

## SYNTHESIS OF OXIMES IN THE MICROWAVE OVEN

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The synthesis of a broad range of oximes has been studied. It was found that the application of microwave heating enhanced dramatically the reaction rate, and practically quantitative yields of oximes were isolated after less than 1-min heating in the most cases. The effect of solvents on the course of the reaction was also studied.

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Microwave oven become to be very popular in the laboratories of synthetic organic chemists. First papers<sup>1-3</sup> dealt with the base-catalyzed ester hydrolysis, S<sub>N</sub>2 reactions and Diels-Alder reactions, and due to a danger of explosion, reactions have been carried out in a special Teflon containers. A major progress has been made by Loupy<sup>4</sup> and Villemin<sup>5,6</sup> who used inorganic carriers like bentonite, alumina or silica as the "containers" (the reactions in dry media). Some authors devised a special modification of microwave ovens which allows to carry the reaction at reflux temperature of the solvent<sup>7</sup> or continuously<sup>8</sup>. Bose et al.<sup>9</sup> found out that in some cases the synthesis in microwave oven using common solvents can be carried out in open reaction vessels. It was proved<sup>9,10</sup> that the acceleration of the reaction rate is caused by combination of the heat and nonspecific interaction between microwaves and reacting molecules. Nearly all informations about acceleration of different organic and organometallic reactions are presented in recent reviews<sup>11,12</sup>. The main goal of this paper was to find a good and rapid method for the synthesis of ferrocenylketoximes required for the synthesis of ferrocenyl heterocycles<sup>13</sup>. The chosen method was also tested for the synthesis of other oximes.

The standard method for the preparation of ketoximes consists in refluxing the mixture of an appropriate ketone and hydroxylamine hydrochloride in pyridine. On the other hand Villemin<sup>14</sup> has proposed the formation of aldoximes as intermediates in synthesis of nitriles from aldehydes and hydroxylamine hydrochloride on KF/Al<sub>2</sub>O<sub>3</sub> in microwave oven. The preparation of benzophenone oxime was also described in ref.<sup>3</sup>. The results given in Table I present our attempts to compare both above mentioned methods with our procedure, i.e. the synthesis of oximes in microwave oven with pyridine as the solvent. The microwave heating reduced markedly the reaction time (1 min versus 45 min). Because pyridine is not a good medium for absorption of microwave

energy, we decided to use various mixtures of ethanol : pyridine as the solvent (ethanol : pyridine being 100 : 0; 10 : 1; 10 : 2; and 1 : 1). Decomposition of the material took place in ethanol as such, and the best solvent proved to be 1 : 1 (v/v) mixture of ethanol and pyridine. The reaction time was reduced from 1 min to 20 s in this case. Villemín's procedure is as good as ours in the case of ferrocenecarbaldehyde but cannot be applied for the synthesis of ferrocenyl ketoximes (exp. 2 and 3). The results given in Table II

TABLE I  
Synthesis of oximes under different conditions

Conditions	Method <sup>a</sup>	Time / Yield, %		
		Fc-CHO	Fc-COCH <sub>3</sub>	Fc-COCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
Ethanol/pyridine 1 : 1 (v/v)	A	20 s / 97	20 s / 98	6 min / 92
	B	45 min / 95	45 min / 97	3 h / 92
Pyridine	A	1 min / 96	1 min / 95	10 min / 65
	B	45 min / 95	45 min / 95	3 h / 92
KF/Al <sub>2</sub> O <sub>3</sub>	A	20 s / 95	13 min / 50 <sup>b</sup>	18 min / <10 <sup>b</sup>

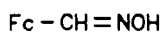
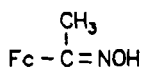
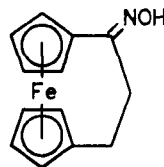
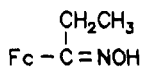
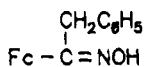
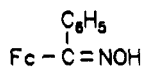
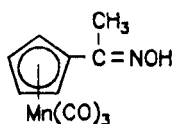
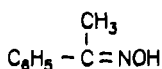
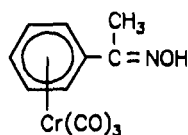
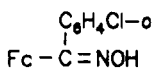
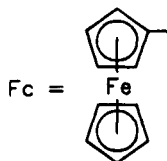
<sup>a</sup> A microwave oven, B classical heating; <sup>b</sup> the material decomposed on prolonged application of microwaves.

