PAPER www.rsc.org/njc | New Journal of Chemistry

Microwave-enhanced radical reactions at ambient temperature Part 3:† Highly selective radical synthesis of 3-cyclohexyl-1-phenyl-1-butanone in a microwave double cylindrical cooled reactor‡

Satoshi Horikoshi,*[ab] Junichi Tsuzuki,[a] Masatsugu Kajitani,[a] Masahiko Abe[c] and Nick Serpone*[d]

Received (in Gainesville, FL, USA) 17th June 2008, Accepted 6th August 2008
First published as an Advance Article on the web 15th September 2008
DOI: 10.1039/b810142f

The microwave-enhanced synthesis of 3-cyclohexyl-1-phenyl-1-butanone (CPB) from crotonophenone and iodocyclohexane in the presence of *t*-BuOOH and triethylborane was examined at ambient temperature and under reflux conditions in bulk solution using no less than four different synthetic protocols. Chemical yields of CPB (93 and 95%, respectively) obtained after 60 and 120 min under microwave dielectric heating coupled to a cooling system (MW/Cool protocol) for a reaction temperature of 20–24 °C exceeded the yields from the reaction occurring at room temperature (24 °C; no microwaves; 40% and 72%) for the same reaction times and temperature. The competitive radical reaction to produce CPB and a small amount of by-products generated from the thermally-induced synthesis by the non-selective radical reaction was restricted solely to the process occurring at ambient temperature (RT protocol), under microwave dielectric heating to reflux (MW protocol) and heating with an oil-bath also to reflux (Oil-bath protocol). By contrast, no by-products were generated or detected for the reaction taking place by the MW/Cool method. Comparison of product yields under conditions of identical temperature conditions must involve some specific microwave effect in the synthesis of the title compound.

1. Introduction

Utilization of microwave radiation as the heat source in organic syntheses is no longer novel as microwave-assisted organic syntheses have been reported in several excellent recent reviews[1–3] and books.[4–8] Many of the studies reported a decrease of reaction times that has been attributed to rapid heating induced by the microwaves (MW), and found to be more effective than conventional heating (typically with an oil-bath). A recent tutorial review has summarized some of the reactions examined up to 2008 in which microwave dielectric heating has proved beneficial compared to the traditional way of heating the reaction mixture.[9]

Interesting reports have also appeared about specific effects of the microwave radiation[1,3–5,7,10] that have been claimed to result (i) from variations in activation parameters, (ii) from enhanced molecular collisions, and (iii) probable highly localized hot spots by analogy with sonochemically assisted processes. In this regard, some of the objectives of recent studies have focused on the causes of this increased efficiency through an examination of microwave thermal and non-thermal effects[11] and hot-spot effects.[12] Despite the several inferences of non-thermal specific effects from the use of microwave radiation in organic syntheses,[1,3–5,7,10] Kappe and co-workers[13] recently re-examined this issue using a dedicated reactor setup that allowed internal reaction temperatures to be measured accurately using fiber-optic probes (thermometers). They concluded that rates are enhanced because of increased temperatures attained by microwave dielectric heating and not by microwave radiation field effects, as isolated product yields and enantiomeric purities of products from both microwave and conventional heating were identical. Apparently, studies of non-thermal effects based on the use of infrared sensors to measure reaction temperatures externally can lead to misleading results owing to temperature gradients within the reaction mixture because of field inhomogeneities in the microwave cavity and inefficient magnetic agitation of the reaction mixture.[13]

Simultaneous combination of cooling and microwave heating, in which care is taken to control microwave dielectric heating through a cooling system, can lead to high product yields by microwave dielectric heating under ambient temperature conditions.[14] Along similar lines, the photoassisted TiO_2

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[a] *Department of Chemistry, Faculty of Science and Technology, Sophia University, 7-1 Kioi-cho, Chiyoda-ku, Tokyo, 102-8554, Japan. E-mail: horikosi@rs.noda.tus.ac.jp*
[b] *Research Institute for Science and Technology, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba, 278-8510, Japan*
[c] *Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba, 278-8510, Japan*
[d] *Dipartimento di Chimica Organica, Universita di Pavia, Via Taramelli 10, Pavia, 27100, Italia. E-mail: nick.serpone@unipv.it; nickser@alcor.concordia.ca*

† Part 1: S. Horikoshi, M. Kajitani, N. Serpone, *J. Photochem. Photobiol., A*. 2007, **188**, 1–4; Part 2: S. Horikoshi, N. Ohmori, M. Kajitani, N. Serpone, *J. Photochem. Photobiol., A*. 2007, **189**, 374–379.

