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Selective Tandem Synthesis of Oximes from Benzylic Alcohols Catalyzed with 2, 3-Dichloro-5, 6-dicyanobenzoquinone

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In spite of many reports in the literature concerning with oxidation of benzylic alcohols to carbonyl compounds with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in stoichiometric amounts or even more, we surprisingly found that benzylic alcohols are directly oxidized to oximes using a catalytic amount of DDQ in the presence of hydroxylamine hydrochloride under solvent-free conditions. The present tandem catalytic method can be efficiently used for preparation of oximes in the presence of some other functional groups with excellent chemoselectivity.

Key Words : Alcohol, Oxime, 2,3-Dichloro-5,6-dicyanobenzoquinone, Tandem synthesis

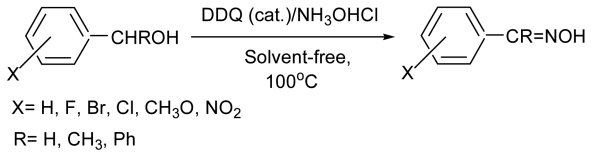
Introduction

Tandem processes that involve multiple chemical transformations in a single-pot with minimal work up and less waste generation have revolutionized synthetic chemistry in recent years.[1] These processes provide the advantage that intermediates do not require isolation where they are unstable or difficult to handle (*e.g.*, toxic, volatile or prone to polymerize). Such direct synthesis routes help to avoid side product formation and loss of starting material as well as to reduce capital investment and operation costs.

On the other hand, oxime is a frequently used functionality in organic synthesis. Oximes are stable and highly crystalline compounds which may be used as intermediates for the preparation of nitriles *via* dehydration,[2,3] amides by the Beckmann rearrangement,[4] nitrones,[5] hydroximinoyl chlorides,[6] nitrile oxides,[6] chiral α-sulfinyl oximes,[7] and nitro compounds.[8] Furthermore, oximes are useful selective α-activating groups[9] and also have served for the protection of carbonyl groups.[10] Some oximes are highly active and effective inhibitors.[11] Also, oximation is a very efficient method for characterization and purification of carbonyl compounds.[4] Therefore, synthetic organic chemists are interested in a facilitation of oxime synthesis from carbonyl compounds or even other sources. The usual method for the preparation of oximes involves treatment of aldehydes or ketones with hydroxylamine hydrochloride in a basic aqueous medium with adjustment of pH.[12] In addition, a large number of other methods have been reported for performing of this transformation.[13-15] However, some methods in this area are not very satisfactory due to drawbacks such as low yields, inability for the preparation of aromatic ketoximes, long reaction times, tedious work up and effluent pollution. Also, as far as we know the reports on the synthesis of oximes directly from alcohols are very less than from aldehydes or ketones especially in a catalytic way. Two reported methods in this area are the use of a two step procedure involving substitution with PPh_3/DEAD/*O*-TBS-*N*-tosylhydroxylamine in toluene-THF and subsequent treatment with CsF in acetonitrile[16] and also the use of activated MnO_2, 4 Å molecular sieves as dehydrating additive and alkoxylamines (and in certain cases, hydroxylamine itself) as their hydrochloride salts or supported on Amberlyst 15 in chlorinated solvent CH_2Cl_2 at reflux for overnight.[17] However, these methods do not contain catalytic process and use stoichiometric amounts of the reagents or even more for the synthesis of oximes from alcohols. For example, in the latter work manganese dioxide is used in excess amounts (5-20 equiv.). Also, recently this transformation has been carried out using gold supported on hydroxyapatite (Au/HAP) (HAP, $Ca_{10}(PO_4)_6(OH)_2$) as catalyst in toluene as solvent at 90 °C under O_2 bubbling.[18] However, these methods also suffer from some other disadvantages such as the use of a two step procedure or reagent that is not easily available, tedious work up especially in the case of using MnO_2, long reaction times, and low yields and also do not provide chemoselectivity or at least, chemoselectivity of the method is ambiguous. Consequently, there is a need for the development of new methods that are more convenient for this important synthetic transformation.

