Scheme 1. **Oxidation of isopropenylbenzenes with $PhI(OAc)_2$−zeolite (NaY) under microwave irradiation**

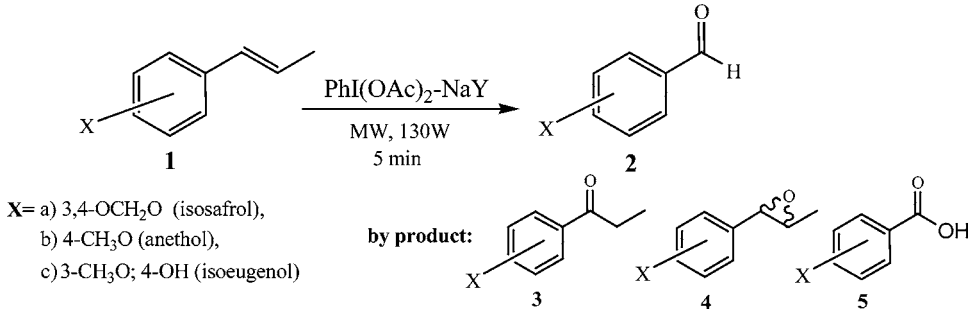

Table 1. **Oxidation of isosafrol**

$PhI(OAc)_2$ (mmol)/ support (g) or solvent (mL)	*t* (min)	*T* (°C)	conv (%)	selectivity (%) **2a**	selectivity (%) byproducts
0.5/6 CH_2Cl_2	5	50	3	29	15 (**3a**), 55 (**4a**)
0.8/3 CH_2Cl_2	30	84[a]	11	100	
0.8/6 CH_3CN	5	100	7	36	17 (**3a**), 37 (**4a**)
0.8/6 CH_3CN	10	100	7	40	19 (**3a**), 39 (**4a**)
0.8/6 CH_3CN	30	110	21	90	6 (**3a**), 4 (**4a**)
0.8/1 g Al_2O_3	3	110	25.5	96	4 (**4a**)
0.8/1 g Al_2O_3	5	110	61	69	5 (**3a**), 26 (**5a**)
0.8/1 g Al_2O_3	30	140	75	57	12 (**3a**), 31 (**5a**)
0.8/0.2 g NaY	**5**	**130**	**89**	**91**	**9 (3a)**
0.8/0.5 g NaY	5	140	72	55	45 (**3a**), 5 (**5a**)
0.8/1 g NaY	5	170	100	62	

[a] 37 psi.

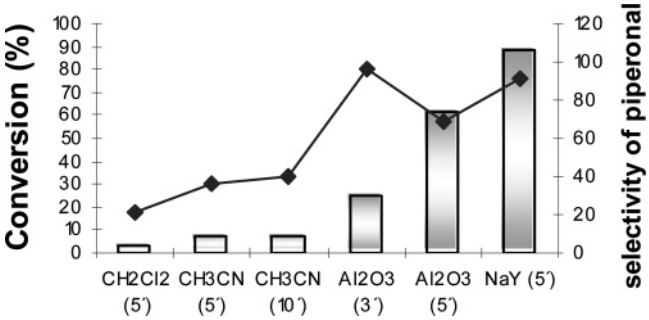

Figure 1. **Oxidation of isosafrol with $PhI(OAc)_2$.**

The analysis of the products obtained after workup revealed the formation of carbonyl compounds as summarized in Table 1. This table shows the more significant results obtained in the oxidation of isosafrol under microwaves, using solventless $PhI(OAc)_2/Al_2O_3$ and/or $PhI(OAc)_2$/NaY. As it can be seen, the use of CH_2Cl_2 or CH_3CN as solvents led to poor conversions.

Alternatively, considerably better conversions were obtained with solventless $PhI(OAc)_2$ on Al_2O_3 (entries 7 and 8) and zeolite NaY (entries 9, 10, and 11). The interaction of the support with $PhI(OAc)_2$ would generate in situ PhIO (more active oxygen donor).

Due to the higher water content in NaY than in Al_2O_3, the in situ formation of iodosobenzene by hydrolysis of $PhI(OAc)_2$ (Figure 1) is more favorable on this support. The larger surface area presented by the zeolite can also play an important role in this comparison, probably inhibiting polymerization of PhIO inside of pores.

In view of our results and also on the basis of earlier results with microwave reactions on solid mineral supports,[2e,f] which normally afford cleaner products, we repeated the reaction using isopropenylbenzenes with supported $PhI(OAc)_2$.

Figure 2 shows the comparison between the oxidation products of different activated propenylbenzenes (mainly aldehydes). The reaction proceeded smoothly providing 91% yield piperonal, 62% *p*-anisaldehyde, and 43% vanillin, using NaY-supported $PhI(OAc)_2$ and 61% yield piperonal, 59% to *p*-anisaldehyde and 35% to vanillin, using Al_2O_3-supported $PhI(OAc)_2$.

The smaller yields observed in the oxidation of isoeugenol could be related to further oxidation of vanillin to other byproducts.

NaY-supported $PhI(OAc)_2$ appears to be a better choice since the reactions, in addition to better yielding, are cleaner and faster.

