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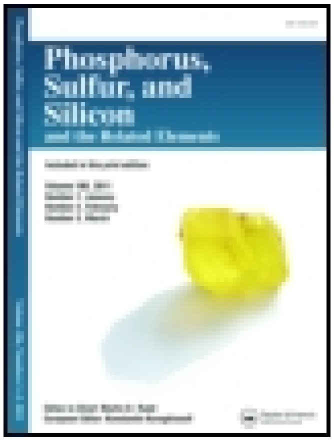

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One-pot, Selective and Mild Conversion of Benzylic Alcohols to gem-Dichlorides Using Chlorodiphenylphosphine and 2,3-Dichloro-5,6-dicyanobenzoquinone as a New and Neutral System

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One-pot, Selective and Mild Conversion of Benzylic Alcohols to *gem*-Dichlorides Using Chlorodiphenylphosphine and 2,3-Dichloro-5,6-dicyanobenzoquinone as a New and Neutral System

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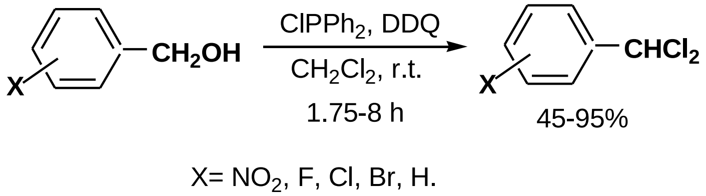
A shortened title of the article to be used as the running head:

“Conversion of Alcohols to *gem*-Dichlorides”

Abstract: A mild and one-pot conversion of benzylic alcohols to their corresponding *gem*-dichlorides is reported for first time using chlorodiphenylphosphine ($ClPPh_2$) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dichloromethane under neutral conditions and at room temperature. The present method can be efficiently used for preparation of *gem*-dichlorides even in the presence of some other functional groups with excellent chemoselectivity.



Keywords: Alcohol, *gem*-dichloride, chlorodiphenylphosphine, 2,3-dichloro-5,6-dicyanobenzoquinone, Chemoselectivity.

Introduction

Geminal dichlorides are very important compounds in organic synthesis[1,2] due to their ability as precursors to transition metal alkylidenes for carbonyl olefination.[2] The product dichloroarylmethanes are useful materials in pharmaceutical and agricultural industries.[3] Several methods have been reported for their synthesis from aldehydes or ketones such as the use of BCl_3,[4] $SOCl_2$/*N,N*-dimethylformamide (DMF),[5] PPh_3/CCl_4,[6] acid halides in the presence of acid catalysts,[7] WCl_6,[8,9] $(PhO)_3P/Cl_2$,[10] and alkylboron chloride derivatives[11] as chlorination reagents. Also, synthesis of *gem*-dichlorides from the reaction of hydrazones with copper (II) chloride-lithium *tert*-butoxide as an oxidizing agent, has been reported,[12a] and also in a minor modification of this procedure, this transformation has been performed *via* treatment of aldehyde- and ketone- derived *N*-*tert*-butyldimethylsilylhydrazones with $CuCl_2$ and a catalytic amount of $Sc(OTf)_3$.[12b] However, these methods contain some disadvantages such as long reaction times, low selectivity, use of toxic reagents, low yields, operation at high temperature or in acidic conditions and formation of undesired products. Also, as far as we know there is no report about the one-pot conversion of alcohols to *gem*-dichlorides in the literature. Consequently, there is a need for the development of convenient methods for the conversion of alcohols to these important compounds.

Results and Discussion

Herein, in continuation of our works on the new applications of trivalent phosphorus[13, 14] and also 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[14, 15] in organic synthesis including the conversion of aldehydes and ketones to *gem*-dichlorides,[16] we now report for first time a mild and one-pot conversion of benzylic alcohols to their corresponding *gem*-dichlorides using chlorodiphenylphosphine ($ClPPh_2$) and DDQ in dichloromethane as solvent at room temperature (Scheme 1).

Scheme 1

First, we selected 4-chlorobenzyl alcohol as a model and optimized the reaction conditions for its conversion to 1-chloro-4-dichloromethylbenzene using $ClPPh_2$ and DDQ. In these reactions, in order to avoid the formation of 4-chlorobenzyl chloride, firstly the alcohol was treated with DDQ producing the related aldehyde and then $ClPPh_2$ was added to the reaction mixture. The results of this study are shown in Table 1.

