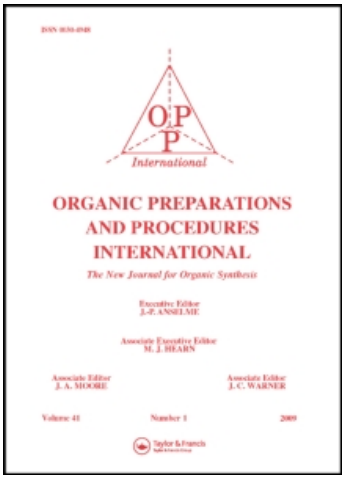

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NITRIC ACID AND PHOSPHORUS PENTOXIDE SUPPORTED ON SILICA GEL AS A MILD AND EFFICIENT SYSTEM FOR THE OXIDATION OF BENZYLIC ALCOHOLS UNDER SOLVENT-FREE CONDITIONS

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NITRIC ACID AND PHOSPHORUS PENTOXIDE SUPPORTED ON SILICA GEL AS A MILD AND EFFICIENT SYSTEM FOR THE OXIDATION OF BENZYLIC ALCOHOLS UNDER SOLVENT-FREE CONDITIONS

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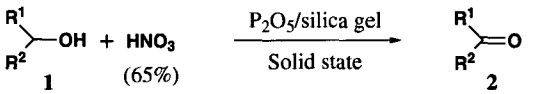
The oxidation of organic compounds is one of the most important reactions in modern organic synthesis. Although new oxidizing reagents have been developed for this purpose,[1-8] unfortunately some suffer at least from one of the following disadvantages such as high cost of preparations, long reaction times, instability, safety concerns for their preparation and tedious work-up procedures. Reactions under solvent-free conditions have received increasing attention in recent years. Significant advantages of these methods over conventional homogenous reactions are that they provide greater selectivity, proceed with enhanced reaction rates, give cleaner products, and involve simple manipulations.[9,10]

In continuation of our previous work,[11,12] we now report an efficient, mild and rapid method for the selective oxidation of benzylic alcohols **1** to the corresponding carbonyl compounds under solvent-free conditions with 65% HNO_3 in the presence of phosphorus pentoxide supported on silica gel as an efficient and mild oxidizing reagent. This oxidizing system has several advantages: 1) compared with previously reported methods, it does not require a large excess of reagent or long reaction times; 2) due to its mild behavior, no over-oxidation to the carboxylic acids was observed.



R^1, R^2 = Alkyl, aryl and H

Scheme 1

The P_2O_5/silica gel was prepared by mixing P_2O_5 and silica gel (0.063-0.2 mm mesh) in a mortar and grinding with a pestle for 1 min to obtain a homogenous mixture.[13] The reagent is stable and may be kept at room temperature for a month without loss of activity. The alcohols are then mixed with one molar equivalent of P_2O_5/silica gel in a mortar at room temperature for 30 seconds followed by grinding the mixture with one equivalent of HNO_3 (65%) for the time speci-

fied in the *Table*. After extraction of the product with ether, evaporation of the solvent affords good to excellent yields of pure products which require no further purification. Benzoin was not oxidized by this reagent after 20 min grinding (*Table*). In comparison to benzylic alcohols, the oxidation of aliphatic alcohols did not occur at all. As shown in the Table, this method is suitable for the oxidation of benzylic alcohols in the presence of aliphatic alcohols.

Table. Oxidation of Alcohols **1** under Solvent-free Conditions[a,b]

Entry	Substrate	Time (min)	Yield (%)	mp or bp (°C/torr) (*lit.* [14,15]) (*lit.*[16,17])	
1	Benzyl alcohol	1	95	176-178/760	(178-179/760)
2	4-Nitrobenzyl alcohol	10	90	103-105	(103-106)
3	3,4-Dimethoxybenzyl alcohol	2	94	280-282/760	(281/760)
4	1-Phenylethanol	2	0	----	
5	1-Phenylethanol	6	95	200-2002/760	(200-2002/760)
6	4-Methoxybenzyl alcohol	1	93	141-143/50	(141-143/50)
7	2-Methoxybenzyl alcohol	1	95	37-39	(37-39)
8	1,1-Diphenylmethanol	6	95	46-48	(47-49)
9	3-Methoxybenzyl alcohol	1	93	141-143/50	(143/50)
10	4-Chlorobenzyl alcohol	3	95	45-48	(45-47)
11	3-Chlorobenzyl alcohol	5	93	211-213/760	(213-214/760)
12	1-(*p*-Bromophenyl)ethanol	5	93	49-52	(49-52)
13	1-(*p*-Chlorophenyl)ethanol	3	90	231-232/760	(232/760)
14	Benzoin	20	0	----	
15	1-(*p*-Bromophenyl)-2-bromoethanol	3	93	107-110	(108-110)
16	Cyclohexanol	20	0	----	
17	1-Tetralol	4	95	126-127/23	(127/23)
18	*n*-Heptanol	20	0	----	
19	*n*-Pentanol	20	0	----	
20	L-Menthol	20	0	----	
21	1-Indanol	3	89	242-244/760	(243-245/760)
22	9-Fluorenol	4	88	81-83	(80-83)
23	4-*t*-Decylcyclohexanol	20	0	----	
24	2-Naphthalenemethanol	4	92	80-82	(79-91)
25	2-Phenylethanol	20	0	----	
26	3-Methylcyclohexanol	20	0	----	
27	2-(*p*-Tolyl)ethanol	20	0	----	

