Aluminium(III) chloride hexahydrate: an efficient and versatile reagent in organic synthesis

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Abstract
A short review on the application of aluminium chloride hexahydrate [$AlCl_3.6H_2O$], a mild, comparatively less toxic, and easily available reagent has been presented. The article is covering those areas of organic synthesis where the $AlCl_3.6H_2O$ was used either as a single reagent or in combination with a co-catalyst.

Keywords: Aluminium chloride hexahydrate, isoxazolidine, chemoselective reduction, deoxygenation, dehydration

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1. Introduction

Development of non-hazardous synthetic methodologies for organic reactions is one of the latest challenges to the organic chemists. In this connection, the use of efficient, non-toxic and inexpensive reagents for various organic transformations is an important research area. Aluminium, a group 13 element, is the most abundant metal in the earth's crust. Anhydrous $AlCl_3$ has been extensively used as a strong Lewis acid in many organic reactions such as Friedel-Crafts reactions, Fries rearrangement, Scholl reaction etc.[1] But, the utility of the hydrated counterpart i.e. $AlCl_3.6H_2O$ is not fully explored yet.

Aluminium(III) chloride hexahydrate is a non-flammable; yellowish-white to colorless deliquescent granular crystals with slight HCl odor. It is highly soluble in water and also soluble in alcohol, ether, glycerol, propylene glycol and acetonitrile. It finds wide application in deodorants and antiperspirant preparations, refining crude oil, dyeing fabrics, manufacturing parchment paper, textile finishing, preserving wood and disinfecting stables. It is also clinically used to control severe excessive sweating called hyperhidrosis. Generally the reagent is prepared either by treating conc. hydrochloric acid to the solution of anhydrous $AlCl_3$ in water followed by saturating with dry hydrogen chloride or heating aluminium hydroxide with conc. hydrochloric acid in a sealed tube. It has been observed that $AlCl_3.6H_2O$ exists in reality as $[Al(H_2O)_6]Cl_3$ and its aqueous solution is acidic due to the ability of the hydrated cation $[Al(H_2O)_6]^{+3}$ to act as proton donor giving $[Al(H_2O)_5(OH)]^{2+}$, $[Al(H_2O)_4(OH)_2]^{+}$, etc.[1c]

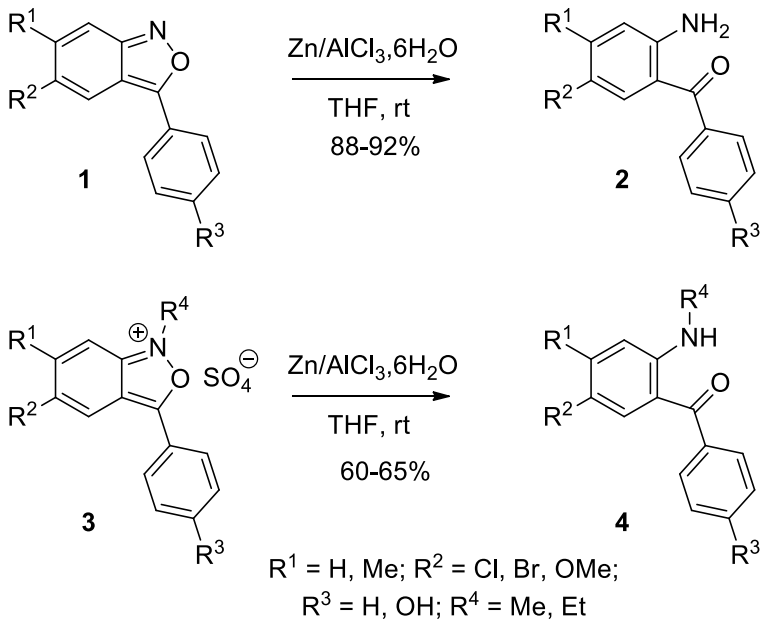
The cost effectiveness, ease of handling, good reactivity, experimental simplicity, and excellent solubility in water and organic solvents render $AlCl_3.6H_2O$ as a promising green reagent and catalyst in organic synthesis. In this review, we will outline over a decade of research work on the development of $AlCl_3.6H_2O$ as a reagent and catalyst in various organic reactions by different group of scientists including us.

2. Reduction reactions

2.1. Reductive cleavage of 2,1-benzisoxazoles

$AlCl_3.6H_2O$ in combination with metallic zinc in moist THF can cleave the 2,1-benzisoxazoles **1** and their ammonium salts **3** to yield *o*-amino and *N*-alkylaminobenzophenones **2** & **4**

