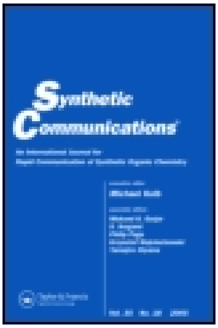

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Microwave Induced 1,3-Depolar Cycloaddition Reactions of Nitrones

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MICROWAVE INDUCED 1,3-DIPOLAR CYCLOADDITION REACTIONS OF NITRONES

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Abstract: 1,3-Dipolar cycloaddition reactions involving unreactive nitrones have been carried out successfully under microwave irradiations. The reaction of nitrones **1** and alkene **2** proceeded regiospecifically at atmospheric pressure and the corresponding isoxazolidines **3** were obtained in high yields.

In the last few years there has been a growing interest in the use of microwave energy in organic synthesis[1] ("MORE Chemistry": Microwave oven induced reaction enhancement). It has been used for a variety of organic reactions such as esterification, etherification, oxidation, hydrolysis, Reformatsky, Knoevenagel and Bischler Napieralski reactions. Many reviews[2] have been published and most publications describe some very important accelerations of reaction rate. Synthesis of derivatives which normally require long reflux periods can be achieved conveniently and more rapidly in a microwave oven[3]. Herein we report the first example of 1,3-dipolar cycloaddition reactions of unreactive nitrones with typical unactivated alkenes both inter and intramolecularly under microwave irradiations. The reaction proceeds efficiently in high yields at ambient pressure within few minutes time and in the absence of solvent.

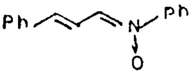
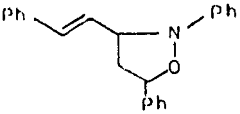
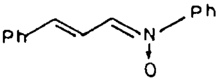
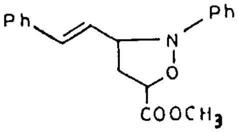
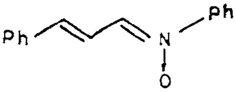
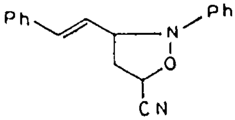
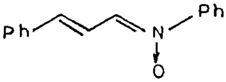
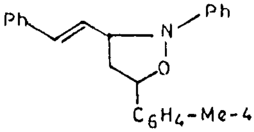
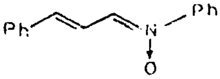
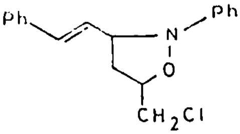
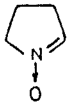
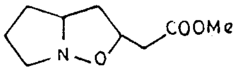
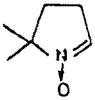
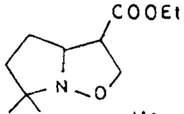
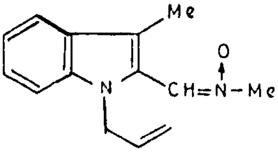
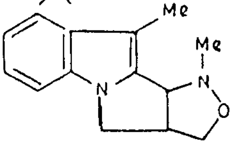
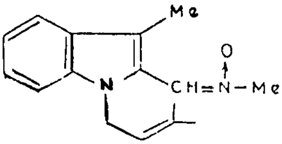
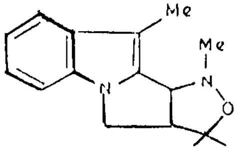
Nitrones and in particular conjugated nitrones[4] are somewhat unreactive dipoles because of considerable charge delocalisation. Recently several cycloadditions of nitrones with various dipolarophiles have been reported[5], but these reactions *require very drastic conditions, high pressure or long reaction times at high* temperature to obtain the corresponding cycloadducts. Therefore we chose to study conjugated nitrones and unactivated alkenes which require long reaction times and drastic thermolytic conditions before they undergo cycloaddition[6a]. The conjugated nitrones were prepared as reported earlier[6] and their thermolytic reactions under refluxing conditions or ultrasound promoted[7] with alkenes were repeated. The same reactions under microwave activations were successfully completed more rapidly (within 6-15 mins) than the thermolytic or sonochemical reactions[7]. All reactions were performed in a commercial microwave oven operating at 2450 MHz frequency. In a typical case, equimolar quantities of α-cinnamyl-N-phenylnitrone (10 mmol) and styrene (10 mmol) were mixed together without solvent in an Erlenmeyer flask and placed in the microwave oven and irradiated for 6 mins. The reaction mixture was allowed to reach room temperature

Table: Comparison of microwave, thermal and ultrasound reactions.

