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Microwave Assisted Nitrile Oxide Cycloaddition

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The application of microwaves in promoting the cycloaddition reactions of maleimides with nitrile oxide using a microwave oven and focused monomode microwave reactor have demonstrated increased reaction rates, yield enhancement and small amount of solvent used over conventional methods of heating.

Key Words: Nitrile oxide, 1,3-Dipolar cycloaddition, Maleimide, Microwave assisted.

INTRODUCTION

Nitrile oxide cycloaddition to olefins is an important transformation[1-6]. The reaction is attractive because it generates two contiguous stereocenters in a single step[7]. Diastereoselective nitrile oxide cycloadditions have been investigated extensively and successful methods are available in literature[8]. Ta-Jung-Lu *et al.*[9] have reported recently 1,3-dipolar cycloaddition of nitrile oxide with 1,3-dioxolanes of α-β unsaturated aldehydes and have successfully enhanced the reactivity of reaction by employing ultrasound irridation[10]. The application of microwaves in promoting organic reactions has received intense attention. Microwave irradiation provides an alternative to conventional heating as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat energy. The use of microwave radiation introduced several new concepts in chemistry, since the absorption and transmission of energy is completely different from conventional mode of heating[11]. Microwave technology provides an excellent rapid method for generating small molecules and 1,3-dipolar cycloadditions in particular are one of the most efficient methods for building structurally diverse 5-membered heterocycles. These are very often core structures of pharmaceutical agents or they represent useful synthetic intermediates towards their synthesis[12-22].

Microwave energy offers numerous benefits for performing synthesis including increased reaction rates, yield enhancements and cleaner chemistries. The time saved by using microwave technology is potentially important in traditional organic synthesis but could be of even greater

importance in high speed combinatorial and medicinal chemistry as well as industrial scale production of chemicals. Inspired by the immense potential of rate acceleration of organic reactions by microwave, we hope to be able to improve reactivity of the cycloaddition by applying microwave technology. Herein, we wish to report a highly efficient microwave promoted 1,3-dipolar cycloaddition reaction of nitrile oxide to maleimides.

EXPERIMENTAL

All the infrared spectra of the synthesized compounds have been recorded on FT-IR Perkin-Elmer spectrophotometer RX-I at Department of Chemistry, Punjabi University, Patiala. The proton magnetic resonance spectra have been run on a Bruker AC-400 NMR spectrometer 400 MHz using TMS as an internal standard and $CDCl_3$ + DMSO as a solvent by SAIF, Punjab University, Chandigarh. Mass spectra were recorded on mass spectrometer VG-70S by NIPER, Mohali. The elemental analyses have been carried out at the Micro analytical Laboratory by SAIF, Punjab University Chandigarh. All melting pointes have been recorded by Gallen-Kamp apparatus and are uncorrected.

General procedure for the synthesis of 3-(4-chlorophenyl)-5-(4-tolyl)-3a,4,6,6a-tetrahydro-4H,6H-pyrrolo[3,4-d]isoxazoline-4,6-dione: This Huisgen reaction was carried out under both conventional and microwave accelerated conditions following a similar procedure in each case. A typical procedure is described under both conditions.

Scheme-I: The mixture of 4-chlorobenzaldoxime (1.55 g, 0.01 mol), N-4-tolymaleimide (1.87 g, 0.01 mol) and chloramine-T (2.49 g, 0.01 mol) in ethanol (15 mL) was placed in 100 mL conical flask. Microwave irradiation (900 W with a frequency of 2450 MHz) was applied for 1 min for this particular reaction and for other derivatives time required for microwave irradiation is given in Table-1. Sodium chloride in the reaction was filtered off and washed with ethanol. The filtrate and washings were concentrated under reduced pressure and the residue was extracted with CH_2Cl_2. The extract was washed first with distilled water and then with 1N aqueous NaOH and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the viscous residue was crystallized from solvent ether. It was recrystallized from solvent ether to give cream coloured amorphous product (73 % yields) m.p. 190 ºC. Then similar method was applied for the synthesis of other derivatives (**3a-3p**).

Scheme-II: The mixture of 4-chlorobenzaldoxime (1.55 g, 0.01 mol), N-4-tolymaleimide (1.87 g, 0.01 mol) and chloramine-T (2.49 g, 0.01 mol) in ethanol (50 mL) was placed in 100 mL round bottom flask. The reaction mixture was refluxed on water bath. The time of reflux for this particular reaction was 3 h. The time of reflux for other derivatives is given in Table-

1. After cooling the reaction mixture, the excess of solvent was evaporated off under vacuum and with usual workup as done in **Scheme-I**. The cycloadduct was recrystallized from solvent ether to give cream coloured compounds (**3a-3p**).

