Pergamon

Tetrahedron Letters 43 (2002) 45–48

TETRAHEDRON
LETTERS

A novel way to prepare *n*-butylparaben under microwave irradiation

Xiangjun Liao,[a] G. S. V. Raghavan[a,]* and V. A. Yaylayan[b]

[a]*Department of Agricultural & Biosystems Engineering, Macdonald Campus of McGill University, 21,111 Lakeshore Road, Ste-Anne-de-Bellevue, Canada QC H9X 3V9*
[b]*Department of Food Science and Agricultural Chemistry, Macdonald Campus of McGill University, 21,111 Lakeshore Road, Ste-Anne-de-Bellevue, Canada QC H9X 3V9*

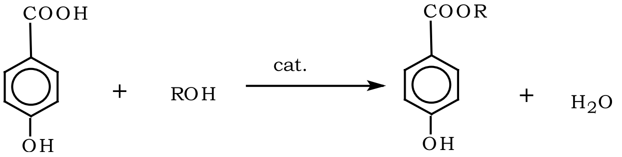
Received 7 September 2001; revised 30 October 2001; accepted 31 October 2001

Abstract—The synthesis of *n*-butylparaben under microwave irradiation in the presence of an inorganic salt $ZnCl_2$ as a catalyst is reported. Using this specific catalyst for the synthesis of the *n*-butylparaben under microwave irradiation, not only shortens the reaction time, but also reduces the pollution from the use of concentrated sulfuric acid and prevents the complicated after-treatment handling problems. The reason for this type of microwave-assisted reaction is also demonstrated from the temperature profiles of the reaction. The ratio of the reactants for the better microwave energy efficiency is discussed. The use of microwave irradiation for the large-scale production of this type of food preservative is therefore feasible. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

p-Hydroxybenzoic acid esters (parabens) have been widely used as antimicrobial preservative agents in food, drugs and cosmetics for more than 50 years due to their broad antimicrobial spectrum.[1] Parabens are very versatile in terms of food preservatives, differing from the other preservatives such as benzoates, propionates and sorbates, because they are not weak acid compounds but have a wide pH range. The antimicrobial activity of parabens is directly dependent on the chain length.[2,3] For example, the ability of *n*-butylparaben to inhibit bacteria is 4 times that of ethylparaben.[4] The increasing use of these types of compounds with relatively low toxicity, good stability, non-volatility and non-irritability in those fields has led to the development of many techniques for the synthesis and assay of these compounds. In general, most methods of paraben synthesis involve the presence of a catalyst such as concentrated sulfuric acid and PTSA (*p*-toluene sulfonic acid). In most cases, large excess of either acid or alcohol is used in the condensation to give a higher yield of the desirable esters (Scheme 1). However, these methods have limitations of general applicability owing to low yields, extensive by-product formation and harsh reaction conditions. In fact, the use of large amounts of condensing reagents and activators should be avoided in order to promote green agricultural food engineering and efficient energy consumption. The direct condensation of acids with alcohols using a small amount of catalyst under microwave irradiation is the most suitable method.

The use of microwave irradiation techniques has profound impact on the solution of the synthesis of this type of compound. Since the appearance of the first papers on the application of microwaves for organic synthesis,[5,6] numerous papers regarding the application of this special technology in organic synthesis have been published.[7] The use of microwaves in the synthesis results in better selectivity, rate enhancement and reduction of thermal degradation and higher energy consumption efficiency when compared to traditional



Scheme 1. The synthesis of parabens (cat. = catalyst such as PTSA, H_2SO_4).

Keywords: *n*-butylparaben; esterification; microwave irradiation; $ZnCl_2$; temperature; ratio.

* Corresponding author: Tel.: 1-514-398-7775; fax: 1-514-398-8387; e-mail: raghavan@macdonald.mcgill.ca

0040-4039/02/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)02065-2

heating. In addition, microwave-assisted synthesis without surplus reactant offers such advantages as the reduction of hazardous explosions and the removal of excess reactants or high boiling solvents from the reaction mixture. Esterification of carboxylic acid in the presence of catalysts such as concentrated sulfuric acid and PTSA by employing microwave energy has been extensively investigated.[8,9] Further, microwave irradiation has also been utilized for the synthesis of parabens using catalysts such as concentrated sulfuric acid, PTSA and inorganic acid.[10–12] However, after checking Scifinder Scholar provided by CAS (Chemical Abstract Service), to the best of our knowledge, there is no literature relevant to the use of $ZnCl_2$ as a catalyst to perform the esterification under microwave irradiation. In this report we describe a fast microwave-induced synthesis of potentially practical use in chemical engineering by esterification of alcohol with *p*-hydroxybenzoic acid in the presence of an inorganic salt $ZnCl_2$ as a catalyst. The results are compared with the traditional synthesis. It not only can save reaction time, but can also reduce the pollution associated with the use of concentrated sulfuric acid and avoid the complicated after-treatment handling problems. Although the reason for microwave-assisted chemical reaction has been extensively investigated, most results contributed to 'hot spot' or 'localized superheating' of the solvent.[13] In our paper, the reason for this microwave-assisted chemical reaction is discussed by making use of temperature data of the reaction mixture during the microwave processing.