Confirmed by comparison with authentic samples (IR, TLC and NMR)[14,15] Yield of isolated products

In order to evaluate the selectivity of the reagent, the competitive reactions shown in Eqs. 1-3 were carried out. When equimolar amounts of 2-phenethyl alcohol and benzyl alcohol were treated with the reagent (one molar requivalent), only benzyl alcohol was oxidized (*Eq. 1*).

$$PhCH_2CH_2OH + PhCH_2OH \xrightarrow[10\ min., grinding]{Solid\ state} \underset{unchanged}{PhCH_2CH_2OH} + \underset{95\%}{PhCHO} \qquad Eq.\ 1$$

Treatment of benzyl alcohol with one molar equivalent in the presence of diphenylmethanol (1 equiv.) led to the exclusive oxidation of diphenylmethanol (*Eq. 2*). Interestingly, in the oxidation

$$PhCHOHPh + PhCH_2OH \xrightarrow[5\ min., grinding]{Solid\ state} \underset{100\%}{PhCOPh} + \underset{unchanged}{PhCH_2OH} \qquad Eq.\ 2$$

of primary alcohols, over-oxidation of products to the corresponding carboxylic acids was not observed. When benzyl alcohol (1 equiv.) was treated with one molar equivalent of the reagent in the presence of thioanisole (1 equiv.), only the alcohol was oxidized (*Eq. 3*).

$$PhSMe + PhCH_2OH \xrightarrow[10\ min., grinding]{Solid\ state} \underset{unchanged}{PhSMe} + \underset{95\%}{PhCHO} \qquad Eq.\ 3$$

In conclusion, we have described an efficient and versatile method for the conversion of benzylic alcohols to the corresponding carbonyl compounds with the following advantages: (a) our reagent is inexpensive and easily handled; it may be stored on the bench for months without loss of activity; (b) the procedure is simple and proceeds under solvent-free conditions at room temperature; (c) the reaction is environmentally friendly and the reaction time is short; (d) the isolation of product is straightforward.

EXPERIMENTAL SECTION

The products were characterized by comparison of their spectral (IR, ^1H NMR) and physical data with those of authentic samples.[14, 15] All ^1H NMR spectra were recorded at 300 and 500 MHz in $CDCl_3$ relative to TMS.and IR spectra were obtained on a Shimadzu 435 IR spectrometer. All reactions were carried out under solvent-free conditions at room temperature in a hood with strong ventilation. The reaction is safe and we did not experience any dangerous events using this procedure under solvent-free conditions.

Preparation of Reagent [(P_2O_5/silica gel (65% w/w)].- In a mortar, 4.5 g of P_2O_5 (31.69 mmol) and 2.5 g of silica gel (0.063-0.2 mm mesh) were ground for one minute to a homogeneous mixture.

Procedure for Oxidation of Alcohols to Carbonyl Compounds.- In a mortar, 0.2 g of P_2O_5/silica gel (1 mmol) and the alcohol (1 mmol) were ground for 30 sec and then 0.5 mL of HNO_3 (65%) was added and the mixture was ground with a pestle for the time specified in the *Table*. Immediately after addition of HNO_3, NO_2 gas was released. The progress of reaction was monitored by TLC (silica gel, EtOAc/*n*-hexane = 20/80) until the alcohol disappeared. When

reaction was completed, the product was extracted with Et_2O (2 x 10 mL), dried ($MgSO_4$) and the solvent by evaporated to yield the pure product without any need for further purification.

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ALTERNATE SYNTHESES OF PRODAN AND ACRYLODAN

Submitted by Steven S. Silvonek, Carl B. Giller and Christopher J. Abelt*
(09/23/05)

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Prodan [6-propionyl-2-(dimethylamino)naphthalene, **6**] was synthesized by Weber and Farris in 1979 as a fluorescent probe of micropolarity.[1] The prodan moiety was attached to thiols and amines in proteins using acrylodan [6-acryloyl-2-(dimethylamino)naphthalene, **12**].[2,3] The covalently bound chromophore is a fluorescent molecular sensor of the labeled sites.[4-6]

We have been interested in preparing derivatives of prodan and acrylodan to understand the nature of the emissive intramolecular charge-transfer state. The literature synthesis of prodan is not convergent.[1] The first step sets the identity of the carbonyl group through a Friedel-Crafts acylation, while aromatic substitution with lithium dimethylamide creates the amine group. Application of this literature method to the preparation of prodan derivatives would require completely separate routes for each one. Acrylodan is prepared from prodan[2] *via* a selenation/oxidation/elimination sequence.[7] Recently in this *Journal*, López and coworkers reported a different method for the synthesis of prodan derivatives where the identity of both the carbonyl and amino groups is established later in the synthetic route.[8] In particular, the carbonyl group is generated by nucleophilic addition of an aryllithium to an aliphatic nitrile. Since organolithiums are strong bases, their addition to aliphatic nitriles is often complicated by the competing α-hydrogen abstraction reaction, which may explain the low yields for the addition step (14-36%) reported by López. This contribution describes an alternate route that avoids these problems and provides a direct preparation of acrylodan.

As with the procedure of López, our alternate preparation began with **4**, the aryllithium derived from **3**, which was prepared by an alkylation/dealkylation route rather than by the acylation/reduction procedure of López. Reaction of the amine **1** with excess MeI afforded the