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DMSO-catalyzed chlorination of alcohols using *N*-phenylbenzimidoyl chloride

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Abstract *N*-phenylbenzimidoyl chloride has been demonstrated as an efficient chlorination reagent catalyzed by dimethyl sulfoxide (DMSO) in conversion of alcohols to corresponding chlorides. The reaction conditions were mild, and most of the substrates gave satisfactory yields. The configuration inversion of the chlorination was proved using optically active phenyl alcohols. The amount of DMSO can be as low as 0.001 eq without reducing the efficiency of the chlorination. A plausible mechanism for the reaction was proposed and proved by experiments. The reaction is stereoselective and potentially chemoselective among primary benzyl alcohols, secondary benzyl alcohols, and unactivated aliphatic alcohols.

Keywords Alcohols · Halogenation · *N*-phenylbenzimidoyl chloride · Sulfoxides

Introduction

Transformation of alcohols into corresponding halides plays an important role in organic synthesis, not only in the laboratory but also at the industrial level. Numerous methods are available to accomplish this conversion under various reaction conditions; e.g., hydrochloric acid [1], thionyl chloride [2, 3], phosphorus chloride [4], N,N–Diphenylchlorophenylmethyleniminium chloride [5], benzoxazolium [6],

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Vilsmeier Haack [7, 8], Viehe salts [9, 10], PPh_3-halogenated reagents [11], (chlorophenylthiomethylene)dimethylammonium chloride [12], halide-based ionic liquids [13], and the complex of 2,4,6-trichloro[1,3,5]triazine and *N*,*N*-dimethylformamide [14] have been reported as viable routes for chlorination of alcohols with high efficiency.

Organocatalysis can accelerate chemical reactions with a substoichiometric amount of an organic compound which does not contain any metal atom [15]. Recently, they have received much attention and been successfully applied to various chemical reactions. DMSO is a common aprotic solvent. It is a favored solvent for a great variety of reactions. It can also be used as an oxidant in the Swern oxidation [16–18], Kornblum reaction [16, 19, 20], etc. In 1995, Snyder reported firstly conversion of alcohols to chlorides by trimethylsilyl chloride (TMSCl) and a catalytic quantity of DMSO [26].

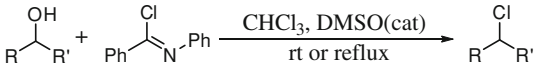
N-phenylbenzimidoyl chloride is easily and quantitatively prepared by reaction of *N*-phenylbenzamide(benzanilide) using thionyl chloride, being isolated as a light-yellow solid [27] which can react with amines or alcohols under basic conditions.

Herein, we introduce *N*-phenylbenzimidoyl chloride as a new chlorination reagent for converting alcohols into corresponding chlorides with DMSO as organocatalyst.

Results and discussion

A number of potential solvents [chloroform, ethyl acetate, toluene, acetone, dichloromethane, and tetrahydrofuran (THF)] were tested using chlorination of 1-benzylethanol as a benchmark. Chloroform gave higher yield and was chosen as the reaction solvent in subsequent experiments. Investigations into the impact of DMSO on the rates of reactions showed that, without DMSO, no chloride products were detected, and increasing the quantity of DMSO above 0.1 eq did not improve the reaction rates or yields. This supports our assumption that DMSO can function as an organocatalyst. To test the efficiency of the DMSO catalyst, we reduced the amount of DMSO from 0.05 to 0.001 eq, with only a slight decrease in reaction rate being observed. This is the most efficient organocatalyst to our knowledge [15]. When other sulfoxides such as tetramethylene sulfoxide and 2-methanesulfinyl-1-phenylethanone were used to catalyze the chlorination, the reaction rates were about half that with DMSO.

The procedure was based on the reaction of *N*-phenylbenzimidoyl chloride with DMSO in chloroform, followed by addition of the alcohols (Scheme 1). Various alcohols were all converted to corresponding chlorides in high yields. The reaction byproduct, *N*-phenylbenzamide, could be precipitated and filtrated by addition of petroleum ether.