Entry	Product	Microwave		Thermal		Ultrasound	
		Time in min.	Yield[a] %	Time in hr.	Yield %	Time	Yield %
1	3a	6	90	34	80[6a]	1h	81[7]
2	3b	10	80	10	61[6a]	-	-
3	3c	6	80	2-3days (room temp.)	66[6a]	-	-
4	3d	10	78	24	70[6a]	50min.	72[7]
5	3e	12	76	20	65[6a]	-	-
6	4	15	85	15	96[9]	-	-
7	5	30	80	4days	98[10]	-	-
8	6	10	80	3	82[11]	-	-
9	7	12	78	4	80[11]	-	-

[a] Yields refer to the yield of pure isolated products.

R = -CH=CH-Ph , R' = Ph

Entry	Nitrone	Dipolarophiles	Product
1		Styrene	
2		Methyl acrylate	
3		Acrylonitrile	
4		4-Methyl styrene	
5		Allyl chloride	
6		Methyl 3-butenoate	
7		Ethyl acrylate	
8		—	
9		—	

and extracted with benzene. After removal of the solvent the residue is recrystallised from petroleum ether which affords the isoxazolidine **3** (entry 1) mp 115°C (lit[6a] mp 115°C) in 90% yield without the formation of any rearranged amide or oxime-O-ether[8]. Similarly, 4-methylstyrene, methyl acrylate, allyl chloride and acrylonitrile were reacted with α-cinnamyl-N-phenylnitrone and the products (3b-e) were obtained in 76-80% yields. Yields and reaction times for thermal, ultrasound and microwave reacions are recorded in Table. The isoxazolidines **3** were the only isolable products and there was no evidence for the formation of any regioisomer. Similarly, 1-pyrroline-1-oxide and 5,5-dimethyl 1-pyrroline-1-oxide were reacted and methyl 3-butenoate and ethyl acrylate respectively. The corresponding 2-carbomethoxy methyl hexahydro pyrrole [1,2-b] isoxazole[9] (entry 6) and ethyl hexahydro-6,6-dimethyl pyrrolo [1,2-b] isoxazole-3-carboxylate[10] (entry 7) were obtained in 85% and 80% yields respectively, without the formation of any other rearranged or isomeric products. To include an example of intramolecular 1,3-dipolar cycloaddition reactions, we carried out the reaction of 2-formyl-3-methyl-N-allylindole and 3-methyl-1-(3'-methylbut-2'-enyl)indole with methylhydroxylamine under microwave irradiations which underwent insitu intramolecular 1,3-dipolar cycloaddition to give the corresponding 1,10-dimethyl-1,3a,4,10b-tetrahydro-3H-isoxazolo[3',4':3,4]pyrrolo[1,2-a]indole (entry 8) and 1,3,3,10-tetramethyl-1,3a,4,10b-tetrahydro-3H-isoxazolo[3',4':3,4]pyrrolo[1,2-a] indole (entry 8&9) respectively, exclusively in 80% yields. All the compounds obtained were confirmed by infrared and ^{1}H NMR spectroscopy and finally by comparison (mp, TLC) with authentic samples[12].

In conclusion, it is noteworthy to mention that this simple and easily reproducible technique in solid state, affords various isoxazolidines in just one-pot in shorter reaction time and with higher yields than the classical or sonochemical reactions in solvents. Moreover, the reaction takes place at ambient pressure and in absence of solvent thereby reducing the risk of hazardous explosion when the reaction was conducted in closed vasel.

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12. In order to determine the reaction rate improvements the thermal reaction were also carried out without microwave energy in the solid state. The reaction proceeds similarly but the completion time is more (3-4 hrs) and the yields are also not satisfactory. Further increasing the reaction time had no significant improvement of yields rather decomposition of products occurred.

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