Scientific Research

A New Facile Route to Chlorination of Alcohols via Lewis Acid AlCl₃

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ABSTRACT

Halogenated aluminates $AlCl_3$, applied as efficient chlorination reagent for hydroxyl groups of substitution alcohols is described. Primary and secondary benzylic alcohols could be transformed into corresponding aromatic halides with almost complete conversion and unique selectivity. As chlorination reagent, $AlCl_3$ has an incomparable advantage over others, such as low material cost, commercial availability as well as convenient product isolation.

**Keywords:** Alcohols; Lewis Acid; Nucleophiles; Chlorination

1. Introduction

Chlorination of alcohols has been accepted as one of the most important and commonly used transformations in organic synthesis and development of such a procedure is still desirable in academia as well as in industrial research [1-3]. However, due to the lower leaving ability, hydroxyl group is hardly substituted under mild conditions [3,4]. The most recent development can be linked to the discovery that the cooperation of $InCl_3$ and $HSiMe_2Cl$ enable chlorodehydroxylation of alcohols into organic chlorides in the presence of benzyl [5]. The other methods utilize Ph_3P-CCl_4 [6-8], PCl_5 [9], thionyl chloride [10], phenylmethyleniminium [10], benzoxazolium [11], Vilsmeier-Haack [12], and Viehe salts [13] as chlorination reagents, among them, HCl involved chlorination process represents the most prominent example of this reaction class [14-18]. Despite intensive research efforts over the past few years, the conversion usually requires elaborate reagents and quite drastic reaction conditions. Apparently, the undesirable reactions are caused, such as the arrangement or breaking of carbon skeleton, or poor functional group compatibility [7,19-21]. Not only that, for these multicomponent or too reactive reaction systems, some limitations keeps them away from industrial scale production. For instance, difficult product separation, large amount of waste disposal, expensive material cost, and low atom efficiency. In this context, the development of efficient reagents to use in mild conditions and improved preparative procedures allowing efficient conversion of alcohols into alkyl halides have interested organic chemists.

During our recent endeavor with the application of $AlCl_3$ in organic synthesis. We explored that $AlCl_3$ demonstrates excellent catalytic behavior in the oxidation of alcohol and Baeyer-Villiger reaction in the presence of H_2O_2 or Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) [22,23]. In the ongoing research programs, we concerned that reaction medias play important role in the Lewis acid $AlCl_3$ promoted transformations, for instance, the oxidation of alcohol reactions could be carried out in water media, and the well known Ritter reaction taken placed in the solvent of acetonitrile [24]. When we treated alcohol with the readily available $AlCl_3$ in 1, 4-dioxane, surprisingly, different transformation was occurred, chlorinated product was obtained with excellent yields (**Scheme 1**). In this communication, we wish to report our preliminary investigation on the solvent modulated chlorination of alcohol reactions. The highlights of our system are the following: 1) it offers simple method to activate hydroxyl group by Lewis acid $AlCl_3$, but no electrophilic substitution on the aromatic rings was detected; 2) The regenerated aluminum salt is precipitated from reaction mixture, which could be separated by filtering. The feature is very attractive because it limits the amount of waste typically generated by traditional chlorination reagents and does not lead to environmentally hazardous byproducts.

2. Results and Discussion

We then selected 3-methylbenzyl alcohol as a typical substrate to optimize the reaction conditions (**Table 1**).
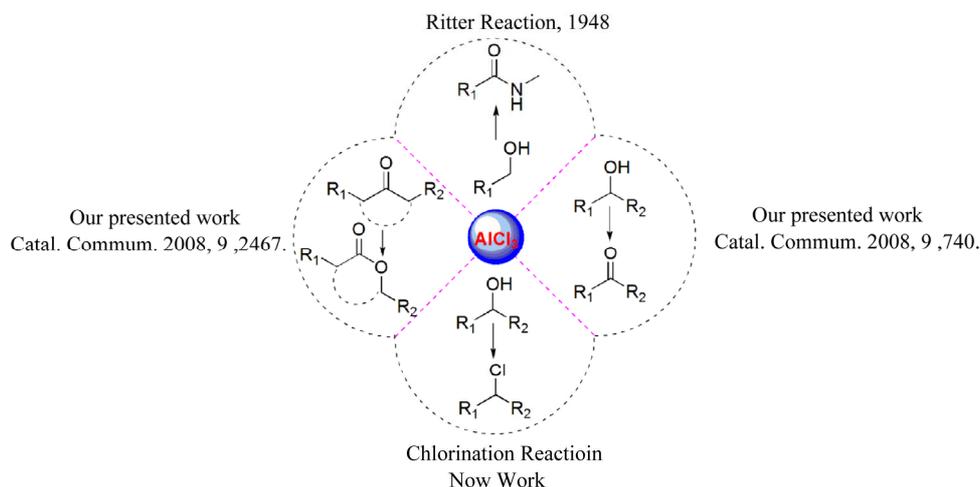
Scheme 1. AlCl₃ involved reactions.