Scheme 1 General method for chlorination of alcohols using *N*-phenylbenzimidoyl chloride

The scope and limitations of the chlorination reaction were explored with various alcohols, and the results are summarized in Table 1. With the primary and secondary alcohols at 70 °C (entries 1, 4–7, and 16; Table 1), the reaction rates are usually faster, requiring ca. 1.5 h for completion. Although benzyl alcohols can also be chlorinated at room temperature (entries 1–12 and 16; Table 1), longer reaction times are required for primary benzyl alcohols (from 6 to 24 h, entries 1–5; Table 1) and secondary alcohols (from 2 to 4 days, entries 6–13; Table 1). Chlorination of aliphatic alcohols (entries 13–15; Table 1) must be performed under reflux conditions of chloroform, indicating that benzyl alcohols have higher reactivity than aliphatic alcohols. However, tertiary alcohol, for example, 1-phenyl-1-(4-methylphenyl)ethanol, only gave elimination product at room temperature. Primary benzyl alcohols with electron-releasing groups are usually superior to electron-withdrawing ones in terms of reaction time at room temperature, but no notable difference in yield was found at either room temperature or 70 °C. The effect of substituting groups to the secondary benzyl alcohols is not remarkable. Optically active alcohol, a sample of (*R*)-1-phenylethanol {$[\alpha]_D^{25}$ +36.19 (c 1, $CHCl_3$), 86.9 %ee}, under the above reaction conditions gave (*S*)-1-phenylethyl chloride {$[\alpha]_D^{25}$ −18.53 (neat), Lit. [25] $[\alpha]_D^{25}$ −23.7 (neat) (entry 16; Table 1)}, corresponding to 96 % inversion of the configuration. Analogously, (*R*)-1-phenyl-1-propanol and (*R*)-1-phenyl-1-butanol gave the corresponding (*S*)-chlorides with over 95 %

Table 1 Conversion of alcohols into corresponding chlorides by *N*-phenylbenzimidoyl chloride and DMSO

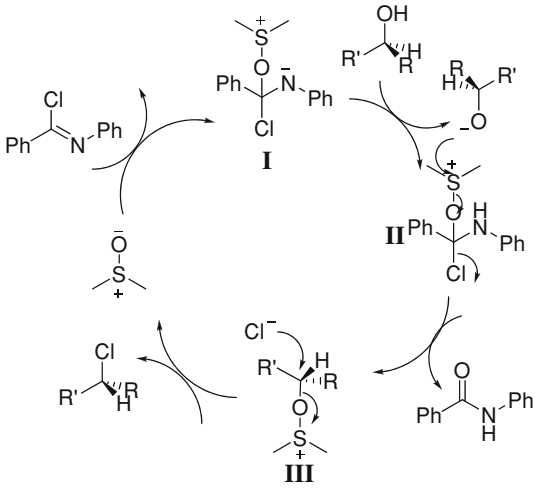
Entry	R	R′	Yield (time)[a]	Yield (time)[b]	Ref.
1	Ph	H	68 (24 h)	70 (1 h)	[21]
2	4-MeOPh	H	75 (6 h)	–	[21]
3	Piperonyl alcohol		80 (6 h)	–	[21]
4	4-ClPh	H	90 (12 h)	90 (1 h)	[21]
5	3-O_2NPh	H	87 (24 h)	85 (1.5 h)	[21]
6	Ph	CH_3	75 (4 days)	73 (1.5 h)	[22]
7	4-FPh	CH_3	54 (4 days)	56 (1.5 h)	[21]
8	4-ClPh	CH_3	82 (4 days)	–	[21]
9	4-BrPh	CH_3	82 (3 days)	–	[21]
10	4-MePh	CH_3	65 (4 days)	–	[21]
11	4-*n*-BuOPh	CH_3	73 (4 days)	–	[21]
12	2-BnOPh	CH_3	77 (2 days)	–	[21]
13	Cholesterol		–	90 (1.5 h)	[23]
14	Cyclohexanol		–	66 (12 h)	[24]
15	4-(6-Methoxynaphthalen-2-yl)butan-2-ol		–	84 (1.5 h)	
16[c]	Ph	CH_3	76 (4 days)	78 (1.5 h)	[25]

[a, b] Yields refer to pure isolated products in mass %, time is in hours or days

[a] Reaction temperature refers to room temperature

[b] Reaction temperature refers to reflux conditions of chloroform

[c] (*R*)-1-phenylethanol



Scheme 2 Plausible mechanism for chlorination of alcohols using *N*-phenylbenzimidoyl chloride

inversion of configuration. This is comparable to the classical conditions using a combination of $SOCl_2$ and pyridine [2, 3].