The best protocol involves mixing of the isopropenylbenzene with 2 equiv of $PhI(OAc)_2$ on NaY (or Al_2O_3) and irradiation of the reaction mixture in a microwave reactor for the specified time (5 min) under solventless conditions. This rapid procedure avoids the overoxidation of isopropenylbenzene to the corresponding carboxylic acid. The microwave irradiations were performed under controlled conditions that make the procedure highly safe, reliable, and reproducible. Single-mode irradiation with monitoring of temperature, pressure, and irradiation power versus time was used throughout.

The discussion on the so-called microwave effect is now an old one. Microwave (MW) irradiation is a rapid way of achieving a desired temperature, sometimes without solvent disturbance.[2] This question was very well addressed by Stadler and Kappe in a Biginelli reaction, for example.[8] Of course, one can claim the same thermal effect in an oil bath. However, in this case very long induction periods are needed,

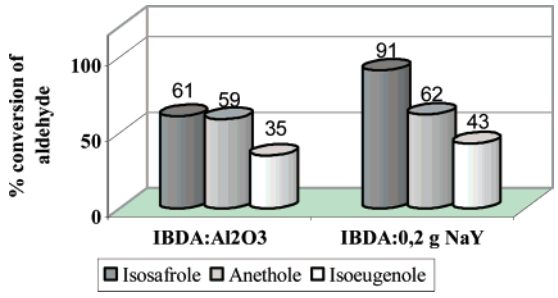

Figure 2. **Oxidation of isopropenylbenzene with $PhI(OAc)_2$.**

and presently, environmental considerations prevent the indiscriminate use of oil baths as well as of unnecessary solvents. A careful mass and energy balance sometimes is needed.[9]

The industrial use of this process deserves further studies. For example, a NOVARTIS group is working on rationalizing the energy working under the solvent boiling point temperature.[10] Other groups are currently working on scaling up under batch[11] or continuous process conditions including the use of microreactors.[12] Although still tricky, solid-state technology is now widely applied in fermentations[13] and polymers[14] and must be adapted to these solvent-free reactions.

In terms of green chemistry it must be emphasized that, although the byproduct iodobenzene cannot be considered friendly to waste or treat, it can be easily recycled upon oxidation with peracetic acid to the original oxidant, iodosobenzene.[15]

Experimental

Equipment. The reactions were monitored utilizing high-resolution gas chromatography. A model HP5890 was used with a HP 1 WCOT column (25 m × 0.32 mm i.d.). H_2 was used as carrier gas at a flow rate of 3.0 mL/min (96 cm/s) with a pressure of 20 psi. The initial temperature was set at 100 °C and the final at 250 °C at a rate of 3 °C/min. The injector was held at 150 °C, and the detector, at 240 °C. The injection was operated at splitless mode for 0.2 μL of injected solution. To confirm, a GC−MS model 5973HP equipped with HP5 capillary column (30 m × 0.25 mm, 0.25 μm film thickness) was used using Helium as carrier gas with a flow rate of 1 mL/min (32 cm/s). The oven temperature was programmed starting from 80 to 260 °C at 3 °C/min. The injector was hold at 150 °C, and the interface, at 240 °C. Mass spectra were obtained (electron impact mode) at 70 eV (EI). Scan mode (1 scan/min; acquisition *m*/*z*: 40−400).

Reactions were carried out with a single-mode cavity Discover Microwave synthesizer (CEM Corporation, NC) producing continuous irradiation at 2455 MHz and an infrared temperature control system.

Typical Procedures. The oxidation of isosafrol to piperonal[16] is representative of the general procedure employed. Isosafrol (0.065 g, 0.4 mmol) and $PhI(OAc)_2$ (0.26 g, 0.8 mmol) on NaY (0.2 g, silica/alumina ratio = 4, surface area = 580 m^2/g) or alumina (1 g, γ-alumina, 180 m^2/g) are mixed thoroughly on a vortex mixer. The reaction mixture is placed in the microwave reactor and irradiated for a period of 5 min. (WARNING: HEATING OF $PhI(OAc)_2$ CAN GENERATE HOT SPOTS UNDER MICROWAVE IRRADIATION. TO AVOID ANY EXPLOSION RISK THE STABILITY OF THE REAGENT MUST BE INVESTIGATED UNDER THESE CONDITIONS IF A SCALE-UP IS TO BE DONE.) The reactions were carried out in open 125 mL flasks at ambient pressure or in closed, conical vessels under pressure. In both cases *P* and *T* were monitored. On completion of the reaction, followed by TLC examination (hexane/AcOEt, 9:1, v/v), the product is extracted with dichloromethane and washed with aqueous sodium bicarbonate solution. The organic phase is separated, dried over magnesium sulfate, and filtered, and the crude product is analyzed by GC−MS. The chromatographic analysis of the sample presented peaks at 8.7 (**1a**), 11.8 (**4a**), 7.4 (**2a**), and 12.8 (**3a**), as compared with authentic samples.

Conclusion

In conclusion, we have described an efficient oxidation procedure for the preparation of various important aldehydes in reproducible conditions, under MW irradiation, avoiding the use of ozone and sulphur or zinc, of course with benign consequences. The advantages of this environmentally benign and safe protocol include simple reaction conditions, short reaction times, and easy workup and use of commercial oxidants. Using isosafrol, isoeugenol, and anethol it was possible to produce piperonal, vanillin and *p*-anisaldehyde, respectively

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Note Added after ASAP Publication. In the version published on the Web August 16, 2006, iodobenzene diacetate was misspelled. The misspellings have been corrected in the version published on the Web August 24, 2006, and in the print issue.

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