Tetrahedron Letters,Vol.27,No.41,pp 4945-4948,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

APPLICATION OF COMMERCIAL MICROWAVE OVENS TO ORGANIC SYNTHESIS.[1]

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SUMMARY: Commercial microwave ovens have been safely used to dramatically reduce the reaction times (at comparable yield) of Diels-Alder, Claisen, and ene reactions. Significant solvent effects were also observed.

Microwave ovens have been virtually ignored as controllable thermal sources for conducting organic reactions.[2,3] The recent paper by Gedye, et.al. prompts us to disclose our independent investigations in this area.[3] Here we report results on reaction vessel design, safety precautions, and solvent choice in a study of thermal reactions.

I. Reaction Vessel/Safety Precautions

Principal considerations in making this equipment applicable for laboratory use are: 1) reaction vessel choice, 2) safety precautions, and 3) assessment of reaction temperature and pressures generated. We have safely conducted organic reactions up to one gram in scale by using either sealed tubes[4a] or screw-cap pressure tubes as reaction containers.[4b] These reaction vessels were placed in either a Nalgene desiccator[5] or a Corian box,[6] each packed with vermiculite,[7] which serves to absorb reaction contents in the event of an explosion.[8] In addition, all microwave-induced thermolyses[9] were conducted in a hood.

II. Temperature Approximation

The nature of microwave heating precludes conventional means of temperature determination.[10,11] However, temperature approximations were obtained by using sealed capillaries containing compounds of known melting points either sealed within or affixed to the reaction container.[12,13] A systematic study determined that inside and outside reaction vessel temperatures differed at most by ± 5°C, thereby allowing use of either method for reliable temperature approximation.

III. Solvent Studies

Figure I shows temperatures attained as a function of irradiation time for *n*-hexane and DMF. In the absence of insulation, hexane reaches a thermal stationary state of ca. 60°C after two minutes, while insulated runs attain temperatures >300°C after ten minutes. We attribute the latter result to coupling of microwave energy with the vermiculite's water of hydration. Empty sealed tube runs (labeled: blank) confirm this conclusion. In contrast, DMF rapidly reaches temperatures >300°C but requires longer irradiation when insulated. Here the ability of vermiculite to absorb microwave irradiation results in partial "shielding" of the sample, hence the longer exposure times necessary to reach comparable temperatures. Our results with diethylene glycol and *n*-hexane (without insulation) suggest the potential for regulating the maximum temperature desired by simple solvent choice.

Figure II illustrates that solvents possessing high dielectric constants superheat rapidly while those with low dielectric constants heat slowly [cf. *N*-methylformamide and *p*-xylene]. In addition, a semi-quantitative relationship exists between the magnitude of the solvent's dielectric constant [at room temperature][14] and its thermal efficiency under these conditions (cf. captions).

FIGURE I

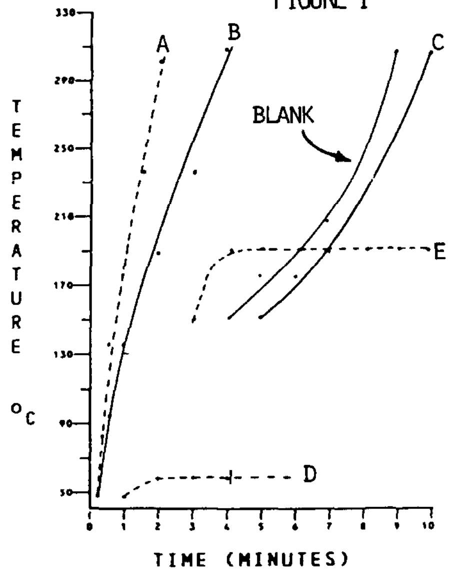
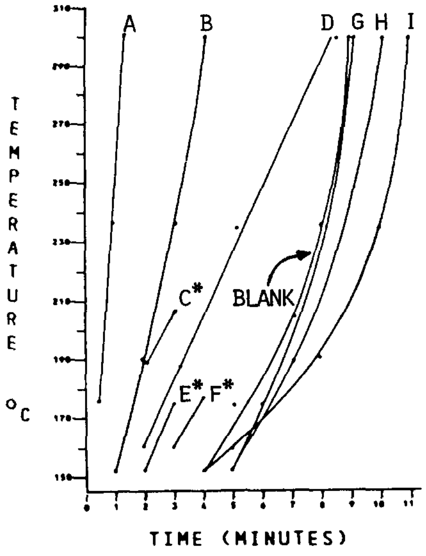


