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HIGHLY ACCELERATED REACTIONS IN A MICROWAVE OVEN : SYNTHESIS OF HETEROCYCLES

Ajay K. Bose,* Maghar S. Manhas, Malay Ghosh, Vegesna S. Raju, Keiko Tabei,
and Zofia Urbanczyk-Lipkowska
Department of Chemistry and Chemical Engineering, Stevens Institute of
Technology, Hoboken, New Jersey 07030, U. S. A.

ABSTRACT- Efficient synthesis of a wide variety of heterocycles on 0.1 to 200 g scale was conducted in organic solvents in a commercial microwave oven in a few minutes at a low energy level. Erlenmeyer flasks were adequate reaction vessels since neither high pressure nor high temperature were involved. Fast monitoring of synthetic reactions was achieved by tlc separation and transfer of tlc spot material directly to a solids probe of a chemical ionization mass spectrometer. Microwave Oven-induced Reaction Enhancement (MORE) chemistry is not due to thermolysis: one reaction was conducted successfully in a reaction vial encased in a block of ice.

INTRODUCTION

Commercial microwave ovens provide a beam of microwaves set for efficient heating of water. Such ovens can serve as a convenient source of heat in the laboratory; their computerized versions are commercially available for the acid digestion of ores and minerals in explosion-proof sealed vessels. Biochemists and organic chemists have conducted hydrolytic[1-6] and other reactions[3,4] in microwave ovens in sealed tubes or in capped Teflon vessels. Highly accelerated rate of chemical reactions observed under these conditions has been ascribed to the high temperature and the high pressure that are reached in minutes. Two recent publications have shown that the generation of high pressure can be avoided in such "thermolysis" reactions in microwave ovens by using reagents adsorbed on alumina or clay.[6,7]

In a preliminary report we have described efficient and rapid synthesis of a variety of β-lactams in a microwave oven without resorting to high pressure or high temperature.[8] We wish to report now that such "Microwave Oven-induced Reaction Enhancement" (MORE) chemistry can be utilized for highly accelerated synthesis of divergent types of heterocycles. Some illustrative examples of MORE chemistry are provided here.

N-PHTHALOYLAMINO ACIDS

Formation of N-phthaloyl derivatives by the reaction of amino acids with phthalic anhydride is a useful procedure which can be conducted on a large scale by using refluxing toluene as the reaction medium, triethylamine as a catalyst and a Dean-Stark water separator as a trap for the water formed in the reaction.[9]

We have found that by substituting N,N-dimethylformamide (DMF) for toluene and using a micro reaction vial with a septum cap as the reaction vessel, N-phthaloylation could be conducted on a few gram scale. When the vial was placed in a microwave oven and "zapped"[10] for 1-3 min at a low power setting of the oven, the formation of phthalimidoacetic acid (1) proceeded in high yield. To establish that no thermolysis was involved, the reaction vial in one experiment was placed in a beaker of water and the water was frozen to a block of clear ice. When this block of ice was zapped for 3 min inside a microwave oven, the outer surface of the ice was melted slightly. Analysis of the contents of the encased reaction vial showed the formation of phthalimidoacetic acid in good yield. It was also found that phthalimidoacetic acid could be prepared on a 100-200 g scale in 5-8 min in a microwave oven. An Erlenmeyer flask covered with a watch glass or funnel was adequate as the reaction vessel. No reflux condenser or Dean-Stark water trap was needed. The yield and the purity of the product were comparable to those reported in 'Organic Synthesis'.[9]

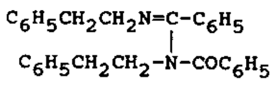
MISCELLANEOUS HETEROCYCLES

We have duplicated under microwave irradiation several preparations described in 'Organic Synthesis' (See Table 1). In each case the reaction in the microwave oven was highly accelerated and the yields were comparable. Barbituric acids (2) were prepared from malonic ester (or phenylmalonic ester) by condensation with urea in ethanol solution in presence of sodium ethoxide.[11] The reaction of ethyl acetoacetate with thiourea in ethanol solution gave 2-thio-6-methyluracil (3).[12] Formic acid served as both the reagent and the reaction medium for the conversion of o-diaminobenzene to benzimidazole(4).[13] Knoevenagel condensation between salicylaldehyde and diethyl malonate leading to ethyl 2H-1-benzopyran-2-oxo-3-carboxylate (5) could be conducted in the absence of any solvent.[14]

BISCHLER-NAPIERALSKI REACTION

We have studied the Bischler-Napieralski reaction in some detail to investigate the role of solvents in reactions under microwave irradiation. Under standard conditions this reaction is conducted in refluxing toluene (or some other hydrocarbon solvent) leading to a 3,4-dihydroisoquinoline (7) in good yield from a β-arylethylamide (6)[15] and phosphorus oxychloride or phosphorus pentoxide. In a microwave oven, toluene proved to be an inadequate energy transfer medium so that no reaction occurred even after several minutes of irradiation. This was not unexpected since Gedye et al.[3] have reported that solvents with higher dipole moment have higher energy transfer rate. Thus, DMF and 1,2-dichloroethane (DCE) are heated much faster in a microwave oven than hexane or carbon tetrachloride. When the reaction was attempted in DMF with phosphorus oxychloride as the condensing agent, an intractable complex mixture was produced upon microwave irradiation. Only trace amounts of (7) was formed when DCE was the reaction medium.

