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ZnO: a versatile agent for benzylic oxidations

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Abstract—Zinc oxide catalyzed oxidation of various alkylbenzenes, naphthalene and 1,2,3,4-tetrahydronaphthalene in air using microwave irradiation or conventional heating in the presence of *N*,*N*-dimethylformamide is described.

1. Introduction

Oxidation is a fundamental transformation in organic synthesis.[1–4] Benzylic oxidation holds a unique place because of its application in industry and academia. Laboratory scale liquid-phase benzylic oxidations are generally carried out with a large excess of chromium or manganese reagents.[3] The metal residues are environmentally undesirable and often cause problems during work-up. Recently, nickel-catalyzed benzylic oxidation of toluenes was reported.[5] Other reagents, which have been used include ceric ammonium nitrate in aqueous acetic acid or in $HClO_4$,[6] potassium bromate,[7] chromium trioxide in acetic anhydride,[8] selenium dioxide,[9] chromyl chloride,[10] silver(II)oxide in phosphoric acid,[11] potassium permanganate adsorbed on alumina,[12] and 3,6-bis(triphenylphosphonium)cyclohexene peroxodisulfate.[13] Many of these reagents are quite expensive and suffer from harsh reaction conditions. Thus, there is a need to develop procedures, which use inexpensive and non-toxic oxidizing agents. Recently, we have reported[14] solvent-free benzylic oxidations using a urea–hydrogen peroxide complex under microwave irradiation.

The most preferred of reagents would be those which are easy to handle, inexpensive, non-toxic and easily removed during work-up. Zinc oxide is a non-toxic, inexpensive and non-hygroscopic white powder. It has been used for a number of organic syntheses in combination with other metal oxides. For instance, zinc oxide in combination with CuO and alumina has been employed for the catalytic oxidation of phenols, *t*-BuOH and methylvinyl ketone;[15] a mixture of CuO, ZnO and TiO_2 has been concerned as catalyst for the hydrogenation of cyclic aliphatic esters and alcohols;[16] ZnO in combination with CuO has been involved in the preparation of *N*-cyclohexylaniline from aniline and cyclohexanol;[17] ZnO in combination with Cu and Cr_2O_3 has served for methanol synthesis;[18] Fe–ZnO catalyst was used for the oxidative dehydrogenation of *n*-butane to butene;[19] a mixture of ZnO, $CuCl_2$, $CaCO_3$ and $MgCO_3$ was advocated as an additive for preventing clinker formation during coal combustion;[20] copper zinc oxide catalyst has been used for ambient temperature carbon monoxide oxidation;[21] ZnO in combination with $CaCO_3$ and SiO_2 has been employed for preparing UV-resistant plastic master batch.[22]

The coupling of microwave (MW) irradiation[23] with the use of catalysts or mineral-supported reagents provides chemical processes with special attributes such as enhanced reaction rates, higher yields, better selectivity and improved ease of manipulation.

Since ZnO is easily available and non-toxic, we wish to report here some efficient ZnO mediated benzylic oxidations under air under MW irradiation using small amounts of DMF, or by conventional heating in an oil-bath equipped with a thermostat using DMF as solvent. To the best of our knowledge, ZnO has not yet been reported as catalyst/mediator for benzylic oxidations. This method provides a noticeable improvement over other existing method as ZnO is not toxic or expensive, work-up being simply reduced to filtration followed

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Keywords: Alkylbenzenes; Zinc oxide; Benzylic oxidations; Microwave irradiation; Oil-bath heating; Selectivity.

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by treatment with crushed ice. Furthermore, ZnO has been shown to interact efficiently with MW radiation to reach 326 °C within 5.5 min when submitted to MW exposition in a commercial oven at a 1 kW emitted power.[24]

The experimental conditions for the oxidation of toluene to benzoic acid were explored either in the absence of solvent or in the presence of DMF or *o*-dichlorobenzene (DCB) under MW irradiation, since these solvents interact strongly with microwaves due to their high polarities. The oxidation efficiency of ZnO was determined on the basis of the amount of ZnO and solvent used. The results are summarized in Table 1.