Table 1

We tried to perform this conversion with two equiv. amount of $ClPPh_2$ and DDQ in CH_2Cl_2 at room temperature. In this case, the corresponding *gem*-dichloride was produced in 70% yield after 2 h (Table 1, entry 1). Increasing of the molar ratio of the reagents to 2.5:2.5 caused an increase in both the yield and the rate of this transformation (Table 1, entry 2). On the other hand, decreasing of the amount of DDQ caused a decrease in the rate and/ or the yield of this reaction (Table 1, entries 2-5). The result of this reaction was not satisfactory under reflux or solvent-free conditions nor in CCl_4 or CH_3CN as the solvent instead of CH_2Cl_2 (Table 1, entries 6-9). Also, no product formation was observed using *N*-chlorosuccinimide (NCS) instead of DDQ. In this case, the alcohol was completely remained intact after 4 h (Table 1, entry 10). This result obviously shows the more efficiency of DDQ compared to NCS for performing of this important one-pot reaction.

Finally, with respect to the results from Table 1, the conditions mentioned in entry 3 of this Table (Alcohol:$ClPPh_2$:DDQ (1:2.5:2); CH_2Cl_2, r.t.) affording the desired *gem*-dichloride in 85% yield after 1.75 h, was selected as the optimized conditions for performing this valuable synthetic transformation and then applied for the one-pot conversion of other benzylic alcohols to their corresponding *gem*-dichlorides. The results are shown in Table 2.

Table 2

As shown in this table, primary benzylic alcohols, as well as Cinamyl alcohol, are conveniently converted to their corresponding *gem*-dichlorides using $ClPPh_2$ and DDQ in CH_2Cl_2 at room temperature in moderate to excellent yields. However, the application of the present method on the conversion of 4-methoxybenzyl alcohol gave 1-dichloromethyl-4-methoxybenzene in only 20% yield after 1 h. This unsatisfactory yield is probably related to the methoxy group in the para position, which decreases the stability of this product toward hydrolysis as described in the literature.[16, 17] Also, the application of the present method to the conversion of secondary benzylic alcohols such as benzhydrol and 1-phenyl ethanol was unsuccessful. In these cases, only the related ketones were produced immediately and no *gem*-dichloride formation was observed. On the basis of this result, we decided to study of the possibility of the conversion of primary benzylic alcohols to their corresponding *gem*-dichlorides in the presence of ketones and also some other compounds containing a specific functional group in binary mixtures. For this purpose, a mixture of 4-chlorobenzyl alcohol and another compound (1:1) was treated with DDQ (2 equiv.) in CH_2Cl_2 at room temperature producing 4-chlorobenzaldehyde followed by the addition of $ClPPh_2$ (2.5 equiv.) to the reaction mixture. The conversion yields of these selective reactions are shown in Scheme 2.

Scheme 2

As shown in this scheme, primary benzylic alcohols can be converted to their corresponding *gem*-dichlorides in the presence of epoxides, carboxylic esters and amides, ketones and phenols with excellent chemoselectivity *via* the present method.

Although the exact mechanism of this reaction is not clear, on the basis of the reports on the reaction of trivalent phosphorus with DDQ[14, 18] or *N*-chlorosuccinimide (NCS)[16] it is assumed that the produced aldehyde from the oxidation of primary benzylic alcohol with DDQ [19] is treated with the complex **A** resulted from the reaction of $ClPPh_2$ with remained DDQ producing **B** (Scheme 3). Then, this intermediate reacts with the released chloride anion affording the intermediate **C.** Finally, the desired *gem*-dichloride is formed *via* attacking of the second chloride anion to this intermediate. The aromatization of DDQ ring and the double bond formation between oxygen and oxophilic phosphorus are assumed as the major driving forces of this transformation.

Scheme 3

Experimental

Solvents, reagents and chemicals were obtained from Merck (Germany) and Fluka (Switzerland) chemical companies. Products are known compounds[4,5,16,20] and were characterized by comparison of their physical data, IR, ^{1}H and ^{13}C NMR spectra with those prepared according to literature procedures. Fourier transform infrared (FT-IR) spectra were recorded on a Perkin Elmer RXI spectrophotometer. NMR spectra were recorded on a Brucker Avance DRX-500 spectrometer. Thin layer chromatography (TLC) was carried out on silica-gel 254 analytical sheets obtained from Fluka. Characterization of an example product is presented in the Supplemental Materials (Figures S 1 and S 2)

Typical procedure for the one-pot conversion of 4-nitrobenzyl alcohol to 1-dichloromethyl-4-nitrobenzene using $ClPPh_2$ and DDQ:

