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NMP-mediated chlorination of aliphatic alcohols with aryl sulfonyl chloride for the synthesis of alkyl chlorides

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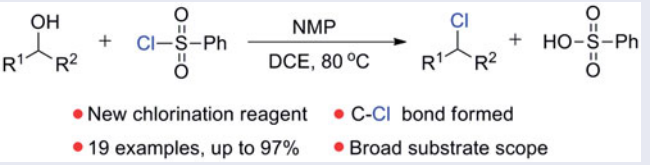
ABSTRACT

NMP-mediated chlorination of aliphatic alcohols has been developed for the synthesis of alkyl chlorides. This facile, efficient and practical approach used simple and readily available aryl sulfonyl chlorides as the chlorination reagent for the construction of C–Cl bond in good to excellent yields with mild conditions and broad substrate scope.

GRAPHICAL ABSTRACT



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KEYWORDS
Alkyl chlorides; aliphatic alcohols; aryl sulfonyl chloride; chlorination; NMP

Introduction

The importance of alkyl chlorides, both in the field of natural products and medical chemistry, have received extensive attention of investigators owing to their potential biological activities (Fig. 1A).[1] In addition, alkyl chlorides are important synthons in organic synthesis and have been employed extensively in various synthetic transformations.[2] As a result of this widespread utility, a number of methodologies have been developed to synthesize alkyl chlorides,[3] Hunsdiecker-type reaction,[4] nucleophilic substitution reaction,[5] radical coupling reaction of organometallic reagent,[6] reductive chlorination of carbonyl compound[7] and transition metal-catalyzed C(sp^3)-H chlorination reaction[8] are examples of some most commonly used methodologies. Among which, the most appropriate method is the nucleophilic substitution reaction in transformation of aliphatic alcohols into alkyl chlorides. However, the conversion of alcohols into the corresponding alkyl chlorides often suffers from a serious limitations due to the use of chlorination reagent,[9] such as HCl, $SOCl_2$, CCl_4, PCl_3 and PCl_5, which prone to hydrolysis, oxidation and toxic, and even to produce the by-product harmful for the

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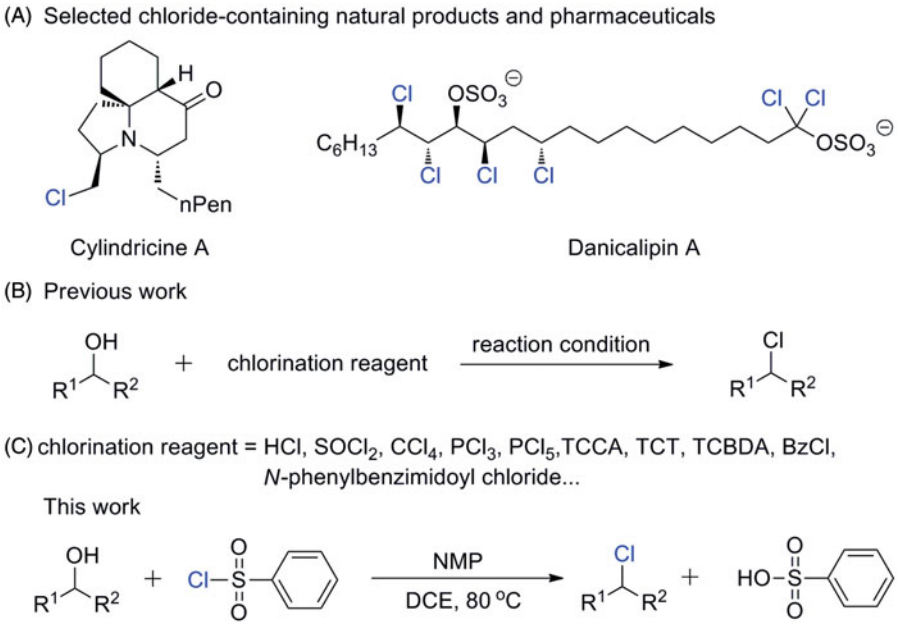


Figure 1. Selected chloride-containing natural products and pharmaceuticals (A); different chlorination reagent for the formation of alkyl chlorides from aliphatic alcohols (B); presented method (C).

environment. To overcome these limitations, the stable and elaborate chlorination reagents[10] such as TCCA, TCT, TCBDA, 3,3-dichloro-1,2-diphenylcyclopropene, *N*-phenylbenzimidoyl chloride, (chloro-phenylthiomethylene) dimethylammonium chloride, *N*,*N*,*N*′,*N*′-tetrachlorobenzene-1,3-disulfonamide and chloride-based ionic liquids, have been developed for the synthesis of alkyl chlorides. However, these chlorination reagents have to be prepared through some complex procedures. These drawbacks still limits the universality of the nucleophilic chlorination of OH groups. Therefore, the development of a simple and efficient chlorination reagent for the synthesis of alkyl chlorides from readily available aliphatic alcohols is still highly desirable.

