Novel and Highly Selective Conversion of Alcohols and Thiols to Alkyl Nitrites with Triphenylphosphine/2,3-Dichloro-5,6-dicyanobenzoquinone/Bu_4NNO_2 System

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Abstract: Alkyl nitrites were prepared in good to excellent yields by treatment of alcohols and thiols with triphenylphosphine/2,3-dichloro-5,6-dicyanobenzoquinone/Bu_4NNO_2 in acetonitrile. This method is highly selective for the conversion of primary alcohols to alkyl nitrites in the presence of secondary and tertiary alcohols and thiols.

Key words: triphenylphosphine, 2,3-dichloro-5,6-dicyanobenzoquinone, alkyl nitrite, alcohol, thiol

Organic nitrites (RONO) belong to a main class of NO donors (O–NO donors).[1,2] Nitric oxide (NO) is currently one of the most studied molecules in the biomedical sciences.[3,4] This interest is driven by the multiplicity of roles that NO plays and by the prospect of developing new drugs to tackle important disease states. Organic nitrites can generate NO in vivo.[5] It is believed that enzymatic catalysis is involved in the NO generation.[6] Some of them, such as butyl nitrite (BN), amyl nitrite (AMN), and isoamyl nitrite (IAMN), have been clinically used as vasodilators for a long time.[7] When used as inhalants they cause vasodilation, increased heart rate, and decreased systolic blood pressure.[8] Also, RONO's show antianginal effects.[1,2,7a]

Apart from wide biological applications of RONO's, they have been used for the nitrosation of thiols.[9] Transesterification between *tert*-butyl nitrite and other alcohols can also be used to synthesize nitrites.[10]

Organic nitrites can be prepared by reacting alcohols with nitrous acid or other nitrosating agents such as nitrosyl chloride (ClNO) in pyridine and nitrosonium salts ($NO^+ BF_4^-$, $NO^+ ClO_4^-$).[11] Recently, it was reported that alkyl nitrites could be synthesized from the reaction of alcohols with gaseous NO in the presence of air, where nitrous anhydride, generated in situ, likely serves as the nitrosating agent.[12]

In this paper, the use of a novel and cheap reagent for efficient conversion of alcohols and thiols to alkyl nitrites is reported.

Recently, we among others have studied the application of $Ph_3P/DDQ/R_4NX$ (X = Cl, Br, I, CN, N_3) for the conversion of alcohols, thiols, selenols and tetrahydropyranyl ethers into their corresponding alkyl halides, cyanides, and azides.[13] Now, we report the transformation of alcohols and thiols into alkyl nitrites by using $Ph_3P/DDQ/Bu_4NNO_2$ system (Scheme 1).

$$\mathrm{RXH} \xrightarrow[\mathrm{CH_3CN,\ reflux}]{\mathrm{Ph_3P/DDQ/}n\mathrm{\text{-}Bu_4NNO_2}} \mathrm{RONO}$$

X = O, S
R = primary, secondary and tertiary alkyl

Scheme 1

In this method, alkyl nitrites were prepared in good to excellent yields under neutral and mild reaction conditions. In order to optimize the reaction conditions, at first the effect of different ratios of $ROH/Ph_3P/DDQ/Bu_4NNO_2$, solvent and temperature for conversion of $PhCH_2OH$ to $PhCH_2ONO$ were examined. Employing a ratio of 1:2:2:2 in MeCN at reflux gave the best result and produced benzyl nitrite after 30 minutes in 98% isolated yield. These optimized conditions were applied for conversion of structurally different alcohols and thiols into their corresponding alkyl nitrites. The results are shown in Table 1.

As shown in Table 1, $Ph_3P/DDQ/Bu_4NNO_2$ is the most efficient system for the preparation of alkyl nitrites from alcohols. In comparison with nonbenzylic alcohols, benzylic ones react faster. Although the capability of DDQ for oxidation of benzylic alcohols has been demonstrated,[14] in our reactions, no oxidative products were observed. We also applied this method for the conversion of thiols to their corresponding alkyl nitrites (Table 1, Entries 14 and 15).

The characteristic ^1H NMR, ^{13}C NMR signals and IR absorptions bands for CH_2–ONO appeared at about 5.6 ppm, 159.7 ppm and 1645 cm^{-1}, respectively.[15]

To estimate the selectivity of this new method, we studied the reaction of some binary mixtures of substrates. Excellent selectivity was observed in the conversion of primary alcohols to the corresponding nitrite in the presence of secondary and tertiary alcohols (Scheme 2, Table 2, entries 1–3). Diphenylmethanol, a benzylic secondary alcohol was selectively converted to the corresponding nitrite in the presence of 1-adamantanol (Table 2, entry 4).