‡ Electronic supplementary information (ESI) available: (1) Gas chromatogram of the composition of products and reagents after 120 min of reaction; (2) GC-MS mass spectral data of the species observed in the gas chromatograms, and (3) proton NMR spectrum of the major product obtained from the MW/Cool protocol. See DOI: 10.1039/b810142f

degradation of the endocrine disruptor bisphenol-A was significantly improved by microwave irradiation under cooling conditions with temperatures measured by fiber-optic probes and efficient magnetic stirring of the reaction mixtures.[15]

For the few reactions tested, combining microwave irradiation with cooling to control the reaction temperature has thus far proven advantageous, although the exact effect(s) of cooling coupled to microwave heating remains somewhat elusive requiring additional experimentation to establish a library of reactions that may lead ultimately to delineate factors that lead to improved yields and shorter reactions times. In this regard, a few studies[16] that examined microwave-enhanced radical reactions ascribed improved product yields and faster kinetics solely to microwave dielectric heating effects. Toward a further understating of microwave effects other than plain heating effects, we herein report the synthesis of 3-cyclohexyl-1-phenyl-1-butanone (CPB) from a reaction involving *tert*-butylhydroperoxide, triethylborane, iodocyclohexane and crotonophenone in THF, a radical reaction that is enhanced by microwave dielectric heating under ambient temperature conditions. The microwave reactor used consisted of an internal cooling system herein proposed as a simple mono-modal experimental reactor.

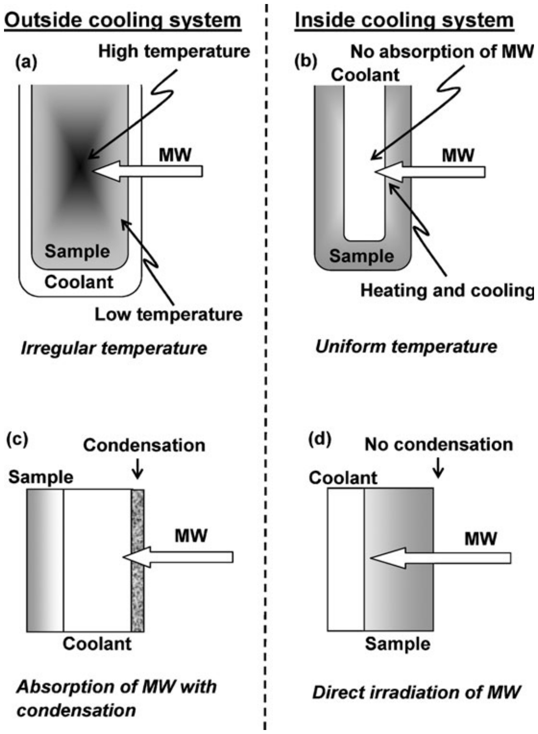


Fig. 2 Cartoon illustrating the possible temperature distribution and microwave irradiation situation that might make the difference in efficiency between internal and external cooling conditions.