Phosphorus pentoxide has been used as the condensing agent for the Bischler-Napieralski reaction. Thus, the 3,4-dihydroisoquinoline (7) was the major product from (6) when refluxing toluene was the reaction medium and phosphorus pentoxide was the condensing agent. When this reaction was conducted in a microwave oven with toluene replaced by DCE, a crystalline product (8) was obtained in nearly quantitative yield. From its molecular weight determined by chemical ionization mass spectrometry this compound appeared to be formed from two molecules of the starting amide with the loss of one molecule of water. Single crystal X-ray diffraction studies[16] on this compound indicated that it was the amidine (8). The same amidine was also obtained when (6) was heated under reflux for 1 h - outside the microwave oven - with phosphorus pentoxide in methylene chloride, chloroform or DCE solution. Intramolecular versions of this amidine forming reaction is under study for the formation of heterocycles.



$$\begin{array}{l} C_6H_5CH_2CH_2N{=}\underset{\displaystyle |}{C}{-}C_6H_5 \\ \quad C_6H_5CH_2CH_2{-}N{-}COC_6H_5 \end{array}$$

(8)

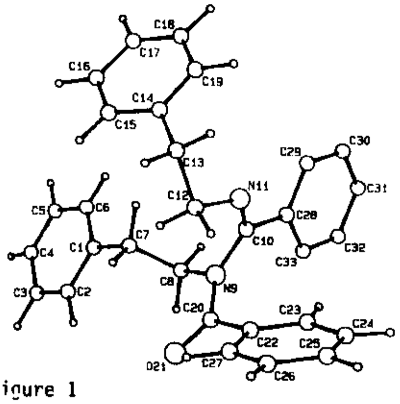
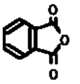
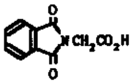
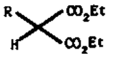
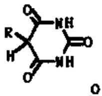
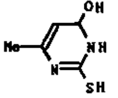
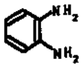
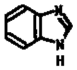
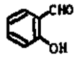
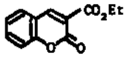
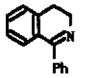
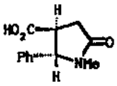
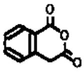
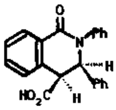


Figure 1

Table 1

Reactans	Product		Yield %	
			Standard reaction (time)	Microwave oven reaction (time)
 , $H_2NCH_2CO_2H$, NEt_3		(1)	83-90 (1.5 h)	65-72 (1-4 min)
 , NH_2CONH_2, NaOEt		(2)	R = H, 72 (7 h) R = Ph, 70 (6 h)	71 (2 min) 30 (3 min)
$MeCOCH_2CO_2Et$, NH_2CSNH_2, NaOEt		(3)	69-84 (8 h)	68 (2 min)
 , HCO_2H		(4)	79 (3 h)	70 (3 min)
 , $CH_2(CO_2Et)_2$		(5)	73 (6 h)	82 (3 min)
 , P_2O_5 (6)		(7)	78 (6 h)	0
 , PhCH=NMe		(9)	82 (36 h) *trans* (major) *cis* (minor)	59 (5 min) *trans*
 , PhCH=NPh		(10)	40 (15 min) *cis*	67 (3 min) *cis*

INTERMEDIATES FOR SOME ALKALOIDS

We have investigated the effect of microwave irradiation on the reaction between Schiff bases and certain acid anhydrides leading to intermediates for various alkaloids. Castagnoli[17] had discovered that the reaction of succinic anhydride with benzylidenemethylamine in refluxing benzene over a period of 36 h led to a mixture of trans (major product) and cis forms of the substituted 2-pyrrolidinone (9) in 82.5% yield. We substituted DMF for benzene and conducted the same reaction in a microwave oven for 5 min and obtained trans (9) in 59% yield. Following Cushman and Madaj[18] we reacted homophthalic anhydride with benzylideneaniline. The same cis compound (10) was obtained inside a microwave oven as outside when the reaction medium was DCE.