Table 1. Study of reaction conditions for the chlorination of 3-methybenzyl alcohol[a].

Entry	AlCl₃ (mmol)	T (°C)	Time (h)	Conv. (%)[b]	Sele. (%)[b]
1	0.5	70	5	58	9
2	1.0	70	5	81	50
3	1.5	70	5	100	94
4	1.75	70	5	100	100
5	2.0	70	5	100	100
6	1.75	30	5	34	46
7	1.75	40	50	62	56
8	1.75	50	5	88	77
9	1.75	60	5	92	82
10	1.75	70	5	100	>99
11	1.75	70	1	76	91
12	1.75	70	2	87	95
13	1.75	70	3	99	98
14	1.75	70	4	99	99

[a]Reaction condition: alcohol (1.0 mmol), 1,4-dioxane 3 mL; [b]Conversion and selectivity were determined by GC analysis.
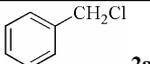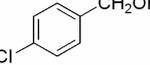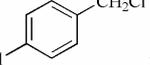
Screening of the common used solvents revealed that this conversion occurred in acetone, THF, toluene, CH_2Cl_2 and $CHCl_3$, these media were inferior in terms of reaction efficiency. 1, 4-dioxane proved to be the most effective one, furnishing the product in >99% conversion, which was probably due to its stronger polarity and better solubility for AlCl₃. The quantities of alcohol and AlCl₃ were varied to find a suitable ratio to provide the maximum yield of 3-methylbenzyl chloride (entries 1-5). When the amount of alcohol and AlCl₃ in a 1:0.5 ratio could produce the corresponding chloride in moderate conversion (entry 1). Increasing the amount of AlCl₃ over 1 equiv significantly increased the conversion of the target product (entries 2-5). Elevated temperature ap-

parently benefit the reaction, when the reaction mixture was warmed to 70°C, 3-methylbenzyl alcohol was transformed into product almost quantitative conversion and providing complete bias to aromatic chloride in a short time (entry 13). Meanwhile, we applie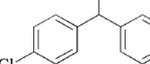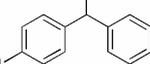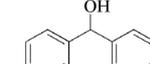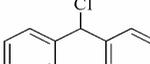d other Lewis acids as chlorination reagent, for instance, $ZnCl_2$, $SnCl_2$, $SnCl_4$, $FeCl_2$, $FeCl_3$, etc.; the transformation could not be occurred under the optimized conditions.

Varity of alcohols were investigated to abroad the scope of the reaction (**Table 2**). Effective transformation was observed in the reaction with the representative aromatic alcohols, all of them could be recovered chemically pure after a simple aqueous workup. For examples, in the cases of **1e**, **1f**, **1g**, methyl and phenoxyl groups exhibited accelerating effect to the chlorination reaction, almost completed conversions and >96% selectivity could be obtained. Electron-withdrawing group also demonstrated no negative effect for the transformation, and nitro moieties tolerated these reaction conditions to furnish the corresponding chlorides **2c** and **2d** in 100% conversion (entries 3 and 4). Compared to benzylic alcohols, benzhydrol and their derivatives' displayed relatively low activities (entries 8-10). It was also noted that as steric hindrance of the alcohol increased and chlorination reaction could be suppressed, for instance, triphenylmethanol gave the corresponding product in low yield. Under the optimal conditions, attempts to convert aliphatic alcohols into aliphatic halides were disappointed. To address this issue, we increased the amount of AlCl₃, and raised the temperature as well as prolonged the reaction time to improve the reaction rate. Under these modified conditions, the chlorination of 1-octanol and cyclohexanol can not be completed; more complicated mixture was produced, and can not be well isolated.