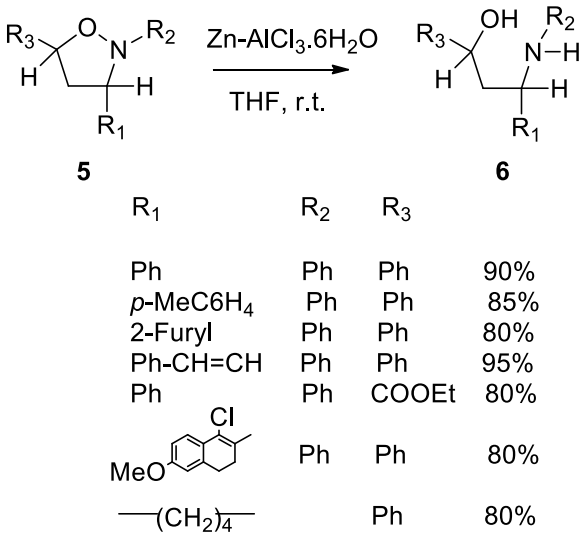
respectively (Scheme 1).[2] *o*-Amino and *N*-alkylaminobenzophenones[3] are the key intermediates for the synthesis of several clinically used drugs of 1,4-benzodiazepine class, e.g., oxazepam, diazepam, flurazepam, alprazolam etc.[4] In addition, appropriately substituted 2-aminobenzophenone derivatives act as antiproliferative agents and antimitotic agents.[5] A wide range of derivatives of 2,1-benzisoxazoles and its salts was successfully investigated under this protocol. It was found that the cleavage of 2,1-benzisoxazoles to furnish corresponding *o*-aminobezophenones occurs in better yield (88-92%) compared to its salts which produced corresponding *N*-alkylaminobenzophenones in moderate yield (60-65%).



Scheme 1

2.2. Reductive cleavage of isoxazolidines

Zn-$AlCl_3$.$6H_2O$ system can also perform the reductive cleavage of the N-O bond of isoxazolidines **5** to produce 1,3-amino alcohols **6**.[6] A variety of isoxazolidine derivatives have been examined and the conversion found to proceed successfully under ambient conditions within a period of short reaction time (Scheme 2). Naturally occurring 1,3-amino alcohols as well as synthetic derivatives thereof exhibit wide ranges of biological activities.[7] They are also widely used as ligands for asymmetric catalysts and synthetic intermediates.[8]



Scheme 2

2.3. Chemoselective reduction of ketones

Chowdhury and Borah[9] developed a mild and chemoselective method for the reduction of aliphatic ketones to the corresponding methylene derivatives using Zn-$AlCl_3.6H_2O$-THF-H_2O system at room temperature. A broad range of structurally diverse ketones **7a-j** have been tested using the catalytic system (Table 1). It was observed that the reaction was more successful for the cyclic ketones (entry 1-5, Table 1) compared to the acyclic ketones (entry 6, Table 1). The reagent could chemoselectively reduce a six membered ring ketone in the preference of a five membered one (entry 3, Table 1). The free ester group and isolated double bonds were unaffected under the reaction condition. It was noteworthy that the ketone **7e** (entry 5, Table 1) was deoxygenated efficiently by this method which under Clemmensen[10] or Wolf-Kishner reduction[11] condition produced a mixture of products. Interestingly, aliphatic and aromatic aldehydes (**7g** & **7h**), aromatic ketones **7i** and α,β-unsaturated ketones **7j** were reduced to the corresponding alcohols (entry 7-10, Table 1).

Table 1. Chemoselective reduction of carbonyl compounds by Zn-$AlCl_3.6H_2O$-THF-H_2O system

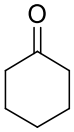
Entry	Substrates	Products	Yield (%)
1	 **7a**	 **8a**	50