In the absence of solvent, no reaction was observed within 6 min while good results were obtained in the presence of DMF. The work-up procedure is indeed easy, requiring only treatment with crushed ice. In addition, there is no alteration in the yield from 0.25 to 1 equiv of DMF except a slight decrease in the irradiation period.

ZnO intervention for benzylic oxidations proved necessary, since no reaction occurred when the oxidation of toluene was performed using either DMF or DCB in the absence of ZnO under MW irradiation (Table 1, entries 8 and 9) for up to 8 min. Furthermore, the necessity of oxygen (air) was evaluated by carrying out the oxidation of toluene (10 mmol) under nitrogen in the presence of ZnO (2.5 mmol) and DMF (5 mL for oil-bath and 2.5 mmol for MW heating) by stirring in an oil-bath at 90 °C or irradiating in a MW oven. No reaction was observed by TLC even after 5 h in the case of oil-bath or 6 min in the case of MW heating, whereas an 83% yield was obtained when 10 mmol of toluene was irradiated under MW together with DMF (2.5 mmol) and ZnO (2.5 mmol) in open vessels.

Table 1. Conditions and results for the ZnO-mediated oxidation of toluene to benzoic acid under MW irradiation

Entry	Experimental conditions[a]			Isolated yield[c] (%)	Temperature (°C)[d]
	Solvent	mmol	Time (min)[b]		
1	—	—	6	No reaction	72
2	DMF	2.5	6	**83**	**95**
3	DMF	5.0	4.5	82	100
4	DMF	10.0	4.25	84	107
5	DCB	2.5	5	45	100
6	DCB	5.0	7	47	105
7	DCB	10.0	6.25	46	107
8[e]	DMF	2.5	8	No reaction	90
9[e]	DCB	2.5	8	No reaction	98
10[f]	DMF	2.5	6	No reaction	96

[a] The experiments were carried out by mixing toluene (10 mmol) and ZnO (2.5 mmol) with the solvent.

[b] Reaction time for which maximum yields were achieved.

[c] Mean value of three experimental runs.

[d] Temperature evaluated at the end of exposure during MW experiment by immersing a glass thermometer into the reaction mixture and was a approximate temperature range.

[e] Experiment conducted without the presence of ZnO.

[f] Experiment conducted under nitrogen atmosphere.

Subsequently, this method was extended to various substituted toluenes bearing electron-withdrawing or electron-donating groups, providing the corresponding benzoic acids in fairly good to excellent yields (Table 2).

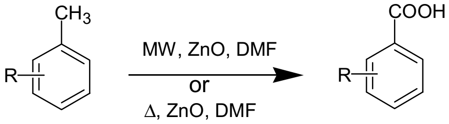
After establishing that benzylic oxidations were performed successfully under MW irradiation, efforts were made to conduct these reactions using conventional heating in which DMF was chosen as solvent and the reaction temperature kept at 90 °C. The best conditions were obtained when toluene (10 mmol), ZnO (2.5 mmol) and DMF (5 mL) were stirred in a pre-heated oil-bath at 90 °C, affording benzoic acid in 81% yield. This method was extended to substituted toluenes, yielding the corresponding benzoic acids in moderate to excellent yields. Significant results for ZnO-mediated benzylic oxidations under both MW irradiation or oil-bath heating are summarized in Table 2. In general, yields obtained with MW irradiation were significantly improved (10–18% points) (entries 3, 5, 9–15) when compared to oil-bath experiments conducted at 90 °C.