So as to apply the system to industrial research, several representative alcohols were tested in more large scale (**Scheme 2**). The typical experimental process as

Table 2. Conversion of aromatic alcohols into the corresponding alkyl halides[a].

Entry	Substrate	Product	Conv. (%)[b]	Sele. (%)[b]	Yield (%)[c]
1	1a	2a	99	99	80
2	1b	2b	100	100	82
3	1c	2c	100	80	
4	1d	2d	100	99	
5	1e	2e	97	96	75
6	1f	2f	100	96	78
7	1g	2g	100	100	84
8	1h	2h	90	80	63
9	1i	2i	99	90	72
10	1j	2j	90	80	
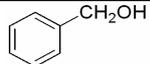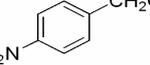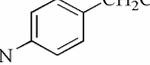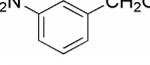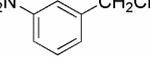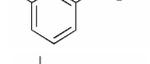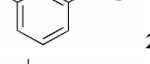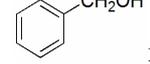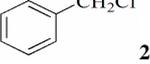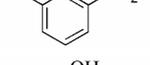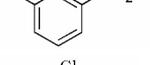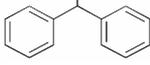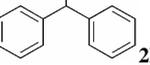
[a]Reaction condition: alcohol (1.0 mmol), 1, 4-dioxane 3 mL, AlCl$_3$ (1.75 mmol), 3 hours, 70°C; [b]Conversion and selectivity were determined by GC analysis. [c]All yields are for pure, isolated products.

2a, yield 89 % **2b**, yield 65 % **2c**, yield 75 %

2h, 54 % **2i**, 60 %
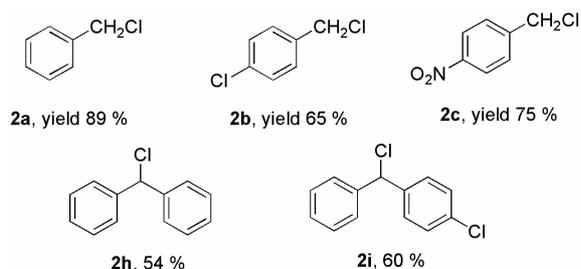
Scheme 2. Larger scale application.
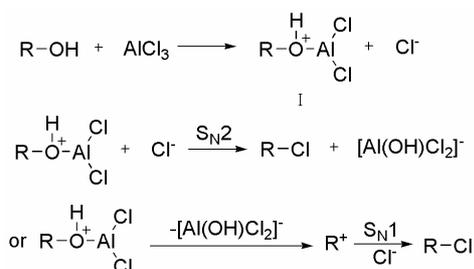
Scheme 3. The plausible reaction mechanism.

$$R-OH + AlCl_3 \longrightarrow R-\overset{H}{\underset{}{O}}\overset{+}{-}Al\overset{Cl}{\underset{Cl}{}} + Cl^-$$

I

$$R-\overset{H}{\underset{}{O}}\overset{+}{-}Al\overset{Cl}{\underset{Cl}{}} + Cl^- \xrightarrow{S_N2} R-Cl + [Al(OH)Cl_2]^-$$

$$\text{or } R-\overset{H}{\underset{}{O}}\overset{+}{-}Al\overset{Cl}{\underset{Cl}{}} \xrightarrow{-[Al(OH)Cl_2]^-} R^+ \xrightarrow[Cl^-]{S_N1} R-Cl$$

follows: AlCl$_3$ were added to a solution of alcohol (20 grams) in 1, 4-dioxane. After stirring at 70°C for 8 - 10 h, the crude products were obtained by distillation or recrystallization with good yields (>54%), especially, most crude product's purity was up to 99%.

Basing on the literature [5,25-27], we have proposed a plausible mechanism for the chlorination of alcohol as depicted in **Scheme 3**. The strong Lewis acid AlCl$_3$ was encapsulated by OH bond of ROH leads to the intermediate **I** which, when R is an aryl groups, decomposes either concertedly or via the formation of a carbocation

into the corresponding alkyl chloride RCl with the evolution of [Al(OH)Cl$_2$]$^-$.