TABLE II  
Synthesis of different oximes in microwave oven or by using classical heating in ethanol/pyridine 1 : 1 (v/v)

No.	Product	Time / Yield, % <sup>a</sup>	
		method A	method B
1	I	20 s / 97	45 min / 95
2	II	20 s / 98	45 min / 97
3	III	20 s / 98	45 min / 96
4	IV	2.5 min / 96	2.5 h / 95
5	V	6 min / 92	3 h / 92
6	VI	8 min / 85	5 h / 80
7	VII	40 s / 95	1 h / 96
8	VIII	45 s / 97	1 h / 97
9	IX	75 s / 96	1 h / 95
10	X	10 min / 0 <sup>b</sup>	7 h / 0 <sup>b</sup>

<sup>a</sup> For A and B see Table I. <sup>b</sup> Material was decomposed and only spots of the product were detected by TLC.

prove that our method suits well for a broad range of different ketones, including the more ferrocene ketones, the thermodynamically less stable cymmatrene as well as  $\eta^6$ -benzenetricarbonylchromium derivatives and aromatics like acetophenone. The yields of the oximes *I* – *IX* were nearly quantitative in most cases but with sterically hindered

*I**II**III**IV**V**VI**VII**VIII**IX**X*

ketones the reaction time must be prolonged to 8 min. (The classical heating needs reaction time up to 5 h). The exception to this rule is *o*-chlorobenzoylferrocene which did not give the oxime *X* but the material was decomposed at prolonged heating in microwave oven. The other interesting difference between the classical and microwave synthesis is formation of just one, thermodynamically more stable, oxime isomer. In some experiments when reaction time is longer than 2 min, the solvent evaporates and the reaction should be interrupted and solvent added again. That means that microwave oven was set up 4 times for 2 min, and not for 8 min (exp. 6). This inconvenience can be avoided by using a small adapter – a kind of condenser (Fig. 1) attached to Erlenmeyer flask, with hexane as cooling medium.

The structure of the products *I* – *LX* was proved by elemental analysis (Table III) and by IR and  $^1\text{H}$  NMR spectra (Table IV). The typical sharp absorption peak for free  $\nu(\text{OH})$  around  $3\ 590 - 3\ 600\ \text{cm}^{-1}$  and a broad peak for hydrogen bond  $\nu(\text{OH})$  around  $3\ 250 - 3\ 300\ \text{cm}^{-1}$  were observed. The  $\delta$ -values for  $-\text{OH}$  of oximes were found near 4.2 ppm, and the usual splitting for  $\alpha$ - and  $\beta$ -hydrogen atoms of substituted cyclopentadienyl ring was also found.

#### EXPERIMENTAL

The starting materials, and the solvents used were purified according to standard procedures.  $^1\text{H}$  NMR spectra were measured in  $^2\text{HCl}_3$  solution on the Tesla BS 587 instrument working at 80 MHz. Tetramethylsilane was used as an internal standard. IR spectra were recorded on Specord IR 75 instrument. Microwave oven DAEWOO (500 W) was used in our experiments.

##### General Procedure for Synthesis of Oximes

The carbonyl derivative (0.7 mmol) and 0.77 mmol of hydroxylamine hydrochloride were dissolved in 5 ml of a chosen solvent. The reaction mixture contained in 50 ml Erlenmeyer flask covered with the glass was placed into the microwave oven (500 W). The reaction was carried out at the reflux temperature of the

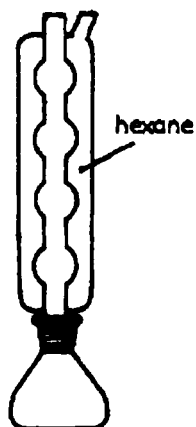


FIG. 1  
The adapter for organic synthesis in microwave oven using organic solvents

solvent and the course of the reaction was monitored by TLC. When the reaction was over, the reaction mixture was cooled down and diluted with water. The product was taken into diethyl ether, the ether solution was washed with water and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The residue left after evaporation of the solvent was chromatographed on  $\text{SiO}_2$  if necessary or crystallised from the mixture benzene-petroleum ether. In the classical experiment, the reaction mixture was heated at the bath temperature 80 – 90 °C for the time given in the tables. The work up of the reaction mixture was the same as described above.