3a: m.p. 180 ºC; IR (KBr): 1769, 1722 ν(>C=O), 1597 ν(>C=N-), 1516, 1496 ν(>C-C<), 1396, 1357, 1355 ν(-NO) cm^{-1}, ^1H NMR (400 MHz) ($CDCl_3$ + DMSO); δ 8.06 (m 4H, aromatic), δ 7.36 (m 5H, aromatic), δ 5.68 (d 1H, H_{6a}, $J_{H6a-H3a}$ = 9.6 Hz), δ 4.90 (d 1H, H_{3a}, $J_{H3a-H6a}$ = 10.2 Hz); Analysis (%), Found: C, 62.48; H, 3.36; N, 8.57; $C_{17}H_{11}N_2O_3Cl$ calcd.: C, 62.47; H, 3.40; N, 8.62.

3e: m.p. 195 ºC; IR (KBr): 1772, 1722 ν(>C=O), 1631 ν(>C=N), 1599, 1496 ν(>C=C<), 1392, 1320 ν(-NO), 1059 ν(C-I), 825, 780, 760 cm^{-1} (1, 4-disubstituted & monosubstituted); ^1H NMR (400 MHz) ($CDCl_3$ + DMSO); δ 7.15, (m 5H, aromatic), δ 7.64 (m 2H, aromatic), δ 6.83, (m 2H, aromatic), δ 5.55, (d 1H, H_{6a}, $J_{H6a-H3a}$ = 6.0 Hz), δ 4.90, (d 1H, H_{3a}, $J_{H3a-H6a}$ = 6.0 Hz); Analysis (%), Found: C, 51.38; H, 2.77; N, 7.05; $C_{17}H_{11}N_2O_3I$ calcd.: C, 51.41; H, 2.79; N, 7.09.

RESULTS AND DISCUSSION

A number of nitrile oxides have been generated *in situ via* dehydrohalogenation of aldoximes using chloramine-T and their 1,3-dipolar cycloaddition reaction with various N-arylmaleimides have been carried out (**Scheme-I**). The cycloaddition occurs by dehydrochlorination of aldoxime to hydroximic acid chloride followed by base catalyzed elimination of hydrochloric acid first to yield the nitrile oxide. This is trapped by dipolarophile as soon as formed to yield the product through a *cis*-addition. To establish the general validity of newly developed method, several selected one-pot microwave syntheses were carried out.

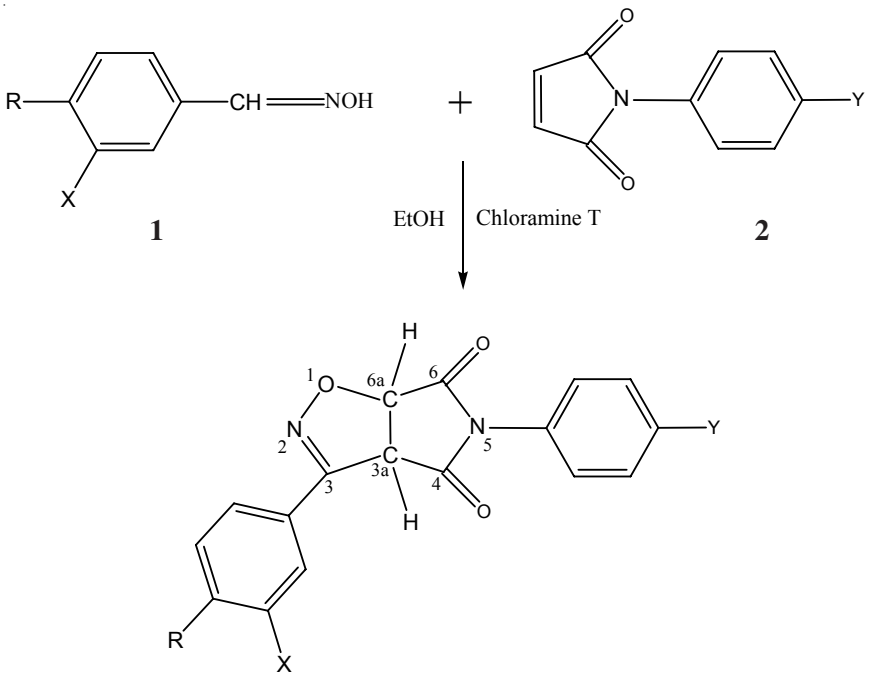
This method appeared to be rapid and economical with a wide range of applications. The reaction was found to proceed smoothly under microwave irradiation with 60-90 s whereas under reflux conditions, 3-6 h was required (Table-1). The products were isolated by simple cold aqueous work-up followed by solvent extraction and finally purified by recrystallization. The IR spectra of these substituted pyrrolo [3, 4-d] isoxazolo-4, 6-diones show two absorption bands in the region 1780-1700 cm^{-1} which have been assigned to carbonyl stretching vibrations of isoxazolo ring. The band in the region 1640-1610 cm^{-1} has been assigned to >C=N- stretching vibrations of isoxazolo ring. The strong to medium intensity bands at 1575-1560 and 1520-1480 cm^{-1} have been assigned to aromatic skeletal stretching vibrations. The band at 1390-1360 cm^{-1} has been assigned to >N-O- stretching vibrations. In the lower region the bands at 840-790 cm^{-1}