2. Experimental

2.1 Experimental setup of the microwave device

A three-pronged microwave double cylindrical cooling reactor with a reflux condenser was located in the waveguide (see Fig. 1). The reaction sample introduced into the reactor was irradiated by continuous 2.45 GHz microwave radiation with an IDX Inc. green-motif I microwave-type apparatus (mono-modal microwave radiation system). The mono-mode reactor provides a reliable homogeneity of the electric field (wave focusing) and accurate control of temperature measured with a fiber-optic probe, thus the possibility of operating under temperature profiles otherwise identical in both kinds of activation, namely microwave and conventional thermal activation.[17] The coolant in the inner cold finger consisted of hexane and dry-ice (solid CO_2) grains. Note that hexane and dry-ice grains absorb no microwave radiation, and control of addition of the dry-ice achieved the desired solution temperature. Although internal heating of a reaction mixture was described by Kappe and Stadler[5] on the characterization of microwave dielectric heating, irregular temperature zones in the reacting solution due to internal heating and external cooling (Fig. 2(a)) are not precluded. No such irregular temperature zones are caused by internal cooling and microwave heating, however (Fig. 2(b)). The advantage of internal cooling rests in the prevention of condensation (Fig. 2(c) and (d)) which can be generated on the reactor surface by cooling the sample externally thereby resulting in a significant attenuation of the microwave radiation reaching the reaction mixture and causing a drop of reaction efficiency.

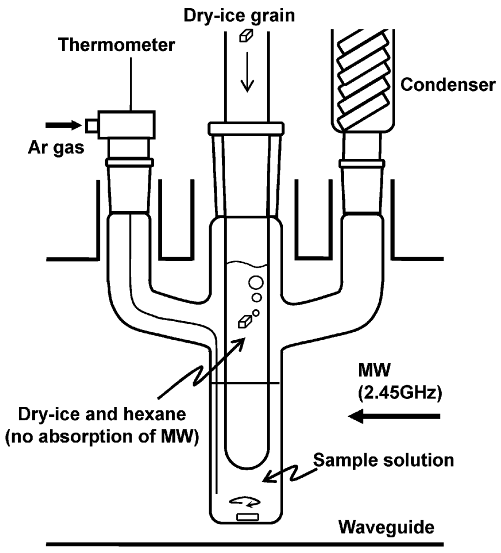
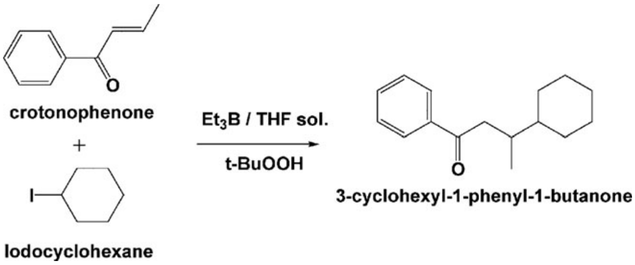


Fig. 1 Details of the experimental setup with a three-pronged microwave double cylindrical cooling reactor single mode system.

For a microwave applied power of 60 W, the temperature could be easily controlled by addition of dry-ice grains as measured by an optical fiber thermometer (FL-2000, Anritsu Meter Co. Ltd.) and a *k*-type sheathed thermocouple. Variations in temperature readings at various positions in the reactor with both probes were less than *ca.* ±2 °C; no temperature differences were evidenced within this error.

2.2 Synthesis of 3-cyclohexyl-1-phenyl-1-butanone (CPB)

A THF solution of triethylborane (2 mmol) was added gradually under an inert argon atmosphere to a vigorously magnetically stirred mixture comprised of iodocyclohexane (1 mmol) and crotonophenone (2 mmol) in the cylindrical reactor of Fig. 1, following which *tert*-butyl hydroperoxide (70% aqueous solution; 1 mmol; *t*-BuOOH; **CAUTION**§[18]) was added slowly to the solution also under argon inert conditions (reaction (1)).



(1)

The synthesis of 3-cyclohexyl-1-phenyl-1-butanone (CPB) was carried out using four different protocols: (a) application of 60 W of microwave radiation while the solution was cooled with dry-ice grains and hexane (MW/Cool); (b) conventional microwave irradiation at a 60 W power level (MW); note that the cold-finger contained only hexane to maintain reaction conditions close to those of the MW/Cool method; (c) conventional heating with an oil-bath (Oil-bath); and (d) synthesis at room temperature with the mixture magnetically stirred (RT). In all cases, reaction times for the syntheses were 60 and 120 min. Products were separated and purified by flash column chromatography over silica gel-300; the eluent was a mixture of dichloromethane and *n*-hexane (1 : 2 volume ratio).