It was observed that in a binary mixture of benzyl alcohol and benzyl thiol, the thiol was intact and the alcohol was

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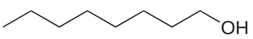
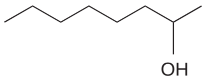
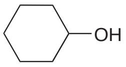
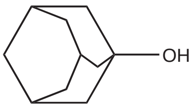
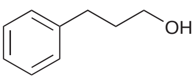
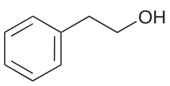
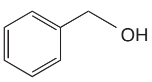
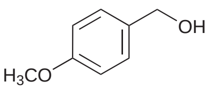
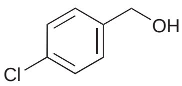
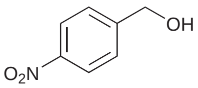
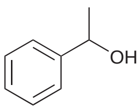
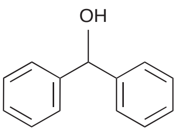
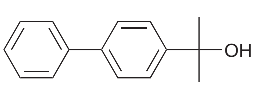
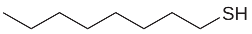
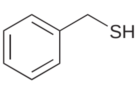
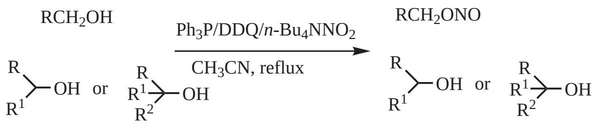
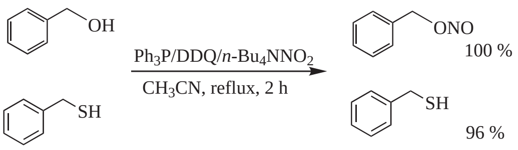
Table 1 Conversion of Alcohols and Thiols into Alkyl Nitrites in Anhydrous Acetonitrile under Reflux Conditions

Entry	Substrate	Time (h)	% Conversion[a]	Yield (%)[b]
1		22	100	95
2		24	100	90
3		27	100	94
4		48	100	89
5		20	100	97
6		20	100	96
7		0.5	100	98
8		0.5	100	98
9		2	100	93
10		24	100	90
11		1	100	97
12		1	100	95
13		48	70	62
14		28	100	91
15		5	100	90

[a] GC yield using internal standard.
[b] Yield of isolated product.



Scheme 2



Scheme 3

selectively converted to the corresponding nitrite (Scheme 3).

In conclusion, the present investigation has demonstrated that the use of $Ph_3P/DDQ/Bu_4NNO_2$ offers a simple, novel, and convenient method for the conversion of wide varieties of alcohols and thiols to their corresponding alkyl nitrites. This method not only shows excellent selectivity between different alcohols, but also between alcohols and thiols. Availability, safety and ease of handling of the reagents, high yields and mildness of the reaction conditions make this method suitable for the direct conversion of alcohols and thiols into nitrites.

Chemicals were obtained from Merck and Fluka chemical companies. FT-IR spectra were recorded on a Perkin Elmer RXI spectrometer. NMR spectra were recorded on a Bruker Avance DPX 250 MHz instrument. The products were purified by column chromatography and the purity determination of the products was accomplished by GC analysis on a Shimadzu model GC 10-A instrument using *n*-octane as internal standard or by TLC on silica gel polygram on SIL G/UV 254 plates.

Conversion of Benzyl Alcohol to Benzyl Nitrite; Typical Procedure

To a flask containing a mixture of DDQ (0.454 g, 2 mmol) and Ph_3P (0.524 g, 2 mmol) in anhyd MeCN (5 mL) was added Bu_4NNO_2 (0.456 g, 2 mmol) under stirring. Benzyl alcohol (0.108 g, 1 mmol) was added and the mixture was refluxed. GC analysis showed that the reaction was complete after 30 min. The solvent was evaporated under reduced pressure. Column chromatography of the crude product on silica gel using *n*-hexane as eluent gave benzyl nitrite in 98% yield.

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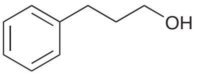
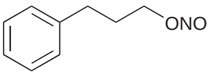
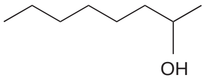
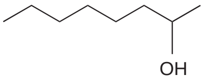
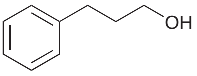
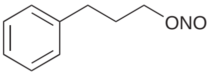
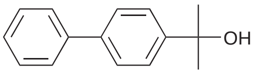
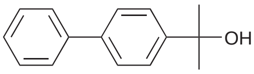
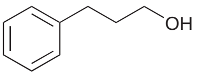
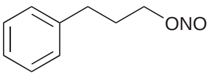
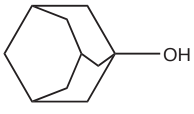
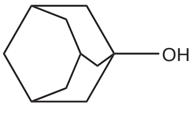
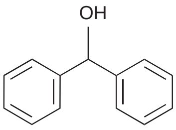
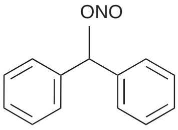
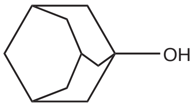
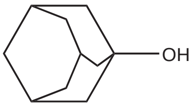
Table 2 Selective Reaction of Different Binary Mixtures with $Ph_3P/DDQ/Bu_4NNO_2$

Entry	Binary Mixture	Products	Time (h)	Yield (%)[a]
1			22	98
				95
2			22	99
				100
3			22	100
				97
4			20	99
				98

[a] GC yield using internal standard.

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