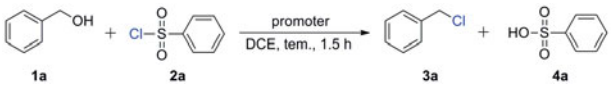
As part of our ongoing work in the field of C–Cl bond formation[11] and for the development more useful chlorination reagent,[12] we try to use inherently safer reagent as chlorination reagent to construct C–Cl bond from the C–OH bond of alcohols. Owing to the lower volatility and lower reactivity towards water, aryl sulfonyl chloride is less toxic and hazardous than classical chlorination agents, such as CCl_4, $SOCl_2$, PCl_3 and $COCl_2$. To date, only limited methods on the chlorination of allyllic alcohol were reported with toluenesulfonyl chloride[13] and methanesulfonyl chloride as chlorination reagents.[14]

We herein present a novel and highly efficient method for the NMP-mediated chlorination of aliphatic alcohols employing cheap, safe and readily available aryl sulfonyl chlorides as the exclusive reagent as shown in Figure 1C.

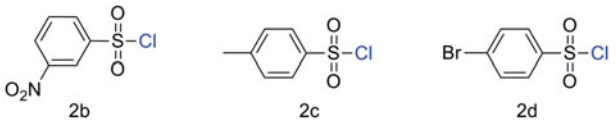
Results and discussion

We started our investigation by choosing benzylic alcohol (**1a**) and benzenesulfonyl chloride (**2a**) as model substrates. Initially, the reaction of **1a** (1.0 equiv.) with **2a**

Table 1. Optimization of the reaction conditions.[a]



Entry	Promoter	Chloride source	Temp. (°C)	Yield (%)[b]
1	NMP	2a	80	97
2	–	2a	80	0
3	DMF	2a	80	90
4	DMAc	2a	80	80
5	DEF	2a	80	88
6	DMPr	2a	80	20
7	NMP	2a	60	59
8	NMP	2a	100	95
9[c]	NMP	2a	80	62
10[d]	NMP	2a	80	75
11[e]	NMP	2a	80	90
12	NMP	2b	80	68
13	NMP	2c	80	51
14	NMP	2d	80	54
15[f]	NMP	2a	80	90

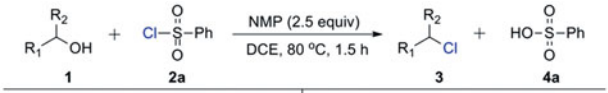


[a]Reaction conditions: **1a** (10 mmol), **2a** (13 mmol), promoter (2.5 equiv.), DCE (3.0 mL) at 80 °C under air for 1.5 h.
[b]Isolated yield.
[c]NMP (1.0 equiv.).
[d]NMP (1.5 equiv.).
[e]NMP (2.0 equiv.).
[f]Without DCE.

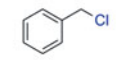
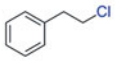
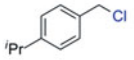
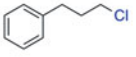
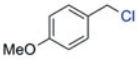
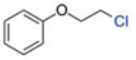
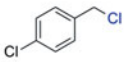
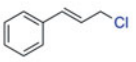
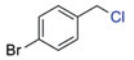
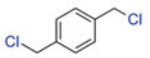
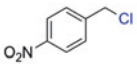
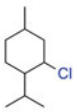
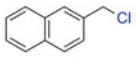
(1.3 equiv.) was performed in DCE (3.0 mL) at 80 °C for 1.5 h under air in the presence of NMP (2.5 equiv.) as promoter. Fortunately, the desired product (chloromethyl)benzene (**3a**) was obtained in yield of 97% (Table 1, entry 1). Then, control experiment was examined, and the reaction was totally shut down in the absence of NMP (Table 1, entry 2). Subsequently, various accelerating agents were screened (Table 1, entries 3–6), and the results showed that the yield of the desired product were more or less suppressed. Then, the influence of temperature were screened (Table 1, entries 7–8), and 80 °C was found to be the ideal reaction temperature. In order to enhance the reaction efficiency, then the loading of the promoter were examined (Table 1, entries 9–11), and the results indicated that the yield of the **3a** was decreased with the reducing of the loading of the promoter.