4-Nitrobenzyl alcohol (0.153 g, 1 mmol) was added to a flask containing DDQ (0.54 g, 2 mmol) in CH_2Cl_2 (5 mL) at room temperature. $ClPPh_2$ (0.45 mL, 2.5 mmol) was added to the reaction mixture after TLC showed the complete conversion of this alcohol to its corresponding aldehyde and stirring was continued for 8 h. The solvent was evaporated. 1-Dichloromethyl-4-nitrobenzene was obtained after short column chromatography of the crude mixture on silica gel 60 (0.063-0.200 mm) using petroleum ether-ethyl acetate (40:1) as eluent in 90% yield, 0.186 g; mp 45-46°C (lit.[20b] 46°C); ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 6.77(s, 1H), 7.75-7.78(m, 2H), 8.25-8.27(m, 2H) ppm; ^{13}C-NMR ($CDCl_3$, 125.77 MHz): δ 70.2, 124.5, 127.8, 146.6, 148.9 ppm.

Conclusions

In conclusion, the present investigation has demonstrated that the use of DDQ and $ClPPh_2$ offers a simple, novel, convenient and one-pot method, avoiding the use of molecular halogen with its harsh handling for the conversion of primary benzylic alcohols to their corresponding *gem*-dichlorides. As far as we know the present method is the first method converting alcohols to *gem*-dichlorides in a direct and one-pot manner. Availability and ease of handling of the reagent; excellent selectivity; avoidance the isolation of the aldehyde, easy workup; and operation at room temperature in neutral media can be considered as other advantages of this new method.