We then studied the use of ZnO for the selective oxidations of one of the methyl groups in dimethylbenzene simply by regulating the amount of ZnO and heating conditions. As a typical example, in the case of 1,2-dimethylbenzene (Table 2, entry 5), when 2.5 mmol of ZnO was used, 2-methylbenzoic acid was obtained in 80% yield under MW exposure within 8 min and 65% yield using oil-bath heating within 1.5 h. However, if the amount of ZnO was doubled, 1,2-dimethylbenzene (Table 2, entry 6) gave phthalic acid in 89% yield using microwaves for 5 min and 75% yield using oil-bath heating for 2 h. Similarly, in the case of 1,4-dimethylbenzene (Table 2, entries 7 and 8), 4-methylbenzoic acid and terephthalic acid can be obtained selectively using either MW irradiation or oil-bath heating.

In the case of toluenes containing an acetoxy group at the 2-, 3- or 4-position (entries 11–13), the reaction proceeded selectively to give 2-, 3- or 4-acetoxybenzoic acids and no phenol (hydrolysis product) was detected by TLC. Furthermore, toluenes substituted at the 3- or 4-position by electron-withdrawing groups such as a nitro moiety were oxidized smoothly to the corresponding benzoic acids in excellent yield (entries 3 and 4). Toluenes substituted by electron rich groups (entries 5–8 and 11) also underwent the oxidation efficiently. In the case of ethylbenzene, where there is a possibility of formation of acetophenone,[17] the reaction took place exclusively to provide benzoic acid and no acetophenone was detected by TLC. The present mild method was also successful for the oxidation of naphthalene and tetralin to phthalic acid, for which generally highly drastic conditions are required.

In order to check the possibility of specific non-thermal MW effect for the ZnO-mediated oxidation of alkylbenzenes, we carried out the oxidation of toluene (Table 2, entry 1) using a pre-heated oil-bath at 95 °C (temperature measured at the end of the reaction in the MW oven) for 6 min keeping all other conditions identical to the MW experiment. It was found that no reaction

Table 2. Results of ZnO-mediated benzylic oxidations in an air atmosphere



Entry	Reactant	Product[b]	MW[a]		Oil-bath[a] (90 °C)	
			Time[c] (min)	Isolated yield[d] (%)	Time (h)	Isolated yield[d] (%)
1	Toluene	Benzoic acid	6	83	2.5	81
2	Ethylbenzene	Benzoic acid	7	85	3	82
3	3-Methyl-1-nitrobenzene	3-Nitrobenzoic acid	3	76	2.15	65
4	4-Methyl-1-nitrobenzene	4-Nitrobenzoic acid	7	85	2	81
5	1,2-Dimethylbenzene	2-Methylbenzoic acid[e,f]	8	80	1.5	65
6	1,2-Dimethylbenzene	Phthalic acid[g]	5	89	2	75
7	1,4-Dimethylbenzene	4-Methylbenzoic acid	6	77	1	73
8	1,4-Dimethylbenzene	Terephthalic acid[e]	5	75	1.15	72
9	2-Methylphenylamine	3-Aminobenzoic acid	5	85	7	76
10	3-Methylphenol	3-Hydroxybenzoic acid	5.5	85	4	73
11	2-Methylphenyl acetate	2-Acetyloxybenzoic acid	9	80	6	70
12	3-Methylphenyl acetate	3-Acetyloxybenzoic acid	6	85	1	67
13	4-Methylphenyl acetate	4-Acetyloxybenzoic acid	8	83	2	72
14	Naphthalene	Phthalic acid	7.5	78	3.15	65
15	1,2,3,4-Tetrahydronaphthalene	Phthalic acid	15	82	3.5	67

[a] The experiments were carried out by mixing appropriate alkylbenzene (10 mmol), ZnO (2.5 mmol) and DMF (2.5 mmol for MW experiment and 5 mL for oil-bath experiment).

[b] All products were characterized by ^{1}H NMR, IR, MS and by comparison with authentic samples.

[c] Microwave irradiation was carried out with pulses of 15 s followed by a 5 s cooling periods.