TABLE III  
Characteristics of prepared oximes I – IX

Com- pound	Formula (M. w.)	M. p. °C	Calculated / Found			
			% C	% H	% N	% Fe
I	$\text{C}_{11}\text{H}_{11}\text{FeNO}$ (229.06)	110 – 113	57.67	4.84	6.11	24.38
			58.66	4.87	6.07	24.15
II	$\text{C}_{12}\text{H}_{13}\text{FeNO}$ (243.09)	169 – 172	59.29	5.39	5.76	22.97
			60.00	5.60	5.47	22.94
III	$\text{C}_{13}\text{H}_{13}\text{FeNO}$ (255.10)	170 – 173	61.21	5.19	5.49	21.89
			61.58	5.15	5.44	22.07
IV	$\text{C}_{13}\text{H}_{15}\text{FeNO}$ (257.12)	134 – 137	60.73	5.88	5.45	21.72
			60.99	5.89	5.38	22.13
V	$\text{C}_{18}\text{H}_{17}\text{FeNO}$ (319.19)	143 – 146	67.73	5.36	4.38	17.49
			68.18	5.37	4.35	17.51
VI	$\text{C}_{17}\text{H}_{15}\text{FeNO}$ (305.16)	169 – 171	66.91	4.95	4.58	18.30
			67.58	4.99	4.54	18.41
VII	$\text{C}_{10}\text{H}_8\text{MnNO}_4$ (261.12)	86 – 93	45.99	3.08	5.36	
			46.31	3.10	5.14	
VIII	$\text{C}_8\text{H}_9\text{NO}$ (135.16)	54 – 55	71.08	6.71	10.36	
			71.06	6.72	10.35	
IX	$\text{C}_{11}\text{H}_9\text{CrNO}_4$ (271.19)	132 – 136	48.72	3.84	5.16	
			48.87	3.32	5.08	

TABLE IV  
Spectral properties of prepared oximes I – IX

Compound	$\nu(\text{OH}) / \nu(\text{OH})^a$ free / bonded	$^1\text{H NMR}$ ( $\text{CDCl}_3$ , $\delta$ )
I	3 590 s / 3 250 b	4.20 s, 5 H ( $\text{C}_5\text{H}_5$ ); 4.35 t, 2 H ( $\text{H}\beta$ ); 4.55 t, 2 H ( $\text{H}\alpha$ ); 4.85 bs, 1 H (OH); 8.00 s, 1 H (=CH-)
II	3 595 s / 3 280 b	2.20 s, 3 H ( $\text{CH}_3$ ); 4.15 s, 5 H ( $\text{C}_5\text{H}_5$ ); 4.30 t, 2 H ( $\text{H}\beta$ ); 4.55 t, 2 H ( $\text{H}\alpha$ ); 4.90 bs, 1 H (OH)
III	3 595 s / 3 270 b	2.40 m, 2 H ( $\text{CH}_2$ ); 2.95 m, 2 H ( $\text{CH}_2$ ); 4.35 bs, 2 H ( $\text{H}\alpha$ ); 4.50 bs, 2 H ( $\text{H}'\alpha$ ); 4.05 bs, 2 H ( $\text{H}\beta$ ); 4.20 bs, 2 H ( $\text{H}'\beta$ )
IV	3 600 s / 3 280 b	1.15 t, 3 H ( $\text{CH}_3$ ); 2.40 – 2.80 q, 2 H ( $\text{CH}_2$ ); 4.15 s, 5 H ( $\text{C}_5\text{H}_5$ ); 4.55 t, 2 H ( $\text{H}\alpha$ ); 4.30 t, 2 H ( $\text{H}\beta$ ); 4.85 bs, 1 H (OH)
V	3 595 s / 3 250 b	4.00 bs, 7 H ( $\text{C}_5\text{H}_5 + \text{CH}_2$ ); 4.50 t, 2 H ( $\text{H}\alpha$ ); 4.35 t, 2 H ( $\text{H}\beta$ ); 4.85 bs, 1 H (OH); 7.35 s, 5 H ( $\text{C}_6\text{H}_5$ )
VI	3 590 s / 3 250 b	4.20 s, 5 H ( $\text{C}_5\text{H}_5$ ); 4.45 t, 2 H ( $\text{H}\alpha$ ); 4.35 t, 2 H ( $\text{H}\beta$ ); 4.85 bs, 1 H (OH); 7.50 s, 5 H ( $\text{C}_6\text{H}_5$ )
VII	3 590 s / 3 300 b	2.00 s, 3 H ( $\text{CH}_3$ ); 4.75 t, 2 H ( $\text{H}\beta$ ); 5.15 t, 2 H ( $\text{H}\alpha$ ); 7.45 s, 1 H (OH)
VIII	3 590 s / 3 290 b	1.85 s, 3 H ( $\text{CH}_3$ ); 5.85 – 6.00 m, 3 H ( $\text{C}_6\text{H}_5$ ); 6.05 – 6.20 m, 2 H ( $\text{C}_6\text{H}_5$ ); 7.35 bs, 1 H (OH)
IX	3 600 s / 3 310 b	2.15 s, 3 H ( $\text{CH}_3$ ); 5.40 m, 3 H ( $\text{C}_6\text{H}_5$ ); 5.75 m, 2 H ( $\text{C}_6\text{H}_5$ ); 8.10 bs, 1 H (OH)

<sup>a</sup> In  $\text{CCl}_4$  ( $\text{cm}^{-1}$ ).

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