FUNDING

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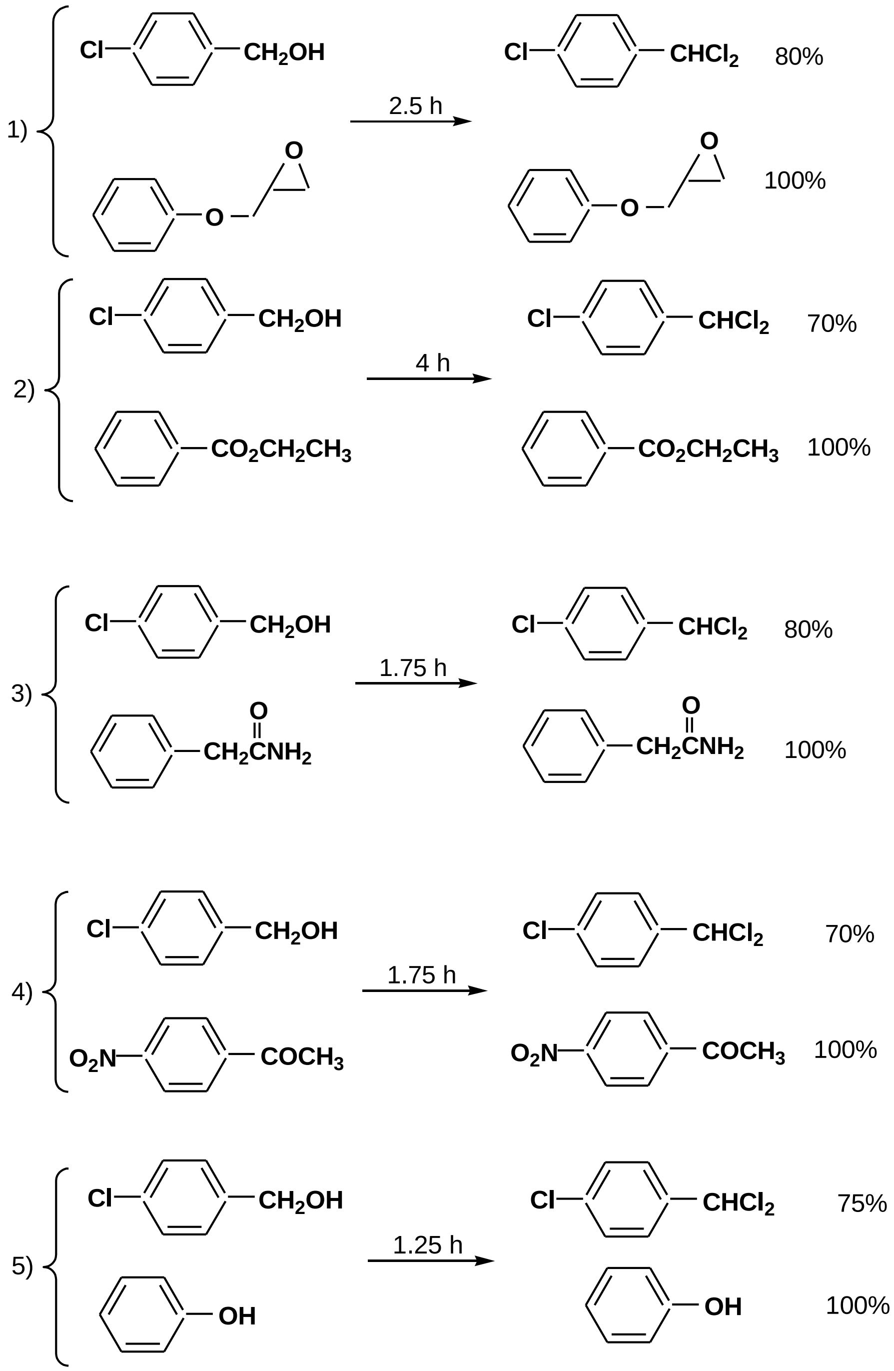
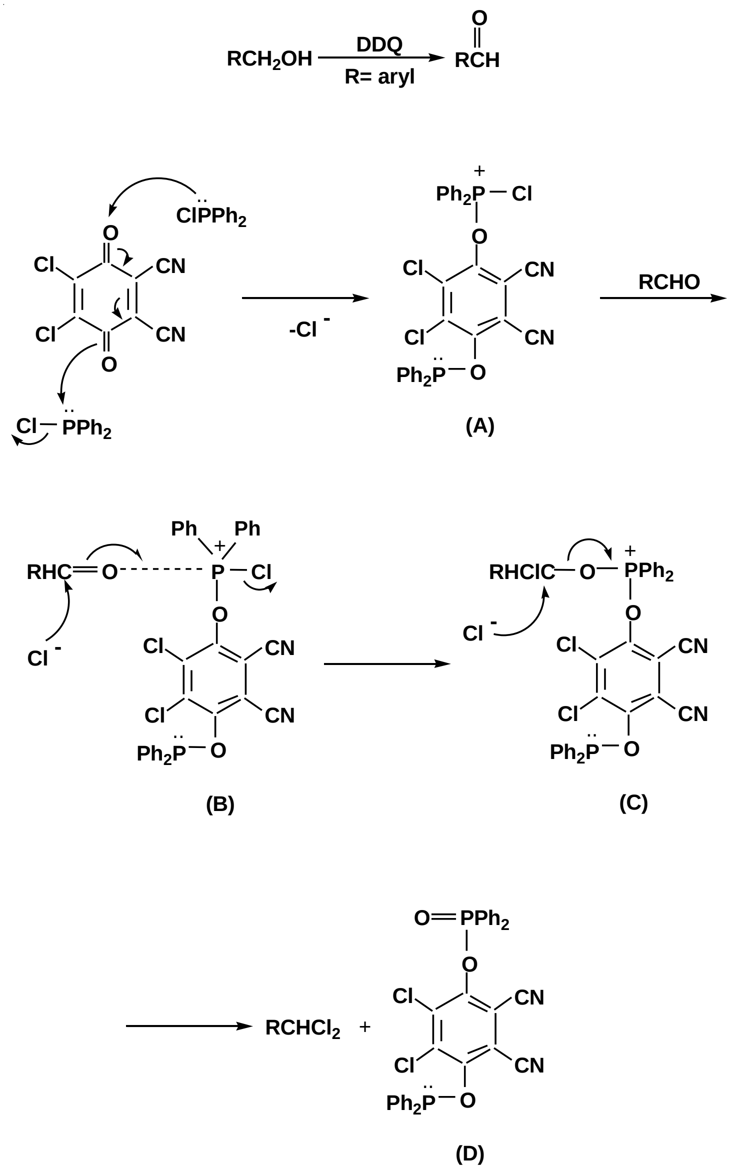
Scheme 1: The mild and one-pot conversion of benzylic alcohols to *gem*-dichlorides using ClPPh$_2$ and DDQ at room temperature. <TI>Comp- make red text in scheme black and add AQ asking author if it is okay to have changed it to black</TI>



Scheme 2: Various chemoselectivities in the one-pot conversion of 4-chlorobenzyl alcohol to 1-chloro-4-dichloromethylbenzene using $ClPPh_2$ (2.5 equiv.) and DDQ (2 equiv.) in CH_2Cl_2 at room temperature.