2. Materials and methods

2.1. Materials

The following chemicals: *n*-butanol, methylparaben, *n*-butylparaben, *p*-hydroxybenzoic acid, PTSA and $ZnCl_2$ were purchased from Sigma-Aldrich, Canada (Ontario). All reagents and catalysts were used without further treatment.

2.2. Experimental procedure

Reactions have been carried out by employing a Synthewave S402 with a mono-mode MW cavity from Prolabo operating at 2450 MHz with power range of 0–300 W in a tubular quartz reactor (250 ml) with irradiation being monitored by PC. The temperature of reaction media was measured continuously with an IR-pyrometer, which was an integral part of the Synthewave 402. For the sake of comparison, reactions were also carried out using traditional heating in the presence of $ZnCl_2$ as a catalyst and reactions were also performed using PTSA as a catalyst in the presence of microwave or conventional heating.

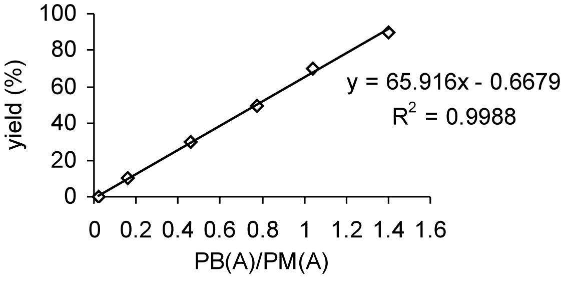


Figure 1. Theoretical calibration line of paraben (yield = number of mol for ester after reaction/number of mol for acid before reaction).

2.2.1. *General procedure 1* (microwave-assisted synthesis). A mixture of 8 ml of butanol, 0.18 g $ZnCl_2$ and 1.72 g *p*-hydroxybenzoic acid was introduced together in the quartz reactor of the synthewave 402 apparatus equipped with a condenser. The irradiation was carried out in the following sequence at 70% power (300 W× 70%): 15 s off, 30 s on; 15 s off, 30 s on; 15 s off, 30 s on; 30 s off, 30 s on; 15 s off, 30 s on. After heating and cooling, the mixture was diluted by ethanol and analyzed by GC. Methylparaben was used as internal standard to calibrate the yield of reaction.

2.2.2. *General procedure 2* (conventional heating method). A mixture of 3.46 g of *p*-hydroxybenzoic acid and 0.35 g $ZnCl_2$ was introduced to 250 ml reaction flask and then 16 ml of butanol was added. The mixture was refluxed on a hotplate for 45 min. After heating and cooling, the product was analyzed as above.

2.2.3. GC analysis. The GC was operated with an injector temperature of 250°C and a helium carrier gas flow rate of 24 ml/min. The GC column was a non-polar general-purpose capillary column [30 m×0.25 mm i.d., 0.25 μm thickness, Phase DB5 (Catalogue No. 122-5032, J&W Scientific Co.)]. The detector (FID) was operated at 250°C and oven temperature was programmed as follows: (1) initial temperature was 100°C; (2) Level 1, 5.0°C/min, 100°C, keep 2 min; (3) Level 2, 10°C/min, 160°C, keep 5 min; (4) Level 3, 10°C/min, 250°C, keep 5 min.

The products were identified by comparison of their GC retention time with those of authentic samples. The yields were calculated from the theoretical standard calibration line.

3. Results and discussion

3.1. The calibration line

The responses of the yields to GC detector were found to be linear (Fig. 1) to the ratio of the peak areas of butylparaben (PB(A)) to the peak area of methylparaben (PM(A)).

3.2. Reaction under conventional heating

3.2.1. PTSA or $ZnCl_2$ as a catalyst. As expected, the butylparaben was successfully synthesized using PTSA as a catalyst by the conventional heating method with a yield of 76%. However, when PTSA was replaced with $ZnCl_2$ as catalyst under the same reaction conditions, the yield was reduced to a meager 5% of the original reaction. The results are shown in Table 1.