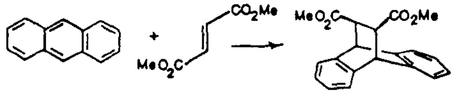
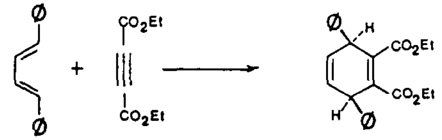
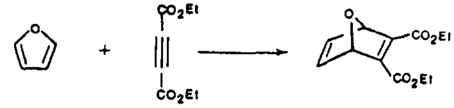
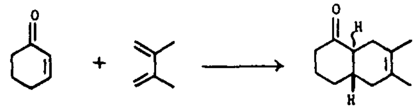
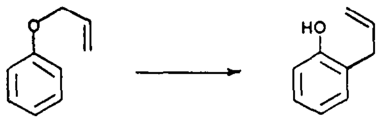
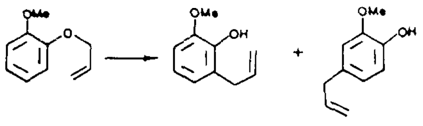
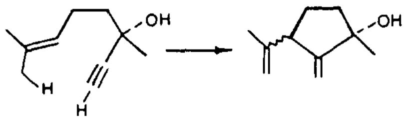
FIGURE II



CAPTIONS: Dashed lines indicate absence of insulation; solid lines represent vermiculite insulated runs. An asterisk (*) indicates that the sealed tubes exploded at longer irradiation times. **Figure I:** **A** and **B** = DMF; **C** and **D** = *n*-hexane; **E** = diethylene glycol. **Figure II:** **A** = *N*-methylformamide (ϵ = 182.4); **B** = dimethylformamide (ϵ = 36.7); **C** = acetonitrile* (ϵ = 37.5); **D** = diethylene glycol (ϵ = 31.7); **E** = ethanol* (ϵ = 24.6); **F** = acetone* (ϵ = 20.7); **G** = triglyme; **H** = *n*-hexane (ϵ = 1.9); **I** = *p*-xylene (ϵ = 2.3).

IV. Thermal Reactions

Efforts to increase the rate and yield of thermal reactions have resulted in the development of an array of experimental conditions to realize these goals (e.g., high pressure;[15] Lewis acid catalysis[16]). The following Table depicts significant decreases in reaction times observed using microwave heating.

	REACTION	MICROWAVE	LITERATURE	CONTROL
1.		3 min^{4a} p-xylene, 92% 160°<187°C	10 min^{17} p-xylene, 90% 138°C	10 min p-xylene, 90% 138°C
2.		10 min^{4a,b} p-xylene, 87% 325°<361°C	72 h^{18} dioxane, 90% 101°C	4 h p-xylene, 67% 138°C
3.		12 min^{4b} NEAT, 55% 325°<361°C	5 h^{19} NEAT, 67% 150°C	5 h NEAT, 81% 150°C
4.		10 min^{4b} NEAT, 66% 325°<361°C	4 h^{20} NEAT, 95% 100°C	4 h NEAT, 68% 100°C
5.		15 min^{4b} NEAT, 25% 400°<425°C	72 h^{21} NEAT, 20% 200°C	a) 3 days, NEAT^{22} 89%, 195°C b) 2 h, NEAT^{22} 75%, 195°C
6.		a) 10 min,^{4b} NEAT 21%, 325°<361°C b) 6 min, DMF 92%, 325°<361°C	6 h^{23} NEAT, 85% 220°C	6 min NEAT, 17% 320°C
7.		a) 12 min,^{4b} NEAT 71%, 370°<400°C b) 5 min,^{4b} DMF 72%, 300°<315°C c) 90 sec,^{4b} N-methylformamide 87%, 276°<300°C	85 min^{23} NEAT, 85% 240°C	a) 45 min NEAT, 71% 265°C b) 12 min NEAT, 92% 320°C
8.		15 min NEAT, 62% 400°<425°C	12 h^{24} NEAT, 85% 180°C	12 h NEAT, 60% 180°C

Several of these results merit further comment. First, solvent choice allows one to vary the rate of temperature rise which accounts for the solvent effects observed (c.f. entries 6-8). Second, several of the reported thermal conditions proved to be unoptimized. In entry 5, for example, excellent yields of octalone products were obtained under control conditions.[22] Finally, the intramolecular rearrangements in entries 6-8 suggest that the results observed are due to thermal effects rather than the influence of pressure.