On the other hand, synthetic chemistry continues to develop various techniques for obtaining better products with less environmental impact. One of the more promising approaches is solvent-free reactions.[19] The elimination of volatile organic solvents in organic syntheses is a most important goal in 'green' chemistry. Furthermore, these reactions have some other advantages such as low costs, simplicity in process and handling, formation of cleaner products, enhanced selectivity, improved reaction rates and prevent waste solvent generation, hazards, and toxicity.

Herein, due to importance of tandem and solvent-free reactions and on the other hand the importance of oximes and their synthesis especially from alcohols and also in continuation of our previous works in the applications of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in organic synthesis[2,20,21] and regarding to its ability to oxidation of



Scheme 1. Tandem conversion of primary and secondary benzylic alcohols to oximes using a catalytic amount of DDQ in the presence of hydroxylamine hydrochloride under solvent-free conditions.

benzylic alcohols to aldehydes and ketones,[22] we now report an ease and chemoselective conversion of primary and secondary benzylic alcohols to oximes *via* a tandem manner using a catalytic amount of DDQ in the presence of hydroxylamine hydrochloride under solvent-free conditions (Scheme 1). It must be noted that in reports based on using DDQ as oxidizing agent for oxidation of benzylic alcohols to aldehydes or ketones, the use of stoichiometric amounts of this oxidant or even more has been reported[22] but the present method converting benzylic alcohols directly to oximes needs to merely a catalytic amount of DDQ in the presence of hydroxylamine hydrochloride.

Results and Discussion

First, we took 4-bromobenzylalcohol as an example and optimized the reaction conditions for its direct conversion to 4-bromobenzaldoxime using a mixture of DDQ and hydroxylamine hydrochloride (NH_3OHCl). The results are shown in Table 1. As shown in this table, this reaction was unsuccessful in CH_2Cl_2, H_2O-ethanol (1:1) and acetonitrile as solvent even under reflux condition (Table 1, entries 1-3) and also under solvent-free conditions at room temperature (Table 1, entries 5, 6). The yield of this reaction was increased with increasing the reaction temperature (Table 1, entry 7). Finally, 4-bromobenzylalcohol was converted to 4-bromobenzaldoxime using DDQ/NH_3OHCl (0.1:4) under solvent-free conditions at 100 °C after 14 h in excellent yield (Table 1, entry 8).

Table 1. Conversion of 4-bromobenzylalcohol to 4-bromobenzaldoxime using a mixture of DDQ and NH_3OHCl in various conditions

Entry	Solvent	Molar ratio[a]	Temp. (°C)	Time (h)	Yield (%)
1	CH_2Cl_2	1:0.1:4	reflux	18	10
2	H_2O-ethanol(1:1)	1:0.1:4	reflux	18	0
3	CH_3CN	1:0.1:4	reflux	8	20
4	-	1:0:4	100	12	0
5	-	1:0.1:4	rt	18	0
6	-	1:0.5:4	rt	1	0[b]
7	-	1:0.1:4	80	14	60
8	-	1:0.1:4	100	14	92
9	-	1:0.1:2	100	8	45
10	-	1:0.1:1	100	8	20
11	-	1:0.1:4	100	14	30[c]

[a]Molar ratio is related to alcohol:DDQ:NH_3OHCl. [b]In this case, the reaction mixture was ground in a glass test tube. [c]In this case, *N*-chlorosuccinimide (NCS) was used instead of DDQ.