Table 1. Continued

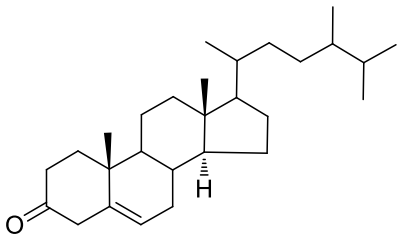
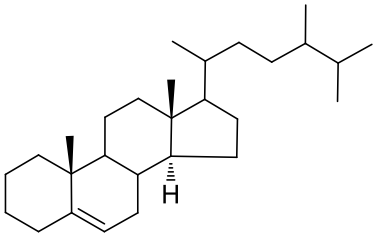
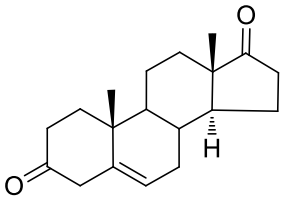
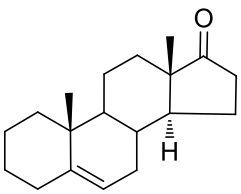
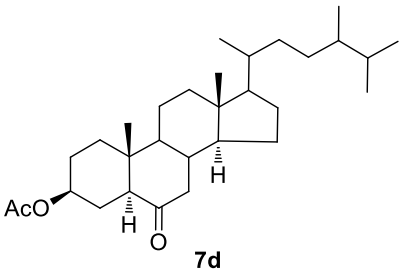
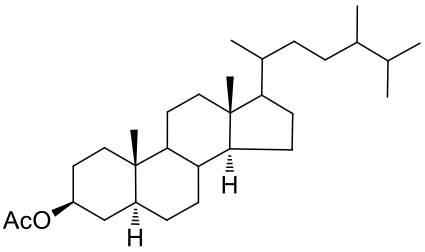
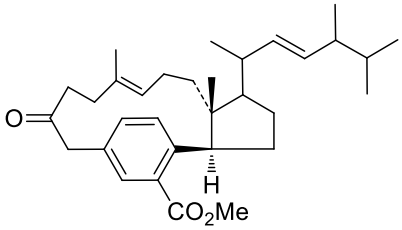
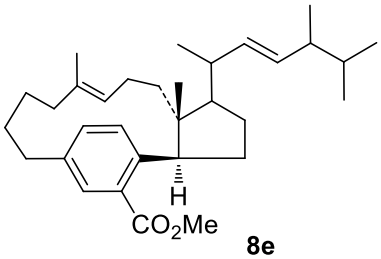
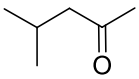
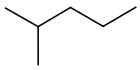
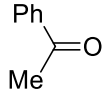
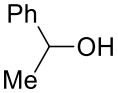
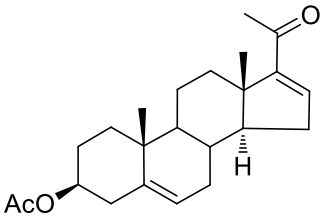
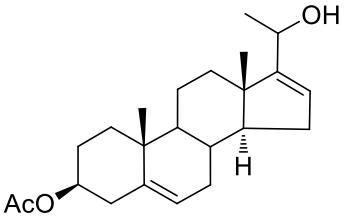
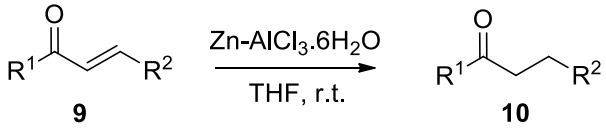
Entry	Substrates	Products	Yield (%)
2	 **7b**	 **8b**	90
3	 **7c**	 **8c**	80
4	 **7d**	 **8d**	60
5	 **7e**	 **8e**	70
6	 **7f**	 **8f**	20
7	$CH_3(CH_2)_{14}CHO$ **7g**	$CH_3(CH_2)_{14}CH_2OH$ **8g**	70
8	PhCHO **7h**	$PhCH_2OH$ **8h**	90

Table 1. Continued

Entry	Substrates	Products	Yield (%)
9	 **7i**	 **8i**	85
10	 **7j**	 **8j**	90

2.4. Chemoselective reduction of C=C bonds of α, β-unsaturated carbonyl compounds



Scheme 3

Konwar et al. showed that the Zn-$AlCl_3.6H_2O$ combination in moist THF can act as an excellent reducing system for the chemo-selective reduction of carbon-carbon double bond of the α,β-unsaturated carbonyl compounds **9** (Scheme 3).[12] The methodology was generalized using different α,β-unsaturated ketones (entry 1-4, table 2), esters (entry 5-6, table 2) and acids (entry 7, table 2). It was observed that the process was also successful for the reduction of ene-diacid (entry 7, Table 2) and ene-diester (entry 6, Table 2). The quinones were reduced to the corresponding dihydroquinones in excellent yields (entries 8 and 9, Table 2). Notably, aromatic and heteroaromatic rings were not affected under the reaction condition.

Table 2. Selective reduction of carbon-carbon double bonds by Zn-$AlCl_3.6H_2O$ system

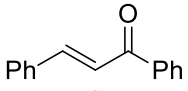
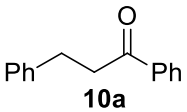
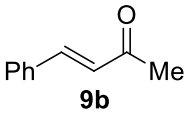
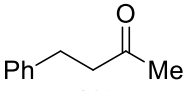
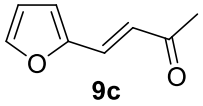
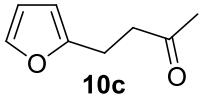
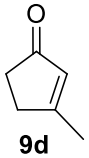
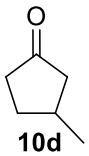
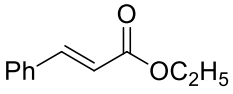
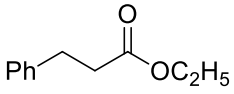
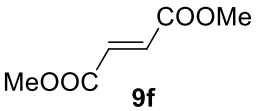
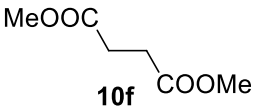
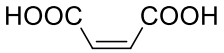
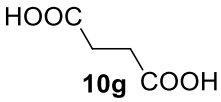
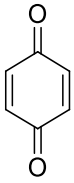
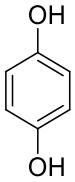
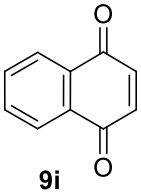
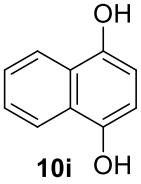
Entry	Substrates	Products	Yield (%)
1	 **9a**	 **10a**	90
2	 **9b**	 **10b**	88

