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MICROWAVE ENHANCED SYNTHESIS OF EPOXYPROPOXYPHENOLS

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ABSTRACT: Phenols were condensed with epichlorohydrin under microwave irradiation. Dramatic reduction in reaction time was observed with excellent yields.

Aryloxypropanolamines belong to an important class of compounds. Number of compounds from this class have been clinically used as β-blocking agents[1-3]. In synthesis of these compounds epoxypropoxyphenols **3** are important intermediates. The preparation of **3** has been achieved by condensation of epichlorohydrin with phenols in presence of quaternary ammonium salt[4], piperidine[5], etc. The most common method is carrying condensation in aqueous sodium hydroxide solution[6-8].

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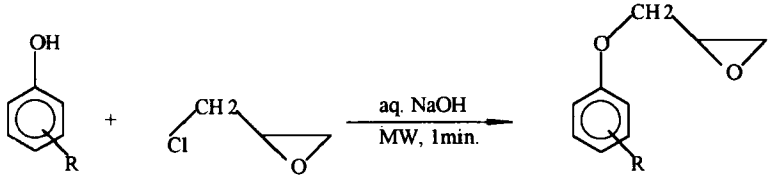
For last few years, microwave heating has been attracted attention of synthetic chemists mainly due to the great reduction of time in microwave assisted reactions. There are several reviews[9,10] available indicating the utility of microwaves in organic synthesis. Microwave heating has been found useful in synthesis of some clinically used drugs like 4-aryl-1,4-dihydropyridines[11,12], pyrimido[1, 6-a] benzimidazole[13]. Microwave oven has been modified[14] and new reaction media has been reported pointing towards possibility of commercialisation of microwave asisted reactions[15].

Williamson ether synthesis has been reported to take place faster in microwave oven[16]. Recently the synthesis of aromatic ethers without solvent and inorganic carrier has been reported under microwave irradiation[17].

We report here the condensation of phenol and epichlorohydrin under microwave irradiation. We found that epichlorohydrin can be condensed with phenols in aqueous sodium hydroxide very rapidly in microwave oven affording **3**.



1 2 3

Yields varied between 65 to 88 % depending upon the nature of the phenol. Even with phenols having electron withdrawing group the reaction was taking place rapidly though with a little reduction in yield. When epichlorohydrin was taken in equilimolar quantity the major product was 1,3-bisphenoxy-2-propanol rather than the epoxypropoxyphenol. With double amount of

Table -1: Glycidyl ether formation under Microwave Irradiation .

Entry	Substrate R	Microwave Heating Time(minutes)	yield (%)	mp*/bp °C (lit)
1	H	1	88	239-4 (112/8)[18]
2	2-Cl	1	88	278-8 (127/4)[19]
3	2-CH_3	1	83	262-3 (136/20)[20]
4	4-CH_3	1	80	271-3 (119/7)[18]
5	2-NO_2	1	64	79*
6	4-NO_2	1	65	74*(73)[21]
7	4-$COCH_3$	1	63	>325-6 (159/3)[22]
8	1-Naphthol	1	69	>335-6 (148/2)[18]

* Melting points of the products.

epichlorohydrin the reaction proceeded smoothly to selectively give the desired product The optimised results are given in table -1.

Thus in conclusion this method is very simple, rapid and safe giving excellent yields of epoxypropoxyphenols when carried out in microwave oven. The reaction carried out side under reflux takes about six hour to complete for unsubstituted phenol. Thus the reaction in microwave is at least 360 times faster than that carried out side.

Experimental Section :

The structure of product were confirmed by using FT-IR and PMR

spectroscopy. FTIR and PMR were recorded using a Jasco-300E FTIR spectrophotometer and Varien EM 360 spectrophotometer (500 Mhz) respectively. All PMR were recorded in $CDCl_3$ using TMS as internal standard (chemical shifts in δ ppm.). The microwave oven used for the reaction was a Kelvinator T-37 magicook model with a power out put of 700 watts.

General procedure :

To the solution of 2-chlorophenol (20 mmol) and aqueous sodium hydroxide (25 mmol in 2 cm^3 of water) epichlorohydrin (40 mmol) was added. The reaction was irradiated in microwave oven for one min. The mixture was cooled and poured in to ice water. The organic layer was separated. The aqueous layer was extracted with methylene chloride. Organic layers were combined and washed with 10 % sodium hydroxide followed by water and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* The product was purifyed by distillation under reduced pressure.

2.76-2.94 (2H , m , ) ; 3.39-3.57 (1H , m , ) ; 3.76-4.17 (2H , m , Ar-O-CH_2) ; 6.90-7.37 (4H , m , Ar-H).

1,2-epoxy (2-methylphenoxy) propane : 2.28-2.30 (3H , s , Ar-CH_3) ; 2.78-2.93 (2H , m , ) ; 3.37-3.40 (1H , m , ) ; 3.75-4.31 (2H , m , Ar-O-CH_2) ; 6.76-7.26 (4H , m , ArH).

1,2 epoxy (4-acetylphenoxy) propane : 2.52-2.56 (3H , s , $COCH_3$) ; 2.75-2.91 (2H , m , ) ; 3.35-3.36 (1H , m , ) ; 3.96-4.31 (2H , m , Ar-O-CH_2) ; 6.90-7.91 (4H , dd , ArH).

1,2 epoxy (4-methylphenoxy) propane : 2.30-2.40 (3H , s , CH_3) ; 2.75-2.98 (2H , m ,) ; 3.40-3.45 (1H , m ,) ; 3.94-4.29 (2H , m , Ar-O-CH_2) ; 6.76-7.39 (4H , dd , ArH).

1,2 epoxy (-napthoxy) propane : 2.80-2.99 (2H , m ,) ; 3.36-3.45 (1H , m ,) ; 4.00-4.43 (2H , m , Ar-O-CH_2) ; 6.86-8.79 (7H , m , ArH).

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