Next, we expected that changing the electronic properties of substituents on the aryl ring would have a significant impact on the efficiency of the reaction. Therefore, we screened a range of aryl sulfonyl chloride bearing electron-withdrawing substituent (*m*-NO_2) or electron-donating substituents (*p*-Me, *p*-Br), and found that the reaction was depressed in the absence of either the electron-withdrawing substituent or the electron-donating substituents on the aryl ring of the aryl sulfonyl chloride (Table 1, entries 12–14). Interestingly, we found that the chlorinations proceed efficiently to afford the desired products in 90% yield even in the absence of any solvent (Table 1, entry 15). Thus, the optimization of the reaction condition was acquired with benzylic alcohol (**1a**)

Table 2. Chlorination of various alcohols.[a]



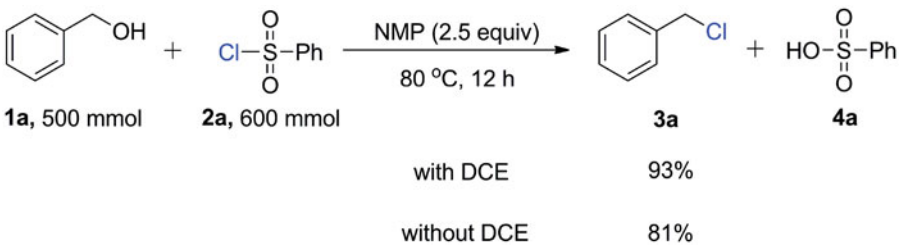
1 2a 3 4a

Entry	Product	Yield(%)[b]	Entry	Product	Yield(%)[b]
3a		97	3l		95
3b		92	3m		96
3c		95	3n		96
3d		94	3o		82
3e		94	3p		90
3f		95	3q		60
3g		92	3u		58
3h		94	3v		76
3i		88	3w		41
3j		97	3x		0
3k		93			

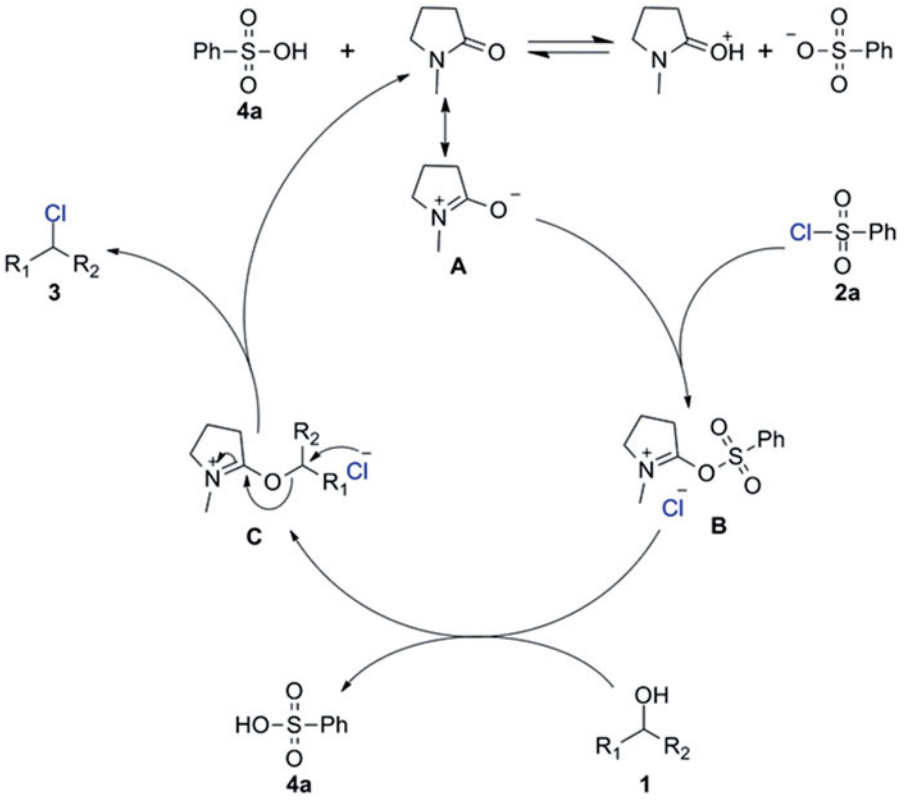
[a]Reaction conditions: **1** (10 mmol), **2a** (1.3 equiv.), promoter (2.5 equiv.), DCE (3.0 mL) at 80 °C under air for 1.5 h.
[b]Isolated yield.