2.3 Characterization of 3-cyclohexyl-1-phenyl-1-butanone (CPB) and by-products

The resulting major product 3-cyclohexyl-1-phenyl-1-butanone (CPB) and a small quantity of by-products (< *ca.* 5%; except for the MW/Cool protocol—see below) were analyzed by GC-MS techniques on a Shimadzu GC/MS Model QP5000 apparatus using an Ultra Alloy column (dimethylpolysiloxane 100%) obtained from Frontier Laboratory Ltd.; helium was the carrier gas. Proton NMR spectra of the CPB product were recorded on a JEOL 500-MHz spectrometer (Model LA500) in CDCl$_3$ solutions against TMS as the reference. Yields of the major product were estimated by determining the actual mass subsequent to the flash column chromatographic separation and purification and are based on the crotonophenone reagent.

3. Results and discussion

3.1 Temperature–time profiles

Temperature–time profiles for the sample solutions under the MW, Oil-bath and MW/Cool protocols are reported in Fig. 3. An initial solution temperature around 20–24 °C was maintained relatively constant by the hexane/dry-ice bath in the MW/Cool method. For the MW protocol, the initial temperature was *ca.* 28 °C increasing rapidly under microwave dielectric heating to reach 78 °C (reflux temperature) after *ca.* 6 min. The corresponding profile of heating the solution by the oil bath protocol was not very different (*ca.* 5 min) from the MW protocol.

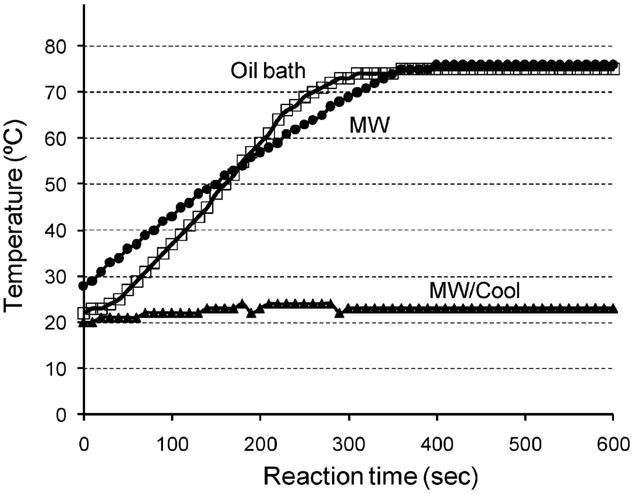


Fig. 3 Graph illustrating the time needed for the solution to reach maximal temperature.

3.2 Synthesis and identification of products

The gas chromatogram of the products (Fig. S1a, ESI‡) from the synthesis of 3-cyclohexyl-1-phenyl-1-butanone obtained by microwave dielectric heating the solution to reflux after 120 min (MW protocol) displays various peaks identified by gas chromatographic methods: crotonophenone, 3-methyl-1-phenyl-1-pentanone (by-product 1), 3-phenyl-4-hexen-3-ol (by-product 2) and boranyl species (see below) with retention times of 6.3, 7.1, 7.9 and 9.45–9.55 min, respectively. The major product 3-cyclohexyl-1-phenyl-1-butanone eluted at a retention time of 10.2 min. Identification of CPB and the by-products was carried out by GC-MS mass spectral techniques (Fig. S1b, ESI‡). Except for the molecular mass peak, the fragmentation patterns tended to be rather similar.

The proton NMR spectrum of the fraction of products (Fig. S2, ESI‡) obtained from the separation of products by flash column chromatography is consistent with the major product being 3-cyclohexyl-1-phenyl-1-butanone.

