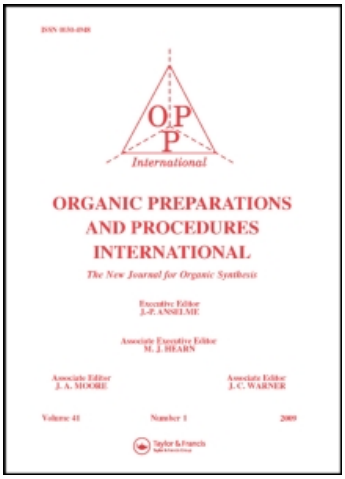

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MICROWAVE-PROMOTED SYNTHESIS OF 1-ARYLOXY-3-ALKYLAMINO-2-PROPANOLS

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OPPI BRIEFS

MICROWAVE-PROMOTED SYNTHESIS OF 1-ARYLOXY-3-ALKYLAMINO-2-PROPANOLS

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(12/09/96)

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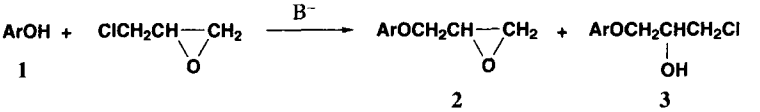
1-Aryloxy-3-alkylamino-2-propanols of the general formula **4** are biologicaly active compounds. The widely used β-adrenolytic drugs (aryloxypropanolamines, β-blockers), such as *propranolol* (Ar = 1-naphthyl), *timolol* (Ar = 4-morpholino-1,2,5-thiadiazol-3-yl), *pindolol* (Ar = 4-indolyl), and *moprolol* (Ar = 2-methoxyphenyl), may be cited here as well known representatives of that group. The simplest and most commonly used method for their preparation consists in a two-step procedure. First, a phenol (**1**) is *O*-alkylated with epichlorohydrin to yield a mixture of the appropriate arylglycidyl ether (**2**) and 1-aryloxy-3-chloropropan-2-ol (**3**). Epichlorohydrin is used in excess and the reaction is carried out in the presence of a base (usually aqueous sodium hydroxide or pyridine in an organic solvent). Depending on the substituent in the phenol, it takes 6-20 hours at reflux or 24-26 hours at room temperature to complete the reaction:[1]



In the second step, the mixture of **2** and **3** is made to react with the appropriate amine (isopropyl- or *tert*-butylamine). Notwithstanding different reaction mechanisms, both **2** and **3** are converted in this step into the same product **4**. This step also requires prolonged heating or at least 24 hours of standing at room temperature.[1]

According to the literature data,[2] some C-alkylations can be accelerated by heating with

microwave. This technique not only reduces the reaction time but also makes it possible to carry out the reaction without any solvent. For example, in a recently published paper,[3] Chinese authors report on a microwave-promoted alkylation of phenol with some particularly reactive alkylating agents, such as benzyl chloride and bromide as well as chloro- and bromoacetophenones.

Microwave heating was now been found to be effective in both steps of the synthesis of aryloxypropanolamines (**4**). Thus, when the reaction between the phenol and epichlorohydrin was carried out on a solid support (powdered mixture of potassium carbonate and sodium hydroxide, the latter being used in an equimolar amount in relation to the phenol reagent) with a small amount of tetrabutylammonium bromide added as the phase transfer catalyst and with microwave (60 W) heating, the time required was roughly one hundred times shorter than in the conventional procedure. Moreover, ^{1}H NMR, IR, and GC analysis revealed that the reaction product was nearly pure glycidyl ether **2** and not a mixture of **2** and **3**. The yields of the arylglycidyl ethers (**2**) prepared and the reaction conditions are presented in Table 1.

The temperature of the sample was measured in each experiment immediately upon termination of the microwave exposure. Reference reactions were then carried out at this temperature on a solid support with conventional heating which was continued until the yield of the products reached at least 80%. These experiments confirmed a substantial effect of microwaves since without irradiation the corresponding reactions required heating for 6-12 hours at 106-112°. As it may be seen from the presented results, microwave irradiation has a significant influence on the efficiency of the glycidyl ethers synthesis. The method can be used to advantage in preparative chemistry.

TABLE 1. Reaction Conditions and Yields of Arylglycidyl Ethers (**2**)

Ar	Time (min)	Temp. (°C)	Yield (%)	^{1}H NMR (δ ppm)	bp. (°C/mmHg)	lit. bp. (°C/mmHg)
3-$CH_3C_6H_4$	5	112	95	2.34(s,3H);2.82(m,2H); 3.34(m,1H);3.92 and 4.22(dd, 2H);6.9(m,4H)	112-115/0.1	107-115/0.1[5]
2-CNC_6H_4	17	106	67	2.83(m,2H);3.41(m,1H); 4.12 and 4.43(dd,2H); 7.33(m,4H)	124-127/0.1	
4-Cl-3-$CH_3C_6H_3$	5	110	81	2.82(m,2H);3.43(m,1H); 4.12(m,2H);7.05(m,3H)	119-123/0.1	120-130/1[5]
1-Naphthyl	2	116	96	2.91 (m,2H);3.4(m,1H); 4.22(m,2H);6.83(m,1H); 7.54(m,4H);7.8(m,1H); 8.32(m,1H)	148-152/0.1	145-149/0.5[7]

Microwaves were also found to promote the second step of the synthesis of 1-aryloxy- 3-alkylamino-2-propanols (**4**). A 30-90-minute irradiation of the mixtures of the glycidyl ether (**2**) and an appropriate amine supported on silica gel gave the aminoalcohols (**4**) in 65-90% yields. The rate of

1-naphthoxyglycidyl ether aminolysis with isopropylamine under microwave irradiation conditions also compared favorably with that observed in experiments with conventional heating at the same temperatures, although the improvement factor was here only five, *i. e.*, much less than in the phenol alkylation step. It is worth noting that the reaction between phenylglycidyl ether and aniline under microwave irradiation conditions was investigated by French authors[4] who did not observe any influence of the irradiation on the reaction rate. The reaction conditions applied in our experiments (power of the microwave oven and irradiation times) as well as the yields of the prepared 1-aryloxy-3-alkylamino-2-propanols are shown in