(1.0 equiv.), benzenesulfonyl chloride (**2a**) (1.3 equiv.) and NMP (2.5 equiv.) in DCE at 80 °C under air (Table 1, entry 1).

With the optimal reaction conditions in hand, we proceeded to investigate the scope of aliphatic alcohols. As shown in Table 2, various benzylic alcohol bearing electron-withdrawing substituents (X=Cl, Br, NO_2) or electron-donating substituents (X=H, ^{i}Pr, OMe) at the para-position of the aryl ring all worked smoothly and produced the desired product in excellent yields (92–97%, **3a**–**3f**). Then, substituents such as bromo-(**1g**), methyl-(**1h**) and methoxy-(**1i**) on the more sterically encumbered position (ortho-position of the aryl ring) produced the expected product in excellent yields (**3g**–**3i**). Additionally, substrates containing bromine at the meta-position of the aryl ring (**1j**)



Scheme 1. Application studies.



Scheme 2. Proposed mechanism.

and one naphthalene moiety (**1k**), even substrates such as aliphatic alcohols with long-chain (**1l**–**1m**), all reacted smoothly and afforded the corresponding product in excellent yields (**3j**–**3m**). Then, substrates bearing heteroatom and double bond could all generate the corresponding alkyl chloride in good yields (**3n**–**3o**). What's more, substrates including diol and secondary alcohol could also well compatible with this reaction system, and to afforded the corresponding product (**3p**–**3u**). Moreover, to enrich the scope of substrates, a tertiary alcohol was investigated in this reaction system. Although the corresponding alkyl chloride was not obtained, the simple alkene was obtained (**3v**), which may be due to the rate of elimination of tertiary alcohol is much faster than its chlorination.[15] Finally, a range of heterocyclic substrates, such as 2,5-dimethylolfuran, furfuryl alcohol and 2-thiophene methanol were screened under the optimized conditions,

unfortunately, none of them could produce desired product. To our delight, 3-pyridinemethanol yield corresponding product (**3w**) in 41% yield.

It is noteworthy that the NMP-mediated chlorination of aliphatic alcohols with aryl sulfonyl chloridefor the synthesis of alkyl chlorides could be effectively scaled up, which will meet the demands of the industry. For example, **1a** (500 mmol), **2a** (600 mmol) and NMP (2.5 equiv.) in the presence or absence of DCE at 80 °C for 12 h, the corresponding product **3a** was obtained with 93% and 81% yields, respectively (Scheme 1).

Based on the above experimental results and previous studies,[11,16] a plausible reaction mechanism was proposed in Scheme 2. Initially, a resonance balance between NMP and active species **A** exists, and then the interaction of benzenesulfonyl chloride **2a** with active species **A** to afford Vilsmeier–Haack type complex **B**. Next, aliphatic alcohol **1** was added, and the hydroxyl group of the alcohol interacts with **B** to produce the intermediate **C** and **4a**. Finally, **C** reacted with chloride ion in S_N2 fashion to produce the corresponding alkyl chloride **3**, and regenerate the NMP, which could be interacts with **4a** to regulate the pH of the reaction system.

Conclusions

In conclusion, we have developed a highly efficient and practical NMP-mediated nucleophilic substitution reaction for the transformation of aliphatic alcohols into alkyl chlorides. In the reaction, simple, readily available and inherently safe aryl sulfonyl chloride emerged as efficient chlorination reagent, and the reaction takes advantage of mild reaction conditions, broad substrate scope and high functional group tolerance, even expected to find broad application in both academia and industry.

Experimental

General procedures for the synthesis of alkyl chlorides

In a round-bottom flask, benzylic alcohol **1a** (10 mmol, 2.0 equiv.), benzenesulfonyl chloride **2a** (13 mmol, 1.3 equiv.) and NMP (2.5 equiv.). Then, DCE (3 mL) were added. The mixture was stirred at 80 °C for 1.5 h. After completion of the reaction (monitored by TLC), water (10 mL) was added and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel to give the desired alkyl chlorides **3a**.

About 97% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.29 (m, 5H), 4.53 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.60, 128.83, 128.69, 128.49, 46.37. GC–MS (%): 126.0 (M^+, 52.58), 91.2 (100).

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