Table 2. Continued

Entry	Substrates	Products	Yield (%)
3	 **9c**	 **10c**	60
4	 **9d**	 **10d**	82
5	 **9e**	 **10e**	88
6	 **9f**	 **10f**	98
7	 **9g**	 **10g**	95
8	 **9h**	 **10h**	100
9	 **9i**	 **10i**	98

2.5. Deoxygenation of organic N-oxides

Dutta and Konwar used Zn-$AlCl_3.6H_2O$ system for the N-deoxygenation of nitrones **11a-g**, heteroarene N-oxides **11h** and azoxy benzenes **11i** to their corresponding imines.[13] The sensitive carbon-carbon double bonds, furan and thiophene remained unaffected under the reaction conditions. Later on Boruah and Konwar replaced zinc with KI and developed even milder reagent system $AlCl_3.6H_2O/KI/CH_3CN/H_2O$ which was effective for the similar N-deoxygenations in hydrated medium at room temperature (Table 3).[14] The best result was obtained when acetonitrile and water was used in 2:1 ratio in the reaction mixtures. Similar to the earlier reagent system the $AlCl_3.6H_2O/KI$ also did not affect the aromatic or heteroaromatic rings.

Table 3. Reduction of organic N-oxides using $AlCl_3.6H_2O$/KI

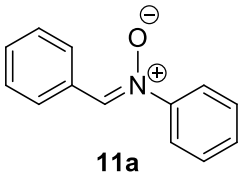
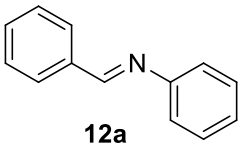
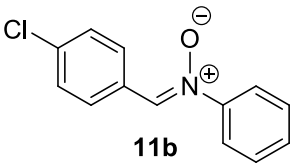
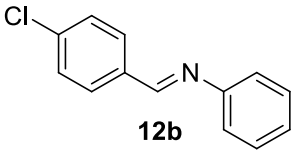
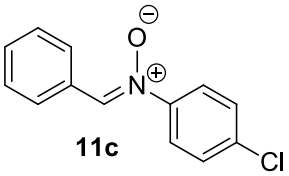
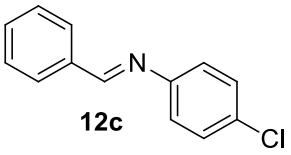
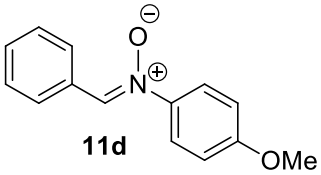
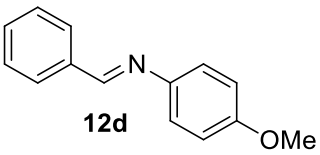
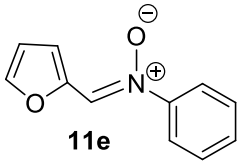
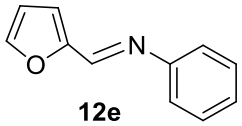
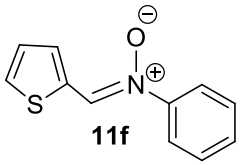
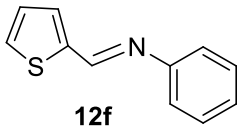
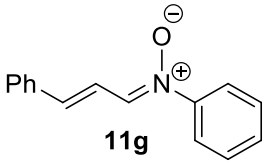
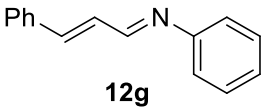
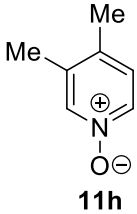
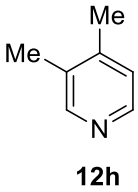
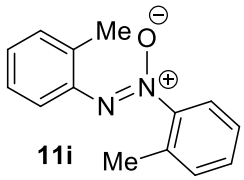
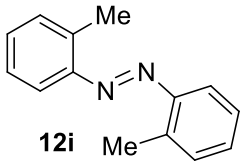
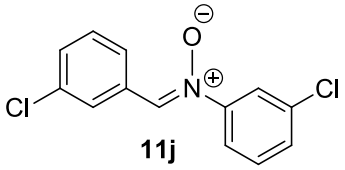
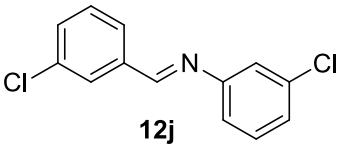
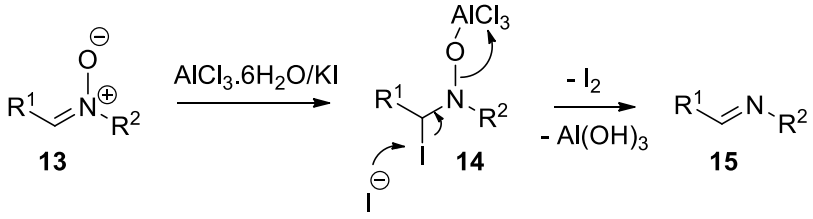
Entry	Substrates	Products	Yield (%)
1	 **11a**	 **12a**	90
2	 **11b**	 **12b**	92
3	 **11c**	 **12c**	85
4	 **11d**	 **12d**	80
5	 **11e**	 **12e**	72
6	 **11f**	 **12f**	75
7	 **11g**	 **12g**	70
8	 **11h**	 **12h**	80