3. Experimental

3.1. General Information

All NMR spectra are recorded on MERCURY (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) spec-

trometers; chemical shifts are expressed in ppm (δ units) relative to TMS signal as internal reference in CDCl$_3$. Gas chromatography (GC) analysis was performed on a Shimadezu GC-2010 equipped with a 15 m × 0.53 mm × 1.5 μm RTX-1 capillary column and a oxyhydrogen flame detector. GC/MS analysis were carried out on a trace HP GC6890/MS5973 equipped with a 25 m × 0.25 mm SE-54 column and a Shimadzu GC-16A gas chromatograph with a 3 m × 3 mm OV-17 column.

3.2. General Procedure for Chlorination Alcohols with AlCl$_3$

To a 10 mL round flask were added 1.0 mmol alcohol, 3 mL of 1, 4-dioxane, and 1.75 mmol AlCl$_3$ (0.234 g). Then the flask was immersed in a preheated 70˚C oil bath for 5 h. The mixture was cooled to room temperature, after filtering, 1 mL water was added to solution, and the sample was extracted with CH$_3$COOC$_2$H$_5$ (3 mL × 4). Then the organic layer was dried over anhydrous Na$_2$CO$_3$ and concentrated to dryness. Isolated product is obtained by column chromatograph. (Petroleum ether/ ethyl acetate = 1 ~ 10:1, V/V). The percentage conversion and reaction selectivity were determined by GC analysis.

3.3. General Procedure for Large Scale Chlorination Alcohols with AlCl$_3$

To a 100 mL round flask were added 20 gram alcohol, 60 mL of 1, 4-dioxane, and 1.75 equiv. of AlCl$_3$. Then the flask was immersed in a preheated 70˚C oil bath for 5 h. The mixture was cooled to room temperature, after filtering, 10 mL water was added to solution in order to hydrolyze the excessive AlCl$_3$, and the sample was extracted with CH$_3$COOC$_2$H$_5$ (30 mL × 4), Then the organic layer was dried over anhydrous Na$_2$CO$_3$ and concentrated to dryness. The crude product can be obtained by recrystallization or distillation.

3.4. The Data for Representative Products

Benzyl chloride (**2a**)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.38 - 7.32 (m, 4H, Ar-H), 4.57 (s, 2H, CH$_2$).
^{13}C NMR (100 MHz, CDCl$_3$): δ = 137.43, 128.68, 128.53, 128.35, 46.23.

4-Chlorobenzyl chloride (**2b**)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.35 - 7.32 (m, 4H, Ar-H), 4.49 (s, 2H, CH$_2$).
^{13}C NMR (100 MHz, CDCl$_3$): δ = 136.02, 134.36, 130.01, 128.985, 45.42.

3-methylbenzyl chloride (**2e**)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.25 - 7.18 (m, 4H, Ar-H), 4.54 (s, 2H, CH$_2$), 2.34 (s, 3H, CH$_3$).
^{13}C NMR (100 MHz, CDCl$_3$): δ = 138.48, 137.38,

129.31, 129.18, 128.64, 125.63, 46.36, 21.32.

2-methylbenzyl chloride (**2f**)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.34 - 7.25 (m, 4H, Ar-H), 4.63 (s, 2H, CH$_2$), 2.48 (s, 3H, CH$_3$).
^{13}C NMR (100 MHz, CDCl$_3$): δ = 137.03, 135.41, 130.56, 129.64, 128.76, 126.183, 44.65, 18.55.

Chlorodiphenylmethane (**2h**)
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.38 - 7.31 (m, 10H, Ar-H), 4.57 (s, H, CH).
^{13}C NMR (100 MHz, CDCl$_3$): δ = 141.07, 128.89, 128.42, 126.03, 41.92.

4. Conclusion

In conclusion, we have demonstrated a novel method for chlorination of alcohols using AlCl$_3$ system under mild conditions. The procedure is more convenient with respect to other reports and can be used as a valid alternative to other methods, so avoiding tedious purifications or the use of more toxic reagents. Further utility of this novel system is currently under investigation.

5. Acknowledgements

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