3.3. Reactions under microwave irradiation

3.3.1. PTSA or $ZnCl_2$ as a catalyst. As expected, the butylparaben was successfully synthesized using PTSA as a catalyst under microwave irradiation. However, the yield was lower than the conventional method due to the much short reaction time. Interestingly, the yield for the use of $ZnCl_2$ was slightly higher than that of the reaction catalyzed by PTSA. The results are also shown in Table 1.

Table 1. Esterification of *p*-hydroxybenzoic acid and *n*-butanol under microwave irradiation and classic heating

Entry	Catalyst	Heating mode	Yield (%)
1		Microwave irradiation	0
2		Conventional heating	0
3	PTSA	Microwave irradiation	41
4	$ZnCl_2$	Microwave irradiation	43
5	PTSA	Conventional heating	76
6	$ZnCl_2$	Conventional heating	3.5

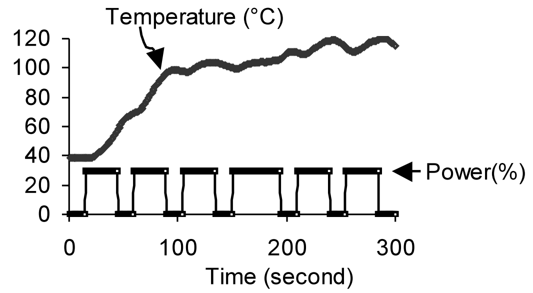


Figure 2. Temperature (°C) profile of esterification under microwave irradiation in the presence of PTSA.

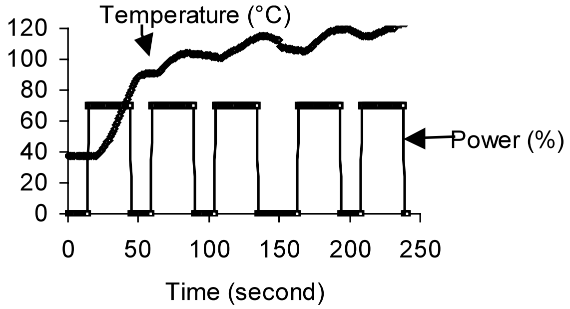


Figure 3. Temperature (°C) profile of esterification under microwave irradiation in the presence of $ZnCl_2$.

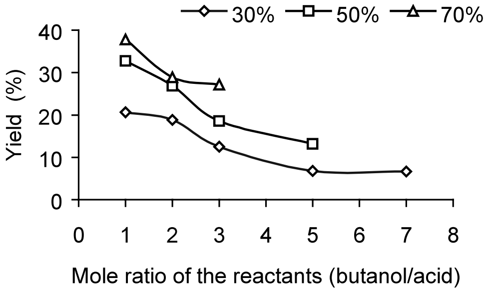


Figure 4. Effect of microwave irradiation power supplied (%) and the ratio of the reactants (molar ratio = butanol/acid) on the yield of esterification.

3.3.2. Temperature profiles of the reaction. The temperature profiles of the esterification of butanol and *p*-hydroxybenzoic acid in the presence of PTSA or $ZnCl_2$ under microwave irradiation are shown in Figs. 2 and 3, respectively.

As can be seen, the temperature under microwave irradiation was slightly higher than the boiling point of butanol (117.6°C). This is in accordance with the previous report by Baghurst and Mingos[13i] and Hoopes et al.[13j] This results in reaction rate enhancement when compared with the synthesis by using classic heating. In classic heating, the temperature provided for the reaction is usually the reflux temperature. The temperature in the case of $ZnCl_2$ as a catalyst was also slightly higher than the boiling point of butanol. This cannot only explain rate enhancement under microwave irradiation, but can also give an explanation for why the desired product could not be successfully produced under conventional heating. According to this, it is important to point out that each catalyst has its exact reaction temperature whether the reaction is performed using microwave heating or conventional heating. The non-thermal effect claimed by some authors probably result from difficulties relating to temperature distribution estimation and keeping the absolutely identical reaction conditions while comparing.

3.4. Effect of microwave parameters

In order to optimize the reaction conditions, a series of experiments in the reactor were performed. Fig. 4 shows the effect of the irradiation power supplied and the ratio of the reactants on the yield of esterification.

As can be seen, an increase in the irradiation power provides an increase in the yield of butylparaben. Interestingly, the yield decreases with an increase in the ratio of the reactants. For example, the higher yield was obtained when the reactant ratio was 1:1. This result is different from the traditional concept that large excess of either acid or alcohol is used in the condensation to give a higher yield of the desirable esters.