Table 3. Continued

Entry	Substrates	Products	Yield (%)
9	 **11i**	 **12i**	72
10	 **11j**	 **12j**	75

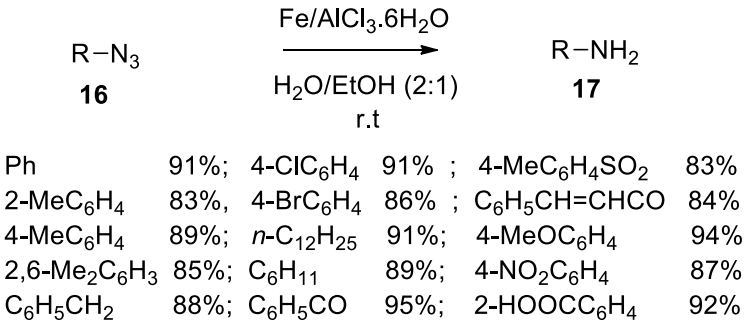
But the expected mechanism for the N-deoxygenation using KI/ $AlCl_3.6H_2O$ is different from the Zn/ $AlCl_3.6H_2O$ system. It is proposed that the $AlCl_3.6H_2O$ which in reality exist as $[Al(H_2O)_6]Cl_3$ in solution[1c] reacts with KI to form $[Al(H_2O)_6]I_3$. The iodide ion thus produced adds to the double bond of **13** and with the help of aluminium performs the deoxygenation to imines **15** through the formation of the intermediate **14** (Scheme 4).[14]



Scheme 4. Proposed mechanism for the deoxygenation of nitrones

2.6. Reduction of azides

The reduction of azides is a most common strategy for the synthesis of primary amines.[15] Li et al.[16] found that Zn/$AlCl_3.6H_2O$ could be used as an effective reagent for the reduction of azides to the corresponding primary amines in water or aq. ethanol at ambient condition. In another method, Zheng et al.[17] also efficiently reduced azides **16** to their corresponding primary amines **17** employing $AlCl_3.6H_2O$ in combination with iron (Scheme 5). The mild reaction condition did not affect sensitive functional groups like nitro, halides, carbonyl and ethers.



Scheme 5. Reduction of azides using Fe-$AlCl_3.6H_2O$ system

3. Dehydration of oximes and amides in hydrated media

Boruah and Konwar[18] showed that the $AlCl_3.6H_2O$/KI reagent system could perform the dehydration of aldoximes **18a-f** and amides **18g** to their corresponding nitriles. The interesting fact was that the dehydration actually was taking place in aqueous medium. The reaction was performed in CH_3CN/H_2O solvent system at 80 °C and there was no report of formation of side products like triazines. The authors showed flexibility of the reagent system using both aliphatic and aromatic aldoximes and amides (entry 1-7, table 4). The mild reaction condition allowed the sensitive functional groups like methyl ether, furan, thiophene etc. to remain intact. It was observed that cyclodehydration of appropriately substituted amides produced isoquinoline derivatives in a similar manner to the Bischler–Napieralski reaction (entry 8, table 4). Interestingly, when ketoximes were allowed to react with the reagent system, the Beckmann rearrangement took place. So open chain ketoximes produced anilides or amides (entry 9, table 4) and cyclic ketoximes produced corresponding lactams (entry 10, table 4).

Table 4. Dehydration of oximes and amides using $AlCl_3.6H_2O$/KI

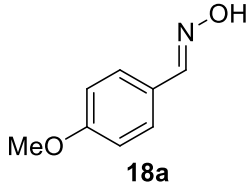
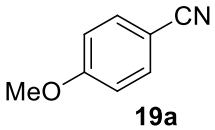
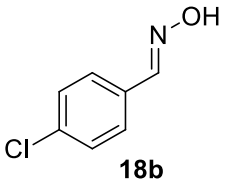
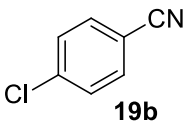
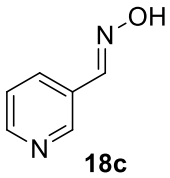
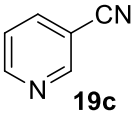
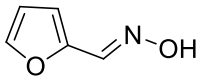
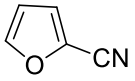
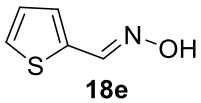
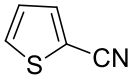
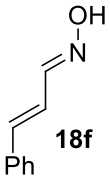
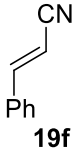
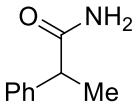
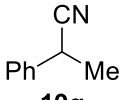
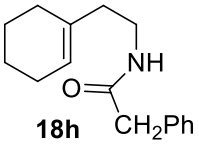
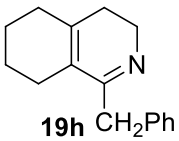
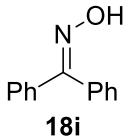
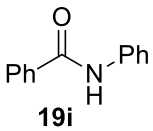
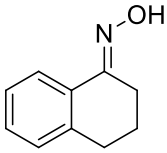
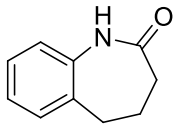
Entry	Substrates	Products	Yield (%)
1	 **18a**	 **19a**	96
2	 **18b**	 **19b**	75