3.3 Chemical yields of 3-cyclohexyl-1-phenyl-1-butanone (CPB)

Chemical yields of 3-cyclohexyl-1-phenyl-1-butanone obtained under various experimental conditions are listed in Table 1. The

Table 1 Chemical yields of 3-cyclohexyl-1-phenyl-1-butanone (CPB) under various experimental conditions

		Yield (%) after:	
Method	Reaction temperature (°C)	60 min	120 min
MW/Cool	20–24	93	95
MW	78 (reflux)	56	53
RT	24	40	72
Oil-bath	78 (reflux)	27	31

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§ *tert*-Butyl hydroperoxide is used as a free radical initiator over a wide temperature range under appropriate redox initiation. It has a high thermal stability compared to other organic peroxides and is one of the safest of the organic peroxides. However, it is still a *peroxide*, and as such under inappropriate conditions it can decompose explosively. However, with proper handling it should cause no major problem.[18]

yield of the major CPB product was nearly quantitative (93 and 95%) for the MW/Cool method, 56 and 53% for the MW method, 40 and 72% for the RT method, and 27 and 31% for the conventional heating method with an oil bath after 60 and 120 min of reaction time, respectively.

Clearly, the most efficient synthesis of CPB occurred for the coupled microwave heating/internal cooling system. The rather unusual greater yields of CPB at room temperature compared to the conventional heating method under reflux with the oil-bath should also be noted. By comparison, the yield obtained under reflux by the microwave dielectric heating method (MW) was about 20–30% greater than by the conventional heating method under otherwise identical temperature conditions. In this regard, we attribute the greater yield of 53–56% from the MW method to some specific microwave effect. Most remarkable, however, are the greater yields of CPB by the internal cooling/MW dielectric heating of the reaction mixture (MW/Cool protocol).

Earlier we reported that the concentration of $^{\bullet}$OH radicals generated from the photoassisted oxidation of water in TiO_2 aqueous dispersions and monitored by electron spin resonance (ESR) techniques under simultaneous irradiation by UV-light and microwaves was significantly increased by irradiation with microwaves relative to UV irradiation alone.[19] By contrast, no increase of $^{\bullet}$OH radicals was obtained by conventional oil-bath heating. Specific microwave radiation effects played a non-insignificant role in this increase, although the *exact* nature of such effects remained somewhat elusive. In the present state of knowledge, we can only speculate on the root cause(s) for such specific microwave effects that input on the greater yields and faster kinetics relative to conventional heating under otherwise identical temperature conditions. As such we begin by considering the relationships that govern the reaction kinetics (given by the rate constant, *k*) and the thermodynamics of the reaction, namely the temperature dependence of the rates, from transition state theory (eqn (2)) and from the empirical Arrhenius equation (eqn (3)):[20]

$$k = (\kappa T/h)\exp(\Delta S^{*}/R)\exp(-\Delta H^{*}/RT) \qquad (2)$$

$$k = pZ\exp(-\Delta E_a/RT) \qquad (3)$$

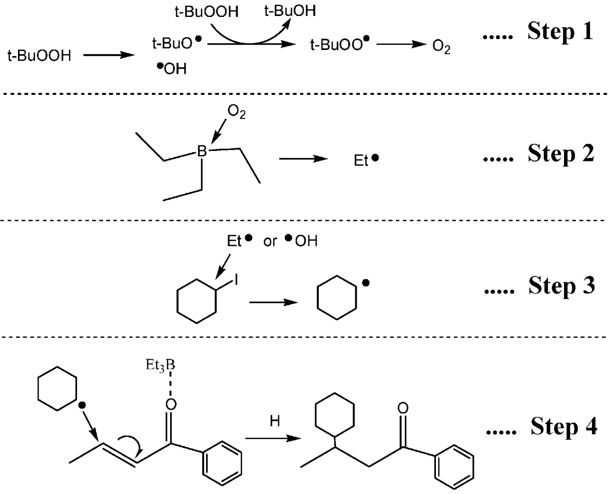
where κ is Boltzmann's constant, T is absolute temperature, h is Planck's constant, ΔS^{*} is the entropy of activation, ΔH^{*} is the enthalpy of activation, R is the gas constant, p is the steric factor, Z is the total collision frequency, and E_a is the activation energy; note that $E_a \approx \Delta H^{*}$ for reactions in liquids so that the pre-exponential factor pZ in eqn (3) is given approximately by eqn (3):