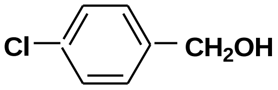
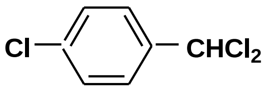
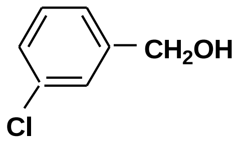
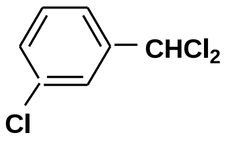
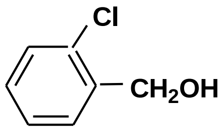
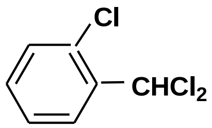
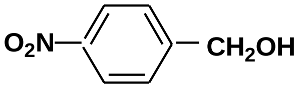
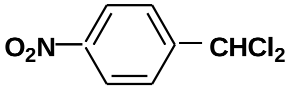
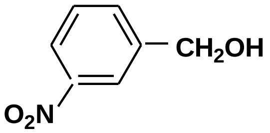
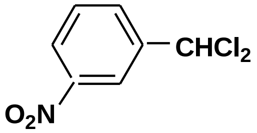
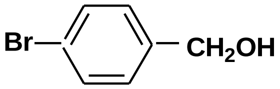
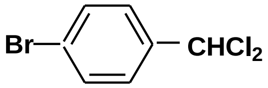
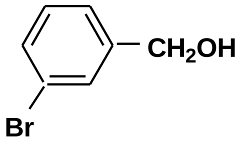
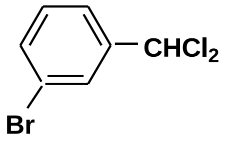
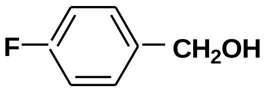
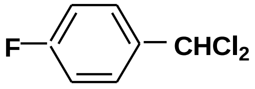
Scheme 3: The suggested mechanism of the one-pot conversion of benzylic alcohols to *gem*-dichlorides using $ClPPh_2$ and DDQ.[14,16,18]

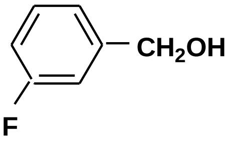
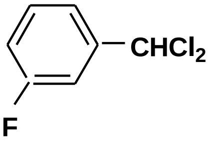
Table 1: Conversion of 4-chlorobenzyl alcohol to 1-chloro-4-dichloromethylbenzene using $ClPPh_2$ and DDQ at room temperature in various conditions.[a]

Entry	Solvent	Molar ratio (Alcohol:$ClPPh_2$:DDQ)	Time (h)	Yield (%)
1	CH_2Cl_2	1:2:2	2	70
2	CH_2Cl_2	1:2.5:2.5	1.25	85
3	CH_2Cl_2	1:2.5:2	1.75	85
4	CH_2Cl_2	1:2.5:1.5	2.5	50
5	CH_2Cl_2	1:2.5:1	1	15
6	CH_2Cl_2	1:2.5:2	2	40[b]
7	-	1:2.5:2	2.25	0[c]
8	CCl_4	1:2.5:2	2	20
9	CH_3CN	1:2.5:2	1.5	60
10	CH_2Cl_2	1:2.5:2	4	0[d]

[a] In these reactions, first alcohol was treated with DDQ producing the related aldehyde and then $ClPPh_2$ was added to the reaction mixture. [b] In this case, the reaction was carried out under reflux condition. [c] In this case, the reaction was performed *via* grinding of the reactants in a glass test tube. [d] In this case, *N*-chlorosuccinimid (NCS, 2 eq.) was used instead of DDQ.

Table 2: One-pot conversion of benzylic alcohols to *gem*-dichlorides using $ClPPh_2$ (2.5 eq.) and DDQ (2 eq.) in CH_2Cl_2 at room temperature.[a]

Entry	Alcohol	*gem*-Dichloride	Time (h)	Yield (%)[b]
1			1.75	80
2			6	61[c]
3			7	48[c]
4			8	90
5			4	88[c]
6			2.25	95
7			3.5	92
8			4	85

9			4	70
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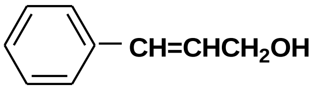
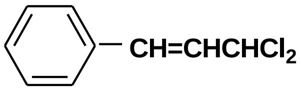
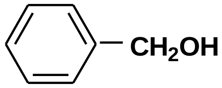
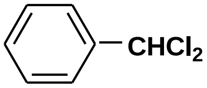
10			1.25	62
11			8	45

[a] In all of these reactions, first alcohol was treated with DDQ producing the related aldehyde and then $ClPPh_2$ was added to the reaction mixture. [b] Isolated yields. [c] In this case, $ClPPh_2$ and DDQ were used in 2.5:2.5 molar ratio.