

STUDY ON THE SYNTHESIS OF UREA-HYDROGEN PEROXIDE AND APPLICATION FOR OXIDATION OF BENZYLIC ALCOHOLS UNDER MICROWAVE ACTIVATION

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Abstract

The Urea-Hydrogen Peroxide complex was synthesized from urea, hydrogen peroxide by using microwave assisted method and characterized by FT-IR. This Urea-Hydrogen Peroxide complex could be employed as an oxidizing agent for metal-free oxidation reaction of benzylic alcohols to carboxylic acids corresponding. This oxidation protocol, carried out under alkaline-water in microwave oven in presence of iodine as a catalyst, was efficient and compatible with a range of benzylic alcohols to afford a direct access to benzoic derivatives in very good yields up to 95.4% and high selectivities.

Keywords: Oxidation reaction; benzylic alcohols; benzoic derivatives; Urea-Hydrogen Peroxide.

1. Introduction

Oxidations are very important reactions in organic transformations including organic synthesis and asymmetric synthesis of natural bioactive or pharmaceutical molecules [1, 2]. Oxidation of alcohols are generally carried out with a large excess of metallic compounds as reagents such as chromium or manganese reagent. The metal residues are always undesirable and often provide problems during work up and purification of the desired products. Furthermore, these oxidation reactions often take place in unsafe organic solvents, generating harmful side products [3]. In the view of green chemistry, the demand for highly efficient and environmentally benign organic synthesis has encouraged the development of mild, safe, and highly selective oxidizers. Among various oxidizing agents, UHP is emerging as a safe, economic and environment friendly reagent. UHP is an inexpensive, stable, and easy to handle source of pure urea and 30% aqueous H₂O₂ solution and UHP is a useful oxidizing agent for many of organic reactions such as: Baeyer-Villiger oxidations of ketones to lactones [4], oxidation of aromatic aldehydes [5], oxidation of sulfides to sulfones [6], epoxidation of cyclic vinylsilanes [7]. Recently, we have reported new results involving a simple procedure for synthesis of UHP and its application for the efficient preparation of thiosulfinate compounds [8]. On the other hand, selective oxidation of alcohols is an essential step in

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organic synthesis, especially, it can be used to produce directly acids [9]. This oxidation normally carried out in hard conditions and used the expensive organometallic complex of rhodium as a catalyst.

In the best of our knowledges, there have been no reported paper related to using UHP for oxidation of alcohols to carboxylic acids, to date. So that, in this paper, we investigated the preparation of UHP and application as an oxidizing agent for preparation of benzoic derivatives directly from benzylic alcohols in alkaline-water by microwave assisted method.

2. Experiment

All reagents were obtained commercially and used without further purification. All reactions have been carried out under a nitrogen atmosphere and dry conditions. The reaction mixtures have been magnetically stirred with teflon stirring bars, and the temperatures were measured externally. All the reactions have been monitored by thin layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F254). The eluents used were mixtures of *n*-pentane and ethyl acetate (EtOAc), with detection by UV light, or a KMnO₄ staining solution. Acros silica gel (60, particle size 0.040-0.063 mm) was used for column chromatography. Reaction was carried out in microwave oven Mas-II Plus, Sineo and Infrared spectrum has been recorded with Spectrum Two, Perkin Elmer at Le Quy Don Technical University. The nuclear magnetic resonance (NMR) spectras have been recorded with Bruker Avance 500 MHz spectrometers at Vietnam National University. ¹H NMR spectra: δ (H) are given in ppm relative to tetramethylsilane (TMS), using δ (DMSO-*d*₆) = 2.50 ppm as internal reference. ¹³C NMR spectra: δ (C) are given in ppm relative to TMS, using δ (DMSO-*d*₆) = 39.5 ppm as internal reference. Multiplicities were designated as singlet (s), doublet (d), triplet (t), multiplet (m) or br (broad).

Synthesis of UHP using microwave assisted method: To a 100 ml glass becker containing 6.01 g of urea (10.0 mmol) with magnetic stir bar, was slowly added solution of H₂O₂ 30% (10.2 ml, 10.0 mmol). The reaction mixture was stirred and then irradiated in microwave oven for 2 min, at 400 W and at 60°C (keep the internal temperature always below 65°C), then cooled to room temperature. The crystal product was collected by filtration, purified by washing with distilled water, and dry to give 7.72 g UHP (75.2% yield), white crystal; IR ν (cm⁻¹) 3428, 3348, 1607, 1152.