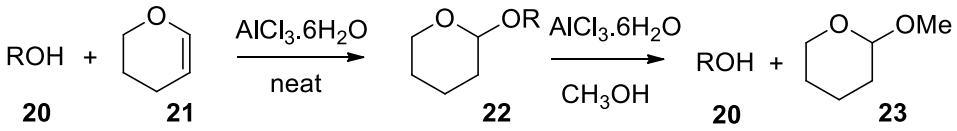
Table 4. Continued

Entry	Substrates	Products	Yield (%)
3	 **18c**	 **19c**	69
4	 **18d**	 **19d**	60
5	 **18e**	 **19e**	67
6	 **18f**	 **19f**	75
7	 **18g**	 **19g**	92
8	 **18h**	 **19h**	87
9	 **18i**	 **19i**	82
10	 **18j**	 **19j**	72

4. Protection and deprotection

4.1. Tetrahydropyranylation and depyranylation of alcohols and phenols

Varma and Namboodiri[19] reported a $AlCl_3.6H_2O$ catalyzed solvent free tetrahydropyranylation of alcohols and phenols by the reaction of aliphatic and aromatic alcohols **20** with 3,4-dihydro-2H-pyran (DHP) (**21**) (Scheme 6). A wide variety of alcohol and phenolic compounds (e.g., 3-hexanol, 4-butanediol, *t*-butanol, cyclohexanol, allyl alcohol, geraniol, 4-chlorobenzyl alcohol, phenol, 4-chlorophenol, 2-naphthol, benzhydrol etc.) were tested and in each case the corresponding THP ethers produced in good to excellent yield (74-96%). No dehydration reaction occurred when acid sensitive alcohols like *t*-butanol were pyranylated under the reaction condition. It was reported that the rate of the pyranylation reaction decreased with increase in substrate to catalyst ratio. In that case increase in the reaction temperature compensated the effect. Also substituted benzyl alcohols and solid alcohols needed comparatively higher temperature (60-80 °C) for the pyranylation. This method can be used for the mono tetrahydropyranylation of diols which is difficult to achieve with conventional methods. The method is also suitable for the moist substrates although the rate of the reaction decreases with increase in the water content. Interestingly, the same reagent can be used for the deprotection of the generated THP ethers. The deprotection is carried out at high substrate to catalyst ratio (500 mmol: 1 mmol) in excess methanol.

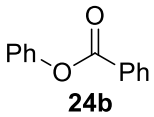
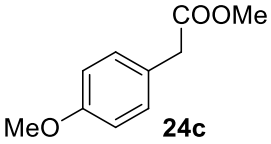
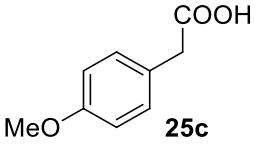
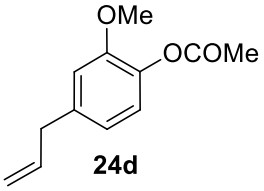
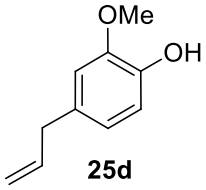
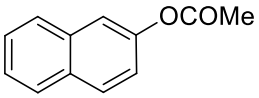
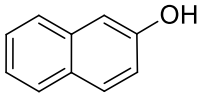
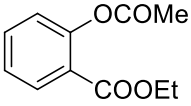
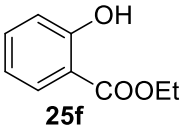
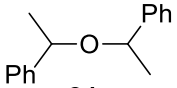
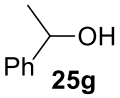
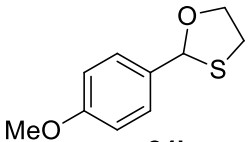
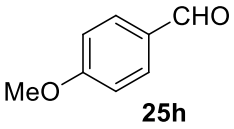
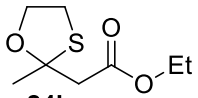
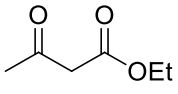
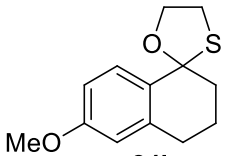
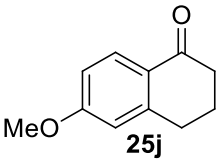