Mechanism

The stereochemical results indicate the occurrence of an S_N2 reaction that may be consistent with the mechanism depicted in Scheme 2. The reactions are exothermal and fast in the DMSO-involved Swern oxidation [19, 20] and Snyder chlorination [4] because very reactive sulfonium intermediates are generated. In our case, the reaction is not that fast, most probably because intermediate I is relatively unreactive, which forms II and generates a better nucleophile alcoholate from the alcohol. The alcoholate reacts with II to yield III. After attack by chloride anion, III yields the product with configuration inversion. The lower reactivity of the intermediates makes it possible to differentiate various types of alcohols according to the reaction rates (Table 1), whereas in the Swern oxidation [19, 20] and Snyder chlorination [4] rates of different types of alcohols are about the same.

Experimental

General

Chloroform was distilled over P_2O_5. All reagents were purchased commercially and used without further purification. Thin-layer chromatography (TLC) was performed on HG/T2354-92 GF254 silica gel precoated plates. ^1H nuclear magnetic resonance (NMR) [0.00 ppm for tetramethylsilane (TMS) as internal standard] spectra were recorded on a Varian Oxford 500 (500 MHz) instrument. Coupling constants are measured in Hertz. Infrared (IR) spectra were recorded using a Bio-Rad Excalibur

FTS3000 spectrometer. Elemental analyses for C, H, and N were performed on a Yanaco CHNCORNER MF-3 elemental analyzer, and the analytical results were within ±0.3 % of the theoretical values. The chiral alcohols were prepared according to Xie, J. etc. [28], and optical rotation was recorded on a PerkinElmer model 341 polarimeter (wavelength of light: 589 nm, temperature: room temperature). The products were separated by isolation method using column chromatography using a 40-cm column packed with silica gel 60 (Merck, 0.063–0.200 μ) and the product eluted with mixture solvents of hexane and ethers. All products reported here are known compounds, and their identity was determined with IR, ^{1}H-NMR or gas chromatography–mass spectrometry (GC–MS).

Typical procedure for chlorination of alcohols

To a mixture of *N*-phenylbenzimidoyl chloride (1.5 mmol) and DMSO (0.05 mmol) in dry chloroform was added an alcohol (1.0 mmol). The reaction mixture was stirred at room temperature for the time periods specified in Table 1 (refluxing was required for aliphatic alcohols). After completion of the reaction, the chloroform was removed under vacuum and petroleum ether was added, then filtrated. The filtrate was evaporated to give corresponding chlorides. After bulb-to-bulb distillation or filtration through silica gel, data for 4-(6-methoxynaphthalen-2-yl)butan-2-ol were as follows: IR (KBr). ν 3,008, 2,930, 1,634, 1,606, 1,455, 1,230, 1,029, 854 cm^{-1}; ^{1}H NMR (500 Hz, $CDCl_3$): δ 7.67 (m, 2H), 7.57 (s, 1H), 7.31 (d, 1H, J = 8.0 Hz), 7.12 (m, 2H), 3.91 (s, 3H), 3.84 (m, 1H), 2.85 (m, 2H), 1.90 (m, 2H), 1.25 (m, 3H). Elem. Anal. Calc. for $C_{15}H_{17}OCl$ (248.7) C 72.42, H 6.88, O 6.43, Cl 14.25; found C 72.60, H 6.71.

Conclusions

The reported procedure can effect conversion of alcohols to corresponding chlorides efficiently under mild conditions and be operated simply. We have demonstrated the application of *N*-phenylbenzimidoyl chloride in chlorination of alcohols with catalytic quantity of DMSO. The reaction is stereoselective and potentially chemoselective among primary benzyl alcohols, secondary benzyl alcohols, and unactivated aliphatic alcohols.

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