

Oxidation of Benzylic Alcohols with Urea Hydrogen Peroxide/Calcium Chloride in PEGDME₂₅₀

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The oxidation of benzylic alcohols to carbonyl compounds is one of the most important and fundamental process in organic chemistry.¹ A number of methods are known for the transformation of benzylic alcohols into the corresponding carbonyl compounds. For examples, benzylic oxidations can be achieved by use of a variety of the oxidants which include $\text{KMnO}_4/\text{MnO}_2$,² $\text{Mn}(\text{OAc})_3/\text{DDQ}$,³ *N*-hydroxyindole/copper(I) chloride,⁴ $\text{NaIO}_4/\text{TEMPO}/\text{NaBr}$,⁵ and oxone.⁶ However, most of these systems required use of large excesses of oxidants, harsh reaction conditions, and expensive promoters. In particular, molecular oxygen has been utilized for the oxidation of benzylic alcohols in combination with complexes of transition metals such as palladium,⁷ ruthenium,⁸ iridium,⁹ cobalt,¹⁰ or copper.¹¹ However, most of the aforementioned reagent systems are generally exotic, toxic, and expensive which limit their practical applications. In addition, hydrogen peroxide is considered to be an ideal green oxidant for the oxidation reactions of alcohols due to its low toxicity and ready availability. However, utilization of hydrogen peroxide for the alcohol oxidation reactions generally required use of transition metal based peroxo-complexes as activators.¹²⁻¹⁶ It is obvious that the utilization of toxic transition metals for alcohol oxidation reactions is not desirable from an environmental point of view. In this increasingly eco-conscious days, development of efficient alcohol oxidation systems with non-toxic, readily available, and inexpensive transition metal-free oxidizing agents still remains a major challenge. In this respect, the use of solid urea hydrogen peroxide (UHP) can be served as safer and greener alternative to the unstable liquid hydrogen peroxide. UHP has been generally used alone or in combination with suitable activators for the various organic transformations.¹⁷⁻²¹ In continuation of our ongoing research program on the development of more ecologically acceptable oxidation protocols, we investigated the use of UHP for the oxidation of benzylic alcohols in the presence of an eco- friendly activator.

Herein, we described the highly efficient and facile oxidation of benzylic alcohols to the corresponding carbonyl compounds using combination of UHP and calcium chloride. To the best of our knowledge, there is no report on the calcium chloride induced oxidation of alcohols with UHP. Initially, we have chosen 1-*p*-tolylethanol as a model substrate to test the solvent effects for the oxidation reactions with UHP/ CaCl_2 system. We compared the results of oxidation

of 1-*p*-tolylethanol in different solvents such as dichloromethane, acetonitrile, ethanol, ethylene glycol, dimethoxyethane, polyethylene glycol 200 (PEG₂₀₀), and polyethylene glycol dimethyl ether 250 (PEGDME₂₅₀). As shown in the Table 1, it was found that PEGDME₂₅₀ is the solvent of choice for the tested oxidation reactions of 1-*p*-tolylethanol to *p*-methylacetophenone. To our surprise, any detectable product formation was not noticed in PEG₂₀₀ even after prolonged reaction times for 24 h at 70 °C. In the optimization of reaction conditions, we found that the oxidation proceeds in a most effective way with 1.5 equivalent of UHP and 0.5 equivalent of calcium chloride. The reaction does not occur in the absence of the calcium chloride. When we investigated effect of other metal chlorides such as MgCl_2 or ZnCl_2 on the same reaction, only a trace amount of oxidized products were detected. Next, the scope and limitations of this process was explored using the optimized reaction conditions: benzyl alcohol (1.0 mmol), urea hydrogen peroxide (1.5 mmol), and calcium chloride (0.5 mmol) in PEGDME₂₅₀ (2 mL) at 70 °C for 4 h. A variety of benzylic alcohols were investigated as summarized in the Table 2. It is clear that all primary and secondary benzylic alcohols were efficiently converted to aldehydes and ketones, respectively. In all the attempted examples of benzylic oxidations, no over-oxidized products were detected whatsoever. In addition, no oxidation was observed on the aromatic rings of benzylic substrates in the course of the processes. Variation of position of substituent to aromatic rings gave no significant difference in term of reaction yields (entries 2-4). Benzylic alcohols bearing electron donating or electron withdrawing substitu-

Table 1. Infuence of solvent for the oxidation of 1-*p*-tolylethanol to *p*-methylacetophenone

Entry	Solvent	T	Time (h)	Yield (%) ^b
1	CH_2Cl_2	Reflux	4	33
2	CH_3CN	Reflux	4	34
3	Ethanol	Reflux	4	62
4	Ethyleneglycol	70 °C	4	70
5	Dimethoxyethane	70 °C	4	60
6	PEG ₂₀₀	70 °C	24	N.R. ^c
7	PEGDME ₂₅₀	70 °C	4	90

^aGeneral conditions: 1-*p*-tolylethanol (1.0 mmol), UHP (1.5 mmol), CaCl_2 (0.5 mmol). ^bIsolated yields. ^cNo reaction.