Scheme 6

4.2. Chemoselective deprotection of esters, ethers, and ketals

The $AlCl_3.6H_2O$/KI system is also useful for the cleavage of the C–O bonds of esters **24a-f**, ethers **24g**, and 1,3-oxathiolanes **24h-j**.[20] The reactions are performed in CH_3CN/H_2O medium at 80 °C. Under the reaction conditions, esters (entries 1-3, Table 5) and acetates (entries 4-6, Table 5) are converted to the corresponding acids and phenols, respectively. The reaction can be used for the chemoselective cleavage of the acetate functionalities in the presence of esters (entry 6, Table 5). Selective cleavage of either esters or acetates can also be achieved successfully without affecting the ether functionalities (entries 3 and 4, Table 5). But ethers also can be cleaved under the reaction condition to provide corresponding alcohols and iodides when only ether functionality is present in the molecule (entry 7, Table 5). The reagent system effectively can deprotect 1,3-oxathiolanes to the corresponding carbonyls (entries 8-10, Table 5). In these cases the deprotection can effectively be performed without disturbing either the ethers (entries 8 and 10, Table 5) or the esters (entry 9, Table 5).

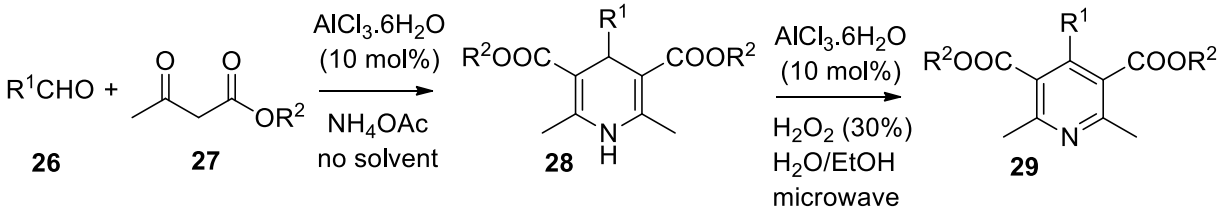
Table 5. Deprotection of esters, ethers, and ketals by $AlCl_3.6H_2O/KI/CH_3CN/H_2O$ system

Entry	Substrate	Product	Yield (%)
1	$CH_2(COOEt)_2$ **24a**	$CH_2(COOH)_2$ **25a**	65
2	 **24b**	Ph-COOH **25b**	78
3	 **24c**	 **25c**	76
4	 **24d**	 **25d**	83
5	 **24e**	 **25e**	90
6	 **24f**	 **25f**	80
7	 **24g**	 **25g**	89
8	 **24h**	 **25h**	90
9	 **24i**	 **25i**	84
10	 **24j**	 **25j**	77

5. Synthesis of 1,4-dihydropyridines and their aromatization

The versatility of the $AlCl_3.6H_2O$ as reagent was proved when it was found to catalyze the one pot three component Hantzsch dihydropyridine synthesis. So a 10 mol% $AlCl_3.6H_2O$ was able to catalyze the condensation of an aldehyde **26**, a beta keto ester **27** and NH_4OAc to produce dihydropyridines **28** at 60 °C in high yields under solvent free conditions (Scheme 7).[21] A broad range of structurally diverse aldehydes (both aromatic and aliphatic) and 1,3-dicarbonyl compounds were used to produce the corresponding dihydropyridines. The sensitive functional groups like furans were unaffected under the reaction condition. Interestingly, it was found that $AlCl_3.6H_2O$ also could catalyze the oxidation of dihydropyridines **28** to the corresponding pyridines **29** in the presence of H_2O_2 under microwave irradiation. Most probably the liberated HCl from $AlCl_3.6H_2O$ reacts with H_2O_2 to produce HOCl which performs the oxidation through the formation of a chlorine free radical.

As both the two steps in the synthesis of pyridines **29** were catalyzed by $AlCl_3.6H_2O$, it was also possible to combine them in one pot following the same protocol. So, substituted pyridines were synthesized by the condensation of aldehyde **26**, beta keto ester **27** and NH_4OAc in the presence of 10 mol% $AlCl_3.6H_2O$ and subsequent oxidation with 30% H_2O_2 in the same pot under microwave irradiation. The product was not separated or purified after the first step and no additional amount of $AlCl_3.6H_2O$ was added in the oxidation step.



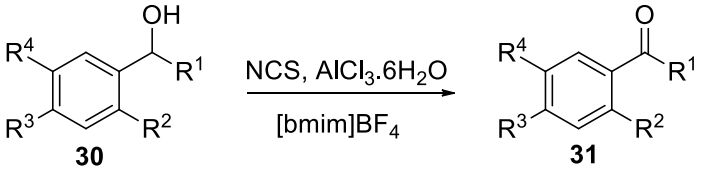
Scheme 7. $AlCl_3.6H_2O$ catalyzed synthesis of 1,4-dihydropyridines and pyridines.

Entry	R^1	R^2	Yield of dihydropyridines **28**	Yield of pyridines **29**
1	C_6H_5	Et	80	99
2	4-$MeOC_6H_4$	Et	77	97
3	4-$O_2NC_6H_4$	Et	75	96
4	4-ClC_6H_4	Et	76	97
5	CH_3	Et	74	96
6	CH_3CH_2	Et	76	95
7	$(CH_3)_2CH$	Et	78	100
8	2-Furyl	Et	73	94
9	C_6H_5	Me	78	98
10	4-$MeOC_6H_4$	Me	75	97

Yield refers to isolated yield (%).