[d] Mean value of the isolated yield for three experimental runs.

[e] For entries 6 and 8, the amount of catalyst used was 5 mmol while all other conditions remain as described in Experimental section.

[f] In case of entry 5, the ^{1}H NMR of crude product obtained after work-up by MW heating approach showed the presence of 2-methylbenzoic acid (88%), phthalic acid (5%) and the rest may be starting materials.

[g] In case of entry 6, the ^{1}H NMR of crude product obtained after work-up by MW heating approach showed the presence of phthalic acid (95%) and no 2-methylbenzoic acid was detected.

took place (TLC), although a yield of 78% was obtained when reaction time was extended to 3.25 h. This observation suggests that the effect of MW irradiation is not purely thermal.

Furthermore, the importance of our method lies in the fact that ZnO can be re-used after simple washing with distilled water and diethyl ether. The results of re-use studies are given in Table 3.

In conclusion, a rapid, economic and environmentally friendly method has been developed for benzylic oxidations using inexpensive and non-toxic zinc oxide under MW irradiation or oil-bath heating. This method may be a good alternative to well-known methods, since the oxidation proceeds expeditiously in high yields. The selectivity can be achieved by regulating the amount of ZnO and the reaction time under MW exposure or oil-bath heating. However, the benefit of the MW method is double, as only a small amount of DMF is required as an additive (25 mol % vs ZnO), and reaction times are far shorter and often lead to better or at least equivalent yields.

Table 3. Results of re-use studies of ZnO for the oxidation of toluene to benzoic acid

No. of uses	MW[a]		Oil-bath heating[a]	
	Time (min)[b]	Yield (%)[c]	Time (h)[b]	Yield (%)[c]
1	6	83	2.5	81
2	7	82	2.75	80
3	8.5	80	3.15	74
4	9.15	76	4	70
5	11	71	4.5	64

[a] The experiments were carried out by mixing appropriate toluene (10 mmol), ZnO (2.5 mmol) and DMF (2.5 mmol for MW experiment and 5 mL for oil-bath experiment). The mixture was irradiated with MW for the indicated period (6–11 min) or stirred in an oil-bath at 90 °C for the indicated period (2.5–4.5 h).

[b] The reaction time where maximum yields were achieved.

[c] Mean value of three experimental runs.

2. General procedure for the ZnO-mediated oxidation of alkylbenzenes

2.1. Microwave (MW) experiment

Alkylbenzene (10 mmol), zinc oxide (0.115 g, 2.5 mmol) and *N*,*N*-dimethylformamide (0.18 mL, 2.5 mmol) were placed in a borosil beaker (50 mL). The mixture was mixed properly with the help of a glass rod (15 s) and then irradiated under safe conditions in a domestic microwave oven at 800 W (LG CHEF MS 192 operating at 2450 MHz providing a maximum output of 800 W) for the reaction times given in Table 2. The reaction mixture was cooled to room temperature and diluted with DMF (5 mL). It was filtered and ice-cold water (100 mL) was added to the filtrate. The solution was extracted with $CHCl_3$ and the solvent was removed under reduced pressure after drying over anhydrous sodium sulfate. Finally, the products were purified either by crystallization from $CHCl_3$–pet. ether or by column chromatography on silica gel using pet. ether as eluant (Table 2). The structures of the products were confirmed by ^1H NMR, IR, MS and by comparison with authentic samples available commercially or prepared according to the literature methods.

2.2. Oil-bath experiment

Alkylbenzene (10 mmol), zinc oxide (0.115 g, 2.5 mmol) and *N*,*N*-dimethylformamide (5 mL) were transferred to a round-bottomed flask (25 mL) equipped with a reflux condenser. The reaction mixture was stirred in a pre-heated oil-bath at 90 °C for the reaction times as given in Table 2. The products were obtained after the same work-up procedure as for the MW-assisted method.

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