FAST MONITORING OF REACTIONS

It is customary in our laboratory to monitor MORE chemistry by a rapid method consisting of thin layer chromatography (tlc) followed by chemical ionization mass spectrometry (CIMS)[19]. Spots on the tlc plate are rapidly and conveniently transferred to a mass spectrometer with a solids probe the tip of which carries a bead of Carbowax 20M made sticky by warming. Molecular weight and fragmentation information from positive ion and negative ion CIMS generally permits quick identification of the products of a reaction - often without the benefit of additional data from ir and nmr spectral measurements.

CONCLUDING REMARKS

Our experiments clearly show that highly accelerated chemical reactions in organic solvents need not be due to the high temperature and high pressure that can be reached in sealed systems when irradiated at high energy level settings of a microwave oven. Reactions at low settings of microwave ovens using DMF, DCE, dioxane, ethanol and esters can be conducted at near room temperature or lower temperatures in a few minutes. Since the reactions proceed very rapidly, the use of reflux condensers, drying tubes, water traps, etc. are redundant for conducting MORE chemistry. If exclusion of air is preferred, a reaction vial with a septum as a cap can be used. Fast monitoring by tlc-cims adds to the overall efficiency of synthetic experiments conducted in a microwave oven. The course of reaction in some cases can be altered by changing the reaction medium. Extension of MORE chemistry to other areas of heterocyclic and non-heterocyclic reactions is in progress in our laboratory.

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REFERENCES

1. S.-T. Chen, S.-H. Chiou, Y.-H. Chu, and K.-T. Wang, Int. J. Peptide Protein Res., 1987, 30, 572, and references cited therein.
2. W. C. Sun, P. M. Guy, J. H. Jahngen, E. F. Rossomando, and E. G. E. Jahngen, J. Org. Chem., 1988, 53, 4414.
3. R. N. Gedye, F. E. Smith, and K. C. Westaway, Can. J. Chem., 1988, 66, 17, and references cited therein.
4. R. J. Giguere, T. L. Bray, and S. M. Duncan, Tetrahedron Lett., 1986, 27, 4945.
5. R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, and J. Rousell, Tetrahedron Lett., 1986, 27, 279.
6. A. B. Alloum, B. Labiad, and D. J. Villemin, J. Chem. Soc., Chem. Commun., 1989, 386.
7. E. Gutierrez, A. Loupy, G. Bram, and E. Ruiz-Hitzky, Tetrahedron Lett., 1989, 30, 945.
8. A. K. Bose, M. Ghosh, K. Tabei, M. Shah, and M. S. Manhas, "Highly Accelerated β-Lactam Synthesis in a Microwave Oven Monitored by TLC-CIMS" presented at the 197th National Meeting of Amer. Chem. Soc., Dallas, TX, April, 1989, ORGN 226.
9. A. K. Bose, Org. Syn. Coll. Vol., 5, 1973, p. 973.
10. Commonly used terms for irradiation (of food) in a microwave oven are "nuked" and "zapped", we prefer the latter.
11. J. B. Dickey and A. R. Gray, Org. Syn. Coll. Vol., 2, 1943, p. 60.
12. H. M. Foster and H. R. Snyder, Org. Syn. Coll. Vol., 4, 1963, p. 638.
13. E. C. Wagner and W. H. Millett, Org. Syn. Coll. Vol., 2, 1943, p. 65.
14. E. C. Horning, M. G. Horning, and D. A. Dimmig, Org. Syn. Coll. Vol., 3, 1955, p. 165.
15. W. M. Whaley and T. R. Govindachari, Org. Reactions, 1951, 6, 124.
16. X-Ray analysis of 8 (crystals grown from ethyl ether/ethyl acetate): 3250 unique reflections were collected on an Enraf-Nonius CAD4 diffractometer using monochromatized MoK$_\alpha$ radiation [μ(MoKα)=0.713 cm^{-1})], $\theta/2\theta$ scan, θ range 0 - 25°. Unit cell parameters refined for 25 reflections are: a = 24.485(4), b = 11.817(2), c = 16.853(3) Å, β=99.95(2)°, Z = 8, d_X = 1.179 g. cm^{-3}. Monoclinic I2/c space group was confirmed during X-ray analysis course. Data were corrected for background, LP and absorption correction based on ψ scans for 4 reflections (maximum and minimum transmission were 97.2 and 99.8%, respectively). Structure was solved by direct methods using MULTAN program, and refined by full-matrix least-squares procedure to an R-factor 0.059, and R_w = 0.071, with weights $w=1/(\sigma^2+.02+1)$. Hydrogen atom positions were found from difference maps and refined.
17. N. Castagnoli, J. Org. Chem., 1969, 34, 3187.
18. M. Cushman and E. J. Madaj, J. Org. Chem., 1987, 52, 907.
19. A. K. Bose, K. Tabei, C. Garai, and P. Mangiaracina, "A Convenient TLC-CIMS Technique for the Location of Unsaturation" presented at the 192nd National Meeting of Amer. Chem. Soc., Anaheim, CA, Sept. 1986, ORGN313.

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