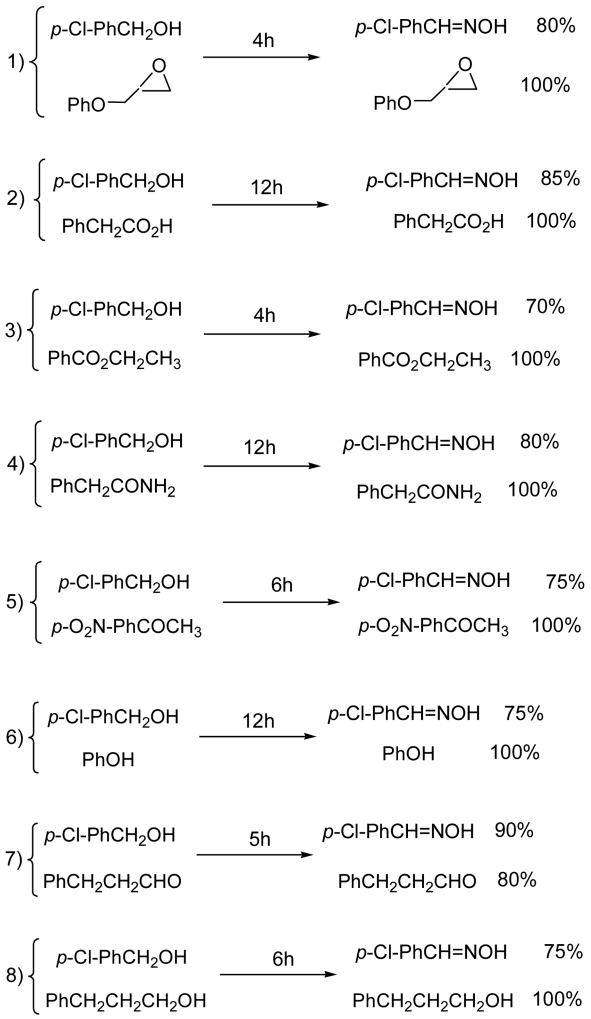
Table 2. Conversion of benzylic alcohols to oximes using a catalytic amount of DDQ (0.1 equiv.) and NH_3OHCl (4 equiv.) under solvent-free conditions at 100 °C

Entry	Alcohol	Oxime	Time (h)	Yield (%)[a]
1	*p*-Br-$PhCH_2OH$	*p*-Br-PhCH=NOH	14	92
2	*m*-Cl-$PhCH_2OH$	*m*-Cl-PhCH=NOH	12	85[b]
3	*o*-Cl-$PhCH_2OH$	*o*-Cl-PhCH=NOH	13	60
4	*m*-O_2N-$PhCH_2OH$	*m*-O_2N-PhCH=NOH	5	40
5	*p*-Cl-$PhCH_2OH$	*p*-Cl-PhCH=NOH	12	94
6	$PhCH_2OH$	PhCH=NOH	6	80[c]
7	*p*-CH_3O-$PhCH_2OH$	*p*-CH_3O-PhCH=NOH	1	60[b]
8	*p*-F-$PhCH_2OH$	*p*-F-PhCH=NOH	13	70
9	*m*-F-$PhCH_2OH$	*m*-F-PhCH=NOH	9	89[c]
10	Ph_2CHOH	Ph_2C=NOH	9	60
11	$PhCH(CH_3)OH$	$PhC(CH_3)$=NOH	1.5	71
12	$PhCH=CHCH_2OH$	PhCH=CHCH=NOH	10	30

[a]Isolated yield. [b]In this case, DDQ/NH_3OHCl was used in 0.1:10 molar ratio. [c]In this case, DDQ/NH_3OHCl was used in 0.1:6 molar ratio.

Omitting of DDQ in this conditions caused to complete unsuccessfulness of this reaction (Table 1, entry 4). Also, it was found that the yield of this reaction is decreased with decreasing of the amount of NH_3OHCl (Table 1, entries 9, 10). In order to compare of the efficiency of *N*-chlorosuccinimide (NCS) with DDQ, we decided to perform of this reaction using NCS instead of DDQ. We found that the desired product was formed in merely 30% yield using NCS/NH_3OHCl (0.1:4) under solvent-free conditions at 100 °C after 14 h (Table 1, entry 11) indicating the higher efficiency of DDQ in this catalytic tandem reaction. We therefore extended the optimized reaction conditions (Table 1, entry 8) for conversion of other benzylic alcohols directly to the corresponding oximes. The results are shown in Table 2.