$$pZ \approx (\kappa T/h)\exp(\Delta S^{*}/R) \qquad (4)$$

Accordingly, the microwave radiation may affect one or more of the above parameters to account for the enhanced reaction kinetics and thus the yields; for example: (i) a decrease of the activation energy $E_a \approx \Delta H^{*}$ of the reaction through a greater stabilization of the activated complex, particularly relevant for polar reactants as they interact more effectively with the microwave radiation field; and/or (ii) an increase in the pre-exponential factor pZ through enhancing the encounter geometry (*i.e.* the steric factor *p*), thus the efficiency of the encounters between reactants, and increasing the number of collisions Z between reactant partners through a greater diffusion of the reactants from their respective solvent cages.

3.4 Proposed steps in the synthesis of 3-cyclohexyl-1-phenyl-1-butanone (CPB)

Four major steps involving radical events and likely implicated in the synthesis of 3-cyclohexyl-1-phenyl-1-butanone are suggested in Scheme 1. In Step 1, the initial stage is the decomposition of the hydroperoxide *t*-BuOOH to *tert*-butyl alcohol and oxygen[21] through formation of hydroxyl and *tert*-butoxy radicals by homolytic scission under microwave dielectric heating or conventional heating,[22] and photochemically under typical laboratory conditions.[21] The *tert*-butoxyl radicals react with *t*-BuOOH to yield *tert*-butyl alcohol and the *tert*-butyl peroxide radical which subsequently dimerizes to the di-*tert*-butyl tetraoxide. Decomposition of the latter yields molecular oxygen and the di-*tert*-butyl peroxide.[23] In Step 2, molecular oxygen interacts with B of the triethylborane structure releasing an ethyl radical,[24] which subsequently extracts the iodine from the C–I bond of iodocyclohexane to yield ethyl iodide and cyclohexyl radicals in Step 3. Dehalogenation of iodocyclohexane by $^{\bullet}$OH radical involvement from Step 1 is also not precluded in the formation of the cyclohexyl radical. In Step 4, the cyclohexyl radical subsequently adds to the position 3 of crotonophenone assisted by triethylborane, which in this instance functions as a Lewis acid. The ensuing carbon-centered radical at the 2-position then reacts with a hydrogen source, for example *t*-BuOH (Step 1), to yield the 3-cyclohexyl-1-phenyl-1-butanone product and the di-*tert*-butyl peroxide. Note that although addition of the cyclohexyl radical to position 2 is also possible, the NMR results reported in Fig. S2 (ESI‡) are consistent with the 3-cyclohexyl-1-phenyl-1-butanone product. No doubt other steps can also be envisaged that would involve the various radicals and other species. Such details were not the scope of the current study, however. Nonetheless, quantification of the products and by-products



Scheme 1 Some inferred steps in the overall synthesis of 3-cyclohexyl-1-phenyl-1-butanone (CPB).

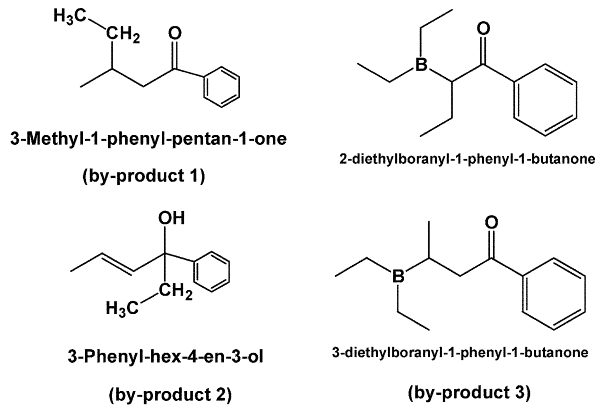
after the 120-min reaction period infers that such other steps were likely less significant, at least toward formation of the major product.