TABLE-1
COMPARISON BETWEEN MICROWAVE-ASSISTED AND CONVENTIONAL METHOD OF SYNTHESIS OF ISOXAZOLINES IN TERMS OF TIME, YIELD, AND AMOUNT OF SOLVENT USED

Compd.	X	R	Y	Microwave			Conventional		
				Time (s)	Yield (%)	Amt. of solvent (mL)	Time (s)	Yield (%)	Amt. of solvent (mL)
3a	H	Cl	H	60	73	15	3	69	100
3b	H	Cl	CH_3	60	73	15	3	70	100
3c	H	Cl	OC_2H_5	60	77	15	3	75	100
3d	H	H	CH_3	60	73	15	3	70	100
3e	H	H	I	60	77	15	3	75	100
3f	H	H	NO_2	60	65	15	3	61	100
3g	H	NO_2	OCH_3	60	77	15	3	75	100
3h	H	NO_2	I	60	76	15	3	73	100
3i	H	NO_2	OC_2H_5	60	78	15	3	75	100
3j	H	OCH_3	H	60	78	15	3	76	100
3k	H	OCH_3	I	60	73	15	3	70	100
3l	H	OCH_3	NO_2	60	75	15	3	70	100
3m	OCH_3	OCH_3	CH_3	60	80	15	3	78	100
3n	OCH_3	OCH_3	OC_2H_5	60	84	15	3	83	100
3o	OCH_3	OCH_3	Cl	60	87	15	3	85	100
3p	OCH_3	OCH_3	H	60	82	15	3	79	100

have been assigned to >C-H deformations of 1, 3, 4-trisubstituted and 1,4-disubstituted aromatic rings. The bands at 780-720 cm^{-1} have been assigned to >C-H deformations of 1,3-disubstituted and mono-substituted aromatic rings. The PMR spectra of these substituted pyrrolo [3,4-d] isoxazolo-4,6-diones show a multiplet at δ 8.95-6.67 that has been assigned to the aromatic protons of the rings. A doublet at δ 5.86-5.67 (equivalent to one proton) has been assigned to H_{6a} coupled to H_{3a}. A doublet at δ 5.01-4.85 (equivalent to one proton) has assigned to H_{3a} coupled to H_{6a} having same coupling constant values. The chemical shift of H_{6a} is expected to downfield as compared to H_{3a} because C_{6a} is attached to an electron-withdrawing carbonyl group on one side and electronegative oxygen atom on other side, whereas C_{3a} is attached to a carbonyl group on one side and only a carbon atom on the other side. Both the doublets have similar coupling constants ($J_{H6a-H3a} = J_{H3a-H6a} = 9.0$ Hz) which indicate the formation of *cis*-pyrrolo [3,4-d] isoxazolo-4,6-dione ring *via cis* addition of activated carbon-carbon double bond of N-arylmaleimide on the substituted aromatic nitrile oxide. In the *cis*-transition state there is a maximum accumulation of double

bonds of the dipole as well as that of dipolarophile. At the transition state C-aryl ring of the dipole and a carbonyl group of the imide ring come parallel to each other in addition to the π-electron overlap of the reaction atoms of the dipole and the dipolarophile and there are no non-bonded steric interactions in this transition state.



R= H, Cl, NO_2, OCH_3; X= H, OCH_3; Y= H, Cl, CH_3, OCH_3, OC_2H_5, I, NO_2

Conclusion

The cycloaddition reaction of N-phenyl maleimides with nitrile oxide furnished the desired isoxazolines in higher yield than the conventional method and the reaction time was considerably shortened. Another advantage of microwave technique is as it requires very small amount of solvent. The solvent free reaction is also possible but products formed with poor yields.

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