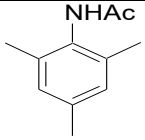
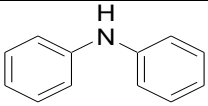
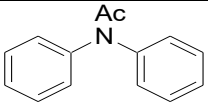
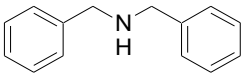
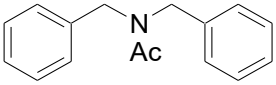
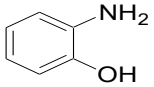
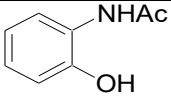
Table II: Comparision of various catalysts employed for the synthesis of phenylacetamide[#]

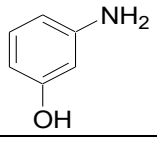
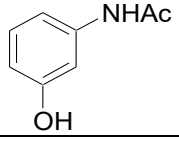
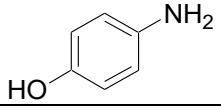
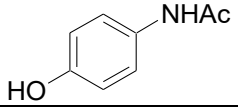
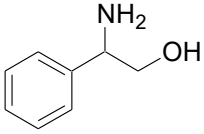
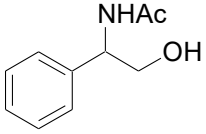
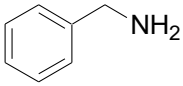
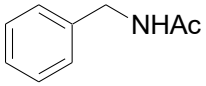
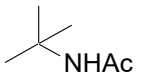
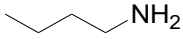
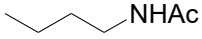
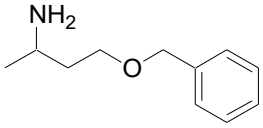
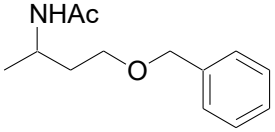
Entry	Catalyst	Solvent	Time (min)	Yield (%)	Ref.
1	Ag(OTf) (1 mol%)	Neat, 80°C	3	99	8b
2	Nano-CdO (10 wt%)	Neat (MW, 80°C)	5	98	8c
3	Sodium dodecyl sulfate (SDS)	H_2O	5-10	83	8e
4	LiCl (5 mol%)	Neat	120	95	8i
5	SCIL (3.5 mol%)	Neat	10	98	9
6	$CaCl_2$ (10 mol%)	Neat	10	97	This work

[#]*Reaction conditions: Aniline: $(Ac)_2O$ (1:1), RT. MW-microwave*

Table III: Synthesis of various acetamides catalyzed by $CaCl_2$

Entry	Amine	Time	Product	Yield (%)	m.p. (°C)
1		10 min		96	113 (114)[8i]
2		30 min		93	109 (112)[6]
3		20 min		94	65 (65-67)[9]
4		20 min		91	152 (152-53)[6]
5		25 min		94	86 (86-87)[6]
6		20 min		96	77-80
7		15 min		95	128 (128-30)[6]

8#		50 min		85	138-40
9		25 min		76	oil
10#		30 min		86	185-187 (186)[8i]
11		30 min		83	86-87 (88)[6]
12		30 min		74	177-79 (178)[6]
13		30 min		71	214 (215-16)[6]
14		50 min		82	183 (184)[6]
15		20 min		85	64-65
16		30 min		72	128-30
17		30 min		96	179-80
18		30 min		94	159-60 (158-60)[6]
19#		120 min		91	179-81 (181-83)[9]
20#		150 min		90	213-14 (211-12)[9]
21		60 min		70	101-03 (100-02)[6]
22		15 min		95	oil
23		30 min		80	207-09 (207-09)[6]

24		30 min		74	144-46 (146-48)[6]
25		30 min		72	168 (166-67)[6]
26		40 min		85	oil
27		10 min		94	58-60 (60-62)[9]
28		30 min		72	oil
29		20 min		68	110-12 (111-13)[9]
30		25 min		90	oil

4. CONCLUSION

In conclusion, described here a simple, convenient and environment-friendly procedure for the amides synthesis using $CaCl_2$ as a mild and cheap catalyst under solvent free conditions. The present procedure shows several advantages such as high yields, shorter reaction times in minutes, clean reactions, safe handling and low cost. Therefore, this new method would be used as an unconventional to other existing methods for the acetamide synthesis.

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