General procedure for oxidation of alcohols with UHP: To a solution of benzylic alcohol (1.0 mmol, 1 equiv), I₂ (25.0 mg, 10 mol%) NaOH solid (40.0 mg, 8.0 mmol, 20 mol%), UHP (1.89 g, 4.0 mmol) in 10 ml H₂O. The mixture was stirred and then irradiated in microwave oven with output of 300 W, at 70°C for 30 minutes. The resulting mixture was cooled at room temperature and hydrolyzed with saturated Na₂S₂O₃ (to eliminate

excess of iodine) and extracted with EtOAc (3 x 30 ml). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel by using a mixture of *n*-hexane/EtOAc (4/1) as eluent to yield pure compound as a colorless liquid (67.8 mg, 55.6%).

Benzoic acid (2a) IR (cm⁻¹): 3060, 2725, 1680, 1602, 1580, 1420, 1280, 745, 690.

***p*-methoxy benzoic acid (2b)** IR (cm⁻¹): 3025, 2840, 1675, 1600, 1425, 1295, 850.

***p*-nitro benzoic acid (2c)** IR (cm⁻¹): 3025, 2540, 1924, 1675, 1600, 1575, 850.

***p*-methylsulfonyl benzoic acid (2d)** IR (cm⁻¹): 3350, 3100, 1675, 1600, 1575, 855. ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm): 10.21 (s, 1H, -OH), 8.18 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.06 (d, *J* = 8.1 Hz, 2H, Ar-H), 3.29 (s, 3H, -CH₃). ¹³C NMR (126 MHz, DMSO-*d*₆) δ (ppm): 160.0, 130.6, 127.7, 43.7.

Phthalic acid (2e) IR (cm⁻¹): 3062, 2870, 1670, 1595, 1497, 1400, 1260, 748.

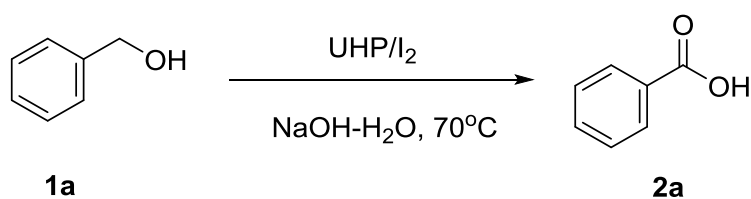
Benzophenone (2f) IR (cm⁻¹): 3050, 1651, 1590, 1575, 1450, 755, 690.

Cyclohexanone (2g) IR (cm⁻¹): 2940, 1702, 1430, 1422, 1347.

3. Results and discussion

Firstly, UHP was synthesized from urea and hydrogen peroxide at molar ratio of 1:1.2, after 30 minutes of reaction at 60°C, UHP was obtained at 69.0% yield as a white crystal [8]. The procedure for preparation of UHP was modified by using microwave activation, after stirred and irradiated at the power level of 400 W in only 2 minutes at 60°C, UHP was obtained at 75.2% yield. UHP was characterized by IR and analysed results are in agreement with the data in literature [8, 10].

Secondly, the application of UHP as an oxidizing agent for oxidation reaction was studied. Initial investigation involved developing the oxidation reaction between benzylic alcohol **1a** and UHP at the molar ratio of 1:1 as model reaction (Scheme 1). Firstly, reaction was carried out in water as solvent in presence of iodine (10 mol%), NaOH (20 mol%) [10]. The reaction mixture was stirred and heated at 70°C until disappearance of the starting materials (90 minutes, monitoring reaction by TLC), the desired product **2a** was obtained in moderate yield of 43%.



Scheme 1. Oxidation of benzylic alcohol 1a.

The oxidation of benzylic alcohol carried out under the same conditions of time and temperature using microwave assisted method at the power level of output at 300 W. It has been found that significant higher yield of desired product was obtained in 55.6% under microwave activation as compared to using normal oil-bath heating.

To continuously optimize this reaction, the power level of microwave output was taken into consideration and the results were shown in the Tab. 1. The power level of 400 W was found to be the most promising as low power level gives low yield and prolongation of reaction time and higher leads to decomposition of the UHP complex thereby resulting in poor efficiency of the reagent.