6. Oxidation of alcohols to carbonyls

Chang et al.[22] developed an efficient and environmentally friendly method for the oxidation of benzylic alcohols **30** (both primary and secondary) to aldehydes and ketones **31** using $AlCl_3.6H_2O$ and NCS in ionic liquid [bmim]BF_4 (Scheme 8). A broad range of benzylic alcohols bearing both electron-donating and electron-withdrawing substituents were oxidized in this oxidation condition. Primary benzylic alcohols reacted at a faster rate compared to secondary alcohols. It was proposed that the oxidation reactions were accomplished by the reaction of alcohols with chlorium ion which was formed by the interaction of NCS with $AlCl_3.6H_2O$. Gogoi et al.[20] also reported a similar oxidation of both primary and secondary alcohols using $AlCl_3.6H_2O$/KI along with DMSO under refluxing condition.



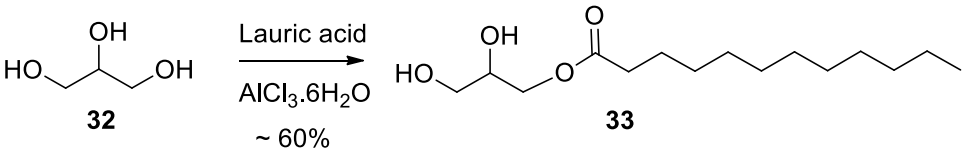
R^1 = H, Me, Et, Ph, PhCO
R^2 = H, MeO
R^3 = Me, F, Cl, Br, NO_2
R^4 = H, MeO

Scheme 8. Oxidation of benzylic alcohols using NCS/$AlCl_3.6H_2O$

7. Miscellaneous reactions

7.1. Esterification of glycerine with lauric acid

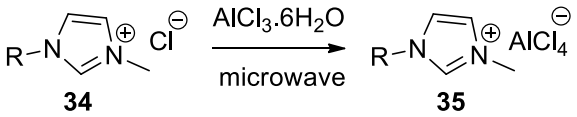
Sugi and coworkers[23] described an efficient method for the selective esterification of glycerine (**32**) with lauric acid using $AlCl_3.6H_2O$ as the catalyst in solvent free condition. The reaction selectively produced lauric acid monoglyceride (monolaurin) **33** in a moderate yield (Scheme 9). It was proved that the product was formed by a direct mono esterification of glycerine, not via the transesterification of lauric acid triglyceride (trilaurin). When the reaction was performed in excess lauric acid the process also produced di and triglycerides, albeit in a lower proportion. The mono- and di-glycerides of long chain fatty acids are widely used in the food, cosmetic and pharmaceutical industry.



Scheme 9. Monoesterification of glycerine with lauric acid

7.2. Preparation of ionic liquids bearing tetrachloroaluminate anions

Namboodiri and Varma[24] reported an efficient method for the preparation of ionic liquid dialkylimidazolium tetrachloroaluminates [C_nMIM][$AlCl_4$] **35** by the reaction of *N,N′*-dialkylimidazolium chloride **34** and $AlCl_3.6H_2O$ in quantitative yield using microwave irradiation (Scheme 10). The authors have prepared three different ionic liquids namely [C_4MIM][$AlCl_4$], [C_6MIM][$AlCl_4$], and [C_8MIM][$AlCl_4$] from respective *N,N′*-dialkylimidazolium chlorides using the procedure. It is to be noted that the ionic liquids with tetrachloroaluminate anion are very useful for several organic reactions. The utility of the synthesized ionic liquids was established by using them as recyclable catalyst for the tetrahydropyranylation and depyranylation of different alcohols.

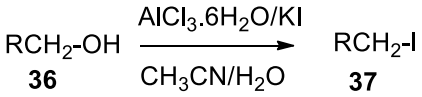


R = butyl, hexyl, or octyl

Scheme 10. Preparation of [C_nMIM][$AlCl_4$] using microwave irradiation

7.3. Iodination of benzyl alcohols

The $AlCl_3.6H_2O$/KI system can also act as an excellent iodinating agent for the iodination of benzyl alcohols **36** to benzyl iodides **37** in hydrated media (Scheme 11).[20] The reaction is equally applicable for different type of benzyl alcohols carrying both electron-donating and withdrawing groups.



R= C_6H_5	91%
p-HOC_6H_4	90%
p-$MeOC_6H_4$	92%
p-ClC_6H_4	88%

Scheme 11. Iodination of benzyl alcohols

8. Conclusions

The exploration of the chemistry of $AlCl_3.6H_2O$ by different group of scientists has resulted in understanding of the applicability of such an efficient and environment friendly reagent and catalyst in diverse range of organic reactions. By virtue of its low toxicity and versatility, it holds considerable promise as a reagent and catalyst. It offers the added advantage of being inexpensive and easy to handle. The results described in this review lead us to hope that there will be new and novel applications of the reagent in the near future.

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