4. Conclusions

This paper describes a microwave-assisted synthesis of butylparaben in the presence of $ZnCl_2$ as a catalyst and identified the reason for the difference between the reaction performed under microwave heating and conventional heating. In direct esterification, the catalytic use of inorganic salts is practical and economical because of its simplicity and applicability to large-sale operations and at the same time avoiding the higher cost of PTSA or the use of concentrated sulfuric acid. Also, this procedure gave the right ratio of reactant, which should be 1:1. With this ratio, the microwave energy efficiency is the highest. Further optimization of the irradiation time and microwave power supplied will be investigated in order to make this microwave technology applicable in the agriculture and food industries.

Acknowledgements

We are grateful for financial support from CIDA (Canada international development agency), NSERC and FCAR funding.

References

1. Soni, M. G.; Burdock, G. A.; Taylor, S. L.; Greenberg, N. A. *Food Chem. Toxicol.* **2001**, *39*, 513–532.
2. Robach, M. C. *Food Technol.* **1980**, *34*, 81–84.
3. Dziezak, J. D. *Food Technol.* **1986**, *40*, 104–111.
4. Zhang, Z.; Zhang, M.; Zhan, D.; Wang, A. *Huagong Shikan*. **1998**, *12*, 24–25.
5. Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279–282.
6. Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945–4948.
7. Kappe C. O. 2001, website: http://www.ang.kfunigraz.ac.at/~kappeco/microlibrary.htm (a lot of references were given on his home page).
8. There are more than 100 papers regarding esterification under microwave irradiation according to the research topic search 'esterification microwave' in Scifinder Scholar provided by CAS (Chemical Abstract Services).
9. (a) Majetich, G.; Wheless, In *Microwave Heating in Organic Chemistry*; Kingston, H. M.; Stephen, J. H., Eds. Microwave-enhanced chemistry—Fundamentals, Sample preparation, and Applications; ACS: Washington DC, 1997; Chapter 8, pp. 455–505; (b) Majetich, G.; Hicks, R. *J. Microw. Power Electromagn. Energy* **1995**, *30*, 27–45; (c) Majetich, G.; Hicks, R. *Radiat. Phys. Chem.* **1995**, *45*, 567–579; (d) Majetich, G.; Hicks, R. *Res. Chem. Intermed.* **1994**, *20*, 61–77; (e) Loupy, A.; Petit, A.; Ramdani, M.; Yvanaeff, C.; Majdoub; Labiad, B.; Villemin, D. *Can. J. Chem.* **1993**, *71*, 90–95; (f) Bram, G.; Loupy, A.; Majdoub, M. *Synth. Commun.* **1990**, *20*, 125–129; (g) Bram, G.; Loupy, A.; Majdoub, M.; Gutierrez, E.; Ruiz-Hitzky, E. *Tetrahedron* **1990**, *46*, 5167–5176; (h) Gutierrez, E.; Loupy, A.; Bram, G.; Ruiz-Hitzky, E. *Tetrahedron Lett.* **1989**, *30*, 945–948.
10. Chen, X.; Hong, P.; Dai, S. *Huaxue Tongbao*. **1993**, 38–39.
11. Liu, W.; Qian, B.; Ji, Y.; Zhang, G. *Huaihai Gongxueyuan Xuebao*. **1999**, 45–46.
12. Zheng, X.; Shan, Y. *Huaxue Shijie*. **1997**, *19*, 12–14.
13. (a) Gedye, R. N.; Wei, J. B. *Can. J. Chem.* **1998**, *76*, 525–532; (b) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233–238; (c) Chemat, F.; Poux, M.; Galema, S. A. *J. Chem. Soc., Perkin Trans.* **1997**, *2*, 2371–2374; (d) Hajek, M. *Collect. Czech. Commun.* **1997**, *62*, 347–354; (e) Westaway, K. C.; Gedye, R. N. *J. Microw. Power Electromagn. Energy* **1995**, *30*, 219–230; (f) Saillard, R.; Poux, M.; Berlan, J.; Audhuy-Peaudecerf, M. *Tetrahedron* **1995**, *51*, 4033–4042; (g) Whittaker, A. G.; Mingos, D. M. P. *J. Microw. Power Electromagn. Energy* **1994**, *29*, 195–219; (h) Mingos, D. M. P. *Rev. Chem. Intermed.* **1994**, *20*, 85–91; (i) Baghurst, D. R.; Mingos, D. M. P. *J. Chem. Soc., Chem. Commun.* **1992**, 674–677; (j) Hoopes, T.; Neas, E.; Majetich, G. The 201st National Meeting of the ACS in Atlanta, CA 'Investigation of the effects of microwave heating on organic reactions', presented on 16 April 1991; ORGN 231.