Table 2. Oxidation of benzylic alcohols with UHP/CaCl₂ in PEGDME₂₅₀

$\text{Ar}-\text{CH}(\text{OH})-\text{R} \xrightarrow[\text{PEGDME}_{250}, 70\text{ }^{\circ}\text{C}]{\text{UHP, CaCl}_2} \text{Ar}-\text{C}(=\text{O})-\text{R}$			
Entry	Substrate	Product	Yield (%) ^a
1	PhCH ₂ OH	PhCHO	82
2	2-MeC ₆ H ₄ CH ₂ OH	2-MeC ₆ H ₄ CHO	80
3	3-MeC ₆ H ₄ CH ₂ OH	3-MeC ₆ H ₄ CHO	78
4	4-MeC ₆ H ₄ CH ₂ OH	4-MeC ₆ H ₄ CHO	90
5	4-MeOC ₆ H ₄ CH ₂ OH	4-MeOC ₆ H ₄ CHO	90
6	4-ClC ₆ H ₄ CH ₂ OH	4-ClC ₆ H ₄ CHO	84
7	4-BrC ₆ H ₄ CH ₂ OH	4-BrC ₆ H ₄ CHO	92
8	4-CF ₃ C ₆ H ₄ CH ₂ OH	4-CF ₃ C ₆ H ₄ CHO	74
9	PhCH(OH)CH ₃	PhCOCH ₃	87
10	4-MeC ₆ H ₄ CH(OH)CH ₃	4-MeC ₆ H ₄ COCH ₃	92
11	4-BrC ₆ H ₄ CH(OH)CH ₃	4-BrC ₆ H ₄ COCH ₃	88
12	4-ClC ₆ H ₄ CH(OH)CH ₃	4-ClC ₆ H ₄ COCH ₃	90
13	C ₆ H ₅ CH(OH)CH ₂ CH ₃	C ₆ H ₅ COCH ₂ CH ₃	90
14	PhCH(OH)Ph	PhCOPh	94
15	Piperonyl alcohol	Piperonal	84
16	α-Tetralol	α-Tetralone	88
17	9-Hydroxyfluorene	9-Fluorenone	95
18	Cyclohexanol	Cyclohexanone	53
19	Octan-2-ol	2-Octanone	35

^aAll yields refer to pure isolated products.

ents gave equally comparable yields. The present system was also applicable to the oxidation of aliphatic alcohols, although the yields of the corresponding ketones were moderate (entries **18** and **19**). Replacement of UHP by 30% aqueous H₂O₂ at the present protocol mainly provided over-oxidized carboxylic acids with small amounts of desired carbonyl compounds. Probably the oxidation proceeds by active oxidant chlorous acid (ClOH) formed *in situ* by the interaction of calcium chloride and UHP activated by hydrogen bonding with PEGDME₂₅₀. Analogous oxidation of primary alcohols to the corresponding carboxylic acids promoted by chlorous acids has been reported.²²

In conclusion, we have developed a new and highly efficient oxidant system for oxidation of benzylic alcohols utilizing combination of UHP and calcium chloride in PEGDME₂₅₀. This new transition metal-free oxidation protocol can be served as an useful alternatives to the oxidation of benzylic alcohols.

Experimental

All the alcohols and PEGDME₂₅₀ were purchased from Aldrich and used as received. The reactions were checked by TLC using silica gel plates. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography. ¹H NMR spectra were measured by the Varian Gemini 2000 (300

MHz) spectrometer tetramethylsilane as an internal standard and CDCl₃ as a solvent. Mass spectra were recorded with a Micromass Autospectrometer. All products were known and identified by comparison of their ¹H NMR spectra with those of reported literature data.

General Procedure. A mixture of benzylic alcohol (1.0 mmol), urea hydrogen peroxide (1.5 mmol) and calcium chloride (0.5 mmol) was stirred in PEGDME₂₅₀ (2 mL) at 70 °C for 4 h. After cooling the mixture to room temperature the product is extracted into diethyl ether (3 × 20 mL), washed with water and dried over MgSO₄. The combined ether extracts were concentrated under reduced pressure and the crude product was purified by flash column chromatography (ethyl acetate/*n*-hexane = 1:3, v/v) to give the desired carbonyl compound.

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