Although the scope and limitations of this process have yet to be fully determined, microwave thermolysis has considerable potential for rapid acceleration of chemical reactions.[25]

REFERENCES

1. Presented in part at the "Second Symposium on the Latest Trends in Organic Synthesis," Blackburg, Virginia, May 1986.
2. Gedye, R.; Smith, F.; Westaway, K.; Humera, A.; Baldisera, L.; Laberge, L.; Rousell, Tetrahedron Lett. **1986**, 26, 279.
3. Other chemical applications of microwave heating are: (a) rapid determination of thermodynamic functions of chemical reactions: Bacci, M.; Bini, M.; Checcucci, A.; Ignesti, A.; Millanta, L.; Rubino, N.; Vanni, R. J. Chem. Soc., Faraday Trans. 1, **1981**, 77, 1503; (b) microwave-induced polymerization: Vanderhoff, J.W., U.S. Pat. 3,432,413 [C.A. 70: 97422v, **1969**]; and (c) wet ashing technique: Keyzer, H. Chemistry in Australia, **1978**, 45, 44.
4. (a) Annealed thick-walled pyrex tubing, 10 mL volume; (b) Ace Glass pressure tube, No. 8648-04, 20 mL volume, used without the O-rings provided.
5. Autoclavable polypropylene desiccator (Fischer, No. 08-642-15; Nalge 5315). An entry port (ca. 1½" diameter) is cut into the desiccator cover. Vessel preparation is conducted as follows: (1) the sealed tube is placed in the bottom of the desiccator on a bed of vermiculite. After placing the cover and securely taping it down, additional vermiculite is added to completely fill the desiccator. After extensive use, the polycarbonate cover suffers considerable deformation.
6. A rectangular box [inside dimensions: 3"x3"x7"] having a bevel-fitted sliding lid was constructed of ¼" Corian — a durable, heat resistant polymer. We recommend this type of container for studies requiring >200°C or prolonged irradiation periods.
7. Vermiculite consists of hydrous silicates of iron, aluminum and magnesium. Although glass wool proved to be an effective insulator, we regard it inferior to vermiculite.
8. Indeed, Gedye and co-workers reported a violent explosion when attempting to oxidize toluene with potassium permanganate. Microwave runs >15 min should be avoided as softening of the teflon stopper occurs with subsequent loss of reaction contents.
9. All thermolysis reactions were carried out using 100% power [600 W, microwave frequency 2450 MHz] in a Sanyo 2500LA microwave oven with digital timing and power controls.
10. For an explanation of microwave heating, see: "Microwave Heating in Freeze-Drying, Electronic Ovens, and Other Applications," David A. Copson, The AVI Publishing Co., Westpoint, CT, **1962**, pp 1-20.
11. As expected, temperature determinations using thermocouples in conjunction with a digital thermometer failed due to arcing.
12. In most cases, the data points presented in Figures I & II represent single acquisitions and only serve as approximations.
13. The following compounds were employed for temperature approximations [mp; °C]: benzophenone [48], deoxybenzoin [55-6], biphenyl [69-72], vanillin [81], benzil [95], resorcinol [109-10], benzoin [134-6], adipic acid [152-67], semicarbazide hydrochloride [177-78, dec.], succinic acid [187-90], D,L-tartaric acid, H_2O [205, dec.], phthalic acid [210-11, dec.], caffeine [236-7], furmaric acid [299-300], L-alanine [315-17], D,L-tyrosine [325, dec.], potassium nitrite [361, yellows], potassium nitrate [370], and lead nitrate [400, emits brown gas].
14. Dielectric constants are temperature dependent. Unfortunately, data regarding these values at elevated temperatures are rare or non-existent.
15. For a recent review, see: Matsumoto, K., Seva, A. Synthesis **1985**, 11, 999.
16. For examples, see: (a) Yates, P.; Eaton, P. J. Am. Chem. Soc., **1960**, 82, 4436; (b) Fray, G.I.; Robinson, R. ibid., **1961**, 83, 249.
17. Organikum, VEB Deutscher Verlag, Berlin **1977**, p 352.
18. Bachmann, W.E.; Scott, L.B. J. Am. Chem. Soc., **1948**, 70, 1458.
19. Lohaus, H. Ann. **1935**, 516, 295.
20. McCulloch, A.W., Stanovnik, B., Smith, D.G., McInnes, A.G. Can. J. Chem. **1969**, 47, 4319.
21. Bartlett, P.D.; Woods, G.F. J. Am. Chem. Soc. **1940**, 62, 2933.
22. These products were isolated by chromatography; distillation undoubtedly causes retro Diels-Alder reaction, hence the low literature yields. The product of entry 5 presumably also undergoes retro Diels-Alder reaction under microwave conditions.
23. Claisen, L.; Eisleb, O.; Kremers, F. Ann. **1919**, 418, 69.
24. Hoffmann, W.; Pasedach, H.; Pommer, H.; Reif, W. Ann. **1971**, 747, 60.
25. A manuscript detailing the application of microwave thermolysis to Finkelstein reactions and intramolecular Diels-Alder and ene reactions is in preparation..

(Received in USA 23 June 1986)