Tab. 1. Effect of the MW power level on the oxidation reaction yield

MW power (W)	300	400	500	600
Yield of 2a	55.6%	72.6%	68.9%	63.8%

The influence of molar ratio between benzylic alcohol **1a** and UHP was also studied. The reaction was carried out in water at 70°C in presence of I₂/NaOH as catalyst, using MW activation at the power level of 400 W, at the alcohol **1a**/UHP molar ratio of 1:1, 1:2, 1:3, 1:4 and 1:5 respectively. It was observed that the reagent molar ratio also exhibited a significant effect on the reaction yield. The yield of desired benzoic acid was increased when the molar ratio from 1:1 to 1:4 with excellent selectivity. Using the excess of UHP for more than 1:4, the reaction conversion kept almost constant that was considered the reaction reached equilibrium (Tab. 2).

Tab. 2. Effect of the benzylic alcohol **1a**/UHP molar ratio on the oxidation reaction yield

Molar ratio	1:1	1:2	1:3	1:4	1:5
Yield of 2a	72.6%	78.4%	82.0%	85.4%	85.3%

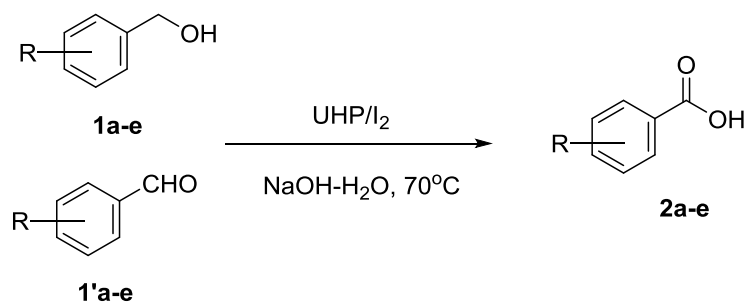
It was found that the reaction yield was significantly affected by the reaction time. The oxidation reaction at 70°C proceeded inefficiently, affording only 45.0% yield after 10 minutes of stirring. As expected, increasing the reaction time led to a dramatic enhancement in the reaction yield. The best yield of 85.5% was obtained after 30 minutes at 70°C and it seemed that the reaction might complete after stirring 30 minutes at the molar ratio alcohol **1a**/UHP of 1:4 (Tab. 3).

Tab. 3. Effect of the reaction time on the oxidation reaction yield

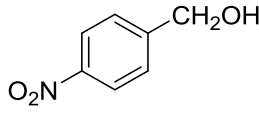
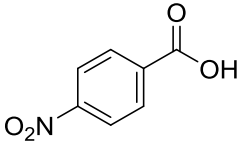
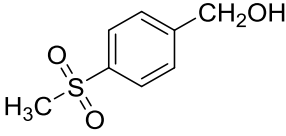
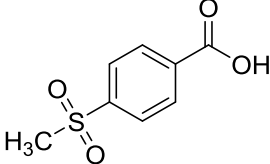
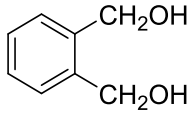
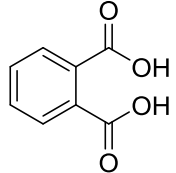
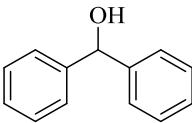
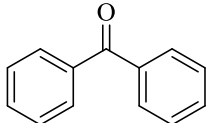
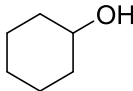
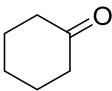
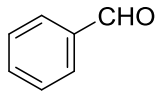
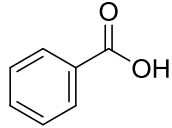
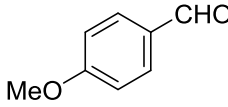
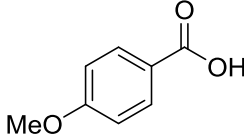
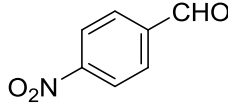
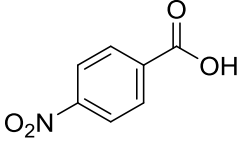
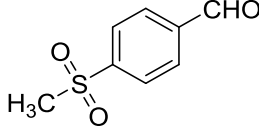
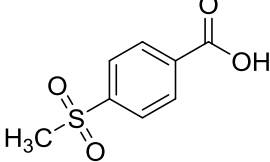
Reaction time (min)	10	20	30	50	70	90
Yield of 2a	45.0%	62.8%	85.5%	85.4%	85.5%	85.4%