3.5 Effect of cooling coupled to microwave irradiation

The radical events of Scheme 1 infer, among others, two likely by-products in the synthesis of 3-cyclohexyl-1-phenyl-1-butanone by microwave and conventional heating prior to purification of the product(s) for the GC-MS analysis. The concurrent formation of two of the by-products are the result of addition of the generated ethyl radical at the 3-position of the crotonophenone skeleton and at the 1-position to yield by-products 1 and 2, respectively (see Scheme 2 and the chromatogram in Fig. S1a, ESI‡). To the extent that the mass spectra (Fig. S1b, ESI‡) of the species with retention times at 9.45 and 9.55 min are identical, we hypothesize that these two chromatographic peaks (Fig. S1a, ESI‡) correspond to the two isomers constituting by-product 3, namely 2-diethylboranyl-1-phenyl-1-butanone and 3-diethylboranyl-1-phenyl-1-butanone that result from addition of the de-ethylated triethylborane from Step 2 onto the olefinic bond positions of crotonophenone. Both the ethyl and hydroxyl radicals from Steps 1 and 2 can attack, albeit non-selectively, both crotonophenone and iodocyclohexane reactants under heating by microwaves (MW) and conventional heating (Oil-bath). For the MW/Cool method, however, the exclusive synthesis of 3-cyclohexyl-1-phenyl-1-butanone suggests selective attack of iodocyclohexane by both ethyl and hydroxyl radicals to produce the cyclohexyl radical. Evidently, the selectivity of the reaction was improved under such cooling conditions for the MW/Cool protocol,[17] otherwise not evident for the other protocols.

3.6 Influence of molecular oxygen

The influence of dissolved oxygen on the overall synthesis and product yields was examined for 60-min irradiation by the microwaves for solutions saturated with molecular oxygen. Yields are reported in Table 2 for the case where both added oxygen and oxygen produced in Step 1 of Scheme 1 was present and for the case where only molecular oxygen was added (no *t*-BuOOH used in this case). In the former case, the chemical yield of 3-cyclohexyl-1-phenyl-1-butanone was *ca.* 100%, whereas a *ca.* 69% yield was obtained under the latter conditions. These observations clearly indicate the key role played by the *t*-BuOOH in the overall reaction. Moreover, they also show the effect of cooling under microwave irradiation in the selectivity of the radical reaction.



3-Methyl-1-phenyl-pentan-1-one (by-product 1)

2-diethylboranyl-1-phenyl-1-butanone

3-Phenyl-hex-4-en-3-ol (by-product 2)

3-diethylboranyl-1-phenyl-1-butanone (by-product 3)

Scheme 2 By-products produced in the synthesis of 3-cyclohexyl-1-phenyl-1-butanone by the MW, RT and Oil-bath protocols.

Table 2 Chemical yields of 3-cyclohexyl-1-phenyl-1-butanone (CPB) by the synthesis with and without *t*-BuOOH with the reactant solution being purged with molecular oxygen

Method	Purging gas	Yield (%)
MW/Cool	O_2	≈100
MW/Cool	O_2 (without *t*-BuOOH)	≈69

Summary

The synthesis yield of 3-cyclohexyl-1-phenyl-1-butanone by microwave dielectric heating is improved for the radical reaction under temperature conditions otherwise identical to those of the conventional heating method and under close temperature control. The greater yields of the product observed for the microwave-induced reaction over those obtained by conventional heating for identical conditions of temperature likely implicate some specific microwave effect(s), the nature of which continues to be a subject of great debate. Cooling coupled to microwave irradiation improved the selectivity of the radical reaction toward a single major product without losing the characteristic advantage(s) of the microwaves. The non-selectivity of the chemical reaction by either conventional or microwave dielectric heating alone could be attenuated by cooling the reaction mixture while being microwave irradiated.

Acknowledgements

We are grateful to the Sophia University-wide Collaborative Research Fund, the Foundation of Research for Promoting Technological Seeds from the Japan Science and Technology Agency to S. H. One of us (N. S.) is grateful to Prof. Albini and his group for their gracious hospitality during his several stays in Pavia during the winter semesters. We are also grateful to one of the reviewers for pointing out some NMR features of our major product from ChemNMR.

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