As shown in this table, primary and secondary benzylic alcohols are directly converted to the corresponding oximes using a catalytic amount of DDQ in the presence of hydroxylamine hydrochloride at 100 °C under solvent-free conditions. Also, cinnamyl alcohol as an allylic alcohol was converted to the corresponding oxime *via* the present method although the yield of the reaction was low in this case (Table 2, entry 12). Based on the data of this Table it is obvious that this tandem catalytic method can also be considered as a way for characterization and purification of benzylic alcohols. In addition, for obtaining deeper insight into the applicability, selectivity and limitations of this new method, the possibility of the conversion of 4-chlorobenzyl alcohol to 4-chlorobenzaldoxime was studied in the presence of some other functional groups in different binary mixtures. For this purpose, a mixture of DDQ/NH_3OHCl (0.1:4) was prepared under solvent-free conditions in an oil bath at 100 °C followed by addition of 4-chlorobenzyl alcohol and other organic compound (1:1). The conversion



Scheme 2. Chemoselectivities in the tandem catalytic conversion of 4-chlorobenzyl alcohol to 4-chlorobenzaldoxime using DDQ/ NH_3OHCl (0.1:4) under solvent-free conditions at 100 °C.

yields obtained for these selective reactions of different binary mixtures are shown in Scheme 2.

As shown in this Scheme, it was found that benzylic alcohols can be directly converted to their corresponding oximes in the presence of epoxides, amides, carboxylic esters or acids, phenols, aldehydes, ketones and nonbenzylic alcohols with excellent chemoselectivity using the present method.

Although the exact mechanism of this reaction is not clear but it seems that probably DDQ hydroquinone is reversed to DDQ under air oxidation in the presence of excess amounts of hydroxylamine hydrochloride in 100 °C so that decreasing of hydroxylamine hydrochloride (Table 1, entries 8-10) or also reaction temperature (Table 1, entries 5 or 7) caused to decrease of the yield of reaction. In confirmation of this view, in previously reports based on oxidation of benzylic alcohols to carbonyl compounds using DDQ in the absence of hydroxylamine hydrochloride, the stoichiometric amounts of this oxidant was needed.[22]

It must be noted that the present method converting benzylic alcohols to oximes is a green method because: 1) It contains a tandem procedure. 2) It is operated under solvent-free conditions. 3) It needs to merely a catalytic amount of DDQ for this transformation.

Conclusion

In conclusion, the present investigation has demonstrated that the use of a catalytic amount of DDQ in the presence of hydroxylamine hydrochloride under solvent-free conditions offers an easy and tandem method for the conversion of primary and secondary benzylic alcohols to their corresponding aldoximes and ketoximes respectively. This method can be used for synthesis of oximes from benzylic alcohols even in the presence of some other functional groups with excellent chemoselectivity. The other significant advantages of the present method are as follow: 1) The catalyst used in this one-pot method is commercially available and easy to handle. 2) The work up of this tandem method is easy. 3) It functions without any additives such as molecular sieves. 4) It is extendable to conversion of allylic alcohols to their corresponding oximes. 5) In addition to synthetic importance, it can be used as a way for characterization and purification of benzylic alcohols and also 6) both primary and secondary benzylic alcohols can be converted to their corresponding oximes *via* the present tandem method.

Experimental

Solvents, reagents and chemicals were obtained from Merck (Germany) and Fluka (Switzerland) Chemical Companies. Products are known compounds[23] and were characterized by comparison of their physical or spectral data with authentic samples. Fourier transform-infrared (FT-IR) spectra were recorded on a Perkin-Elmer RXI spectrophotometer. Nuclear magnetic resonance (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.

General Procedure for the Conversion of Benzylic Alcohols to Oximes Using NH_3OHCl Catalyzed with DDQ. Benzylic alcohol (1 mmol) was added to a flask containing DDQ (0.0227 g, 0.1 mmol) and NH_3OHCl (0.278 g, 4 mmol) under solvent-free conditions in an oil bath at 100 °C. The mixture was stirred until TLC showed the completion of the reaction. The crude mixture was subjected to column chromatography on silica gel 60 (0.063-0.200 mm) using petroleum benzine-ethyl acetate (30:1) as eluent to give the corresponding oxime (40-94%). The results are shown in Table 2.

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