Finally, the study was then extended to the oxidation reaction of UHP with different benzylic alcohols. The reaction carried out in MW power level of 400 W for 30 minutes at 70°C in presence of I₂/NaOH as catalyst, in alkaline-water, at the alcohol/UHP molar ratio of 1:4. Experimental results showed that the nature of alcohol structure exhibited a significant effect on the reaction yield. Benzylic alcohols substituted at the 4-position by electron withdrawing groups such as nitro or mesyl (CH₃SO₂-) groups were oxidized smoothly to the corresponding benzoic acids in excellent yields up to 95.4% (entries 3, 4). Alcohol with the electron donating group at the 4-position was also undergone oxidation efficiently (entry 2). Furthermore, scopes of this reaction were continuously studied with different substrates such as 1,2-phenylenedimethanol (two functional groups of hydroxyl: entry 5), secondary benzylic alcohol (entry 6) or cyclohexanol (entry 7). The obtained results showed that this reaction was compatible with the wide range of alcohols and the desired products were afforded in good yields. The extension of this oxidation was also investigated to aldehydes (entries 8-11), the reaction worked indeed very well. Under the identical reaction conditions for oxidation of alcohols, the carboxylic acids were also given in very good yields correspondingly. In all cases, the oxidizing agent UHP combined with I₂/NaOH was compatible for oxidation reaction of derivatives of benzylic alcohols or benzaldehydes to acids correspondingly in very good to excellent yield (Tab. 4).

Tab. 4. Oxidation of alcohols and aldehydes to compounds 2



Entry	Alcohol 1 and aldehyde 1'		Desired product 2		
	No.	Structure	No.	Structure	Yield* (%)
1	1a		2a		83.5
2	1b		2b		82.1

Entry	Alcohol 1 and aldehyde 1'		Desired product 2		
	No.	Structure	No.	Structure	Yield* (%)
3	1c		2c		93.8
4	1d		2d		95.4
5	1e**		2e**		85.4
6	1f		2f		89.6
7	1g		2g		75.6
8	1'a		2a		84.3
9	1'b		2b		81.9
10	1'c		2c		94.1
11	1'd		2d		95.6

*Yield of isolated products

** Alcohol **1a**/UHP at the molar ratio of 1:8, I₂ (20 mol%), NaOH (40 mol%)

4. Conclusion

In summary, we have reported a very simple procedure for preparation of urea-hydrogen peroxide by using microwave assisted method and its application for oxidation reaction. The UHP was given in 75.2% yield after only 2 minutes of irradiating and this complex has emerged a useful oxidizing agent for synthesis acids directly from alcohol or aldehyde. Using 4 equivalents of UHP, the methodology was efficient and compatible for versatile derivatives of benzylic alcohols or benzaldehydes as starting materials. We have found that the optimal condition of this reaction was microwave irradiation at 400 W, at 70°C, at the alcohol/UHP molar ratio of 1:4, in alkaline-water as a solvent and after 30 minutes magnetic stirring, desired products were obtained from very good to excellent yield up to 95.6%. It was evident that this pathway could be streamlined this reaction and applied this methodology for total synthesis of nature bioactive molecule in the future.

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NGHIÊN CỨU ĐIỀU CHẾ VÀ ỨNG DỤNG UREA-HYDROGEN PEROXIDE CHO PHẢN ỨNG ÔXI HOÁ CÁC DẪN XUẤT ALCOHOL BENZYLIC BẰNG PHƯƠNG PHÁP VI SÓNG

Bùi Thùy Trang, Lê Văn Hòa, Cao Hải Thường

Tóm tắt: *Phức chất Urea-Hydrogen Peroxide đã được nghiên cứu điều chế từ urea, hydrogen peroxide bằng phương pháp vi sóng và được chứng minh cấu trúc bằng phương pháp phổ hồng ngoại FT-IR. Phức chất Urea-Hydrogen Peroxide đã được ứng dụng làm tác nhân ôxi hóa không sử dụng kim loại cho các hợp chất alcohol benzylic thành acid carboxylic tương ứng. Trong điều kiện chiếu vi sóng, sử dụng I₂ như là chất xúc tác, phương pháp này chứng tỏ là tương thích và hiệu quả để ôxi hóa các alcohol benzylic trực tiếp tạo thành các dẫn xuất của acid benzoic với độ chọn lọc cao và hiệu suất lên tới 95,4%.*

Từ khoá: Phản ứng ôxi hoá; alcohol benzylic; dẫn xuất acid benzoic; Urea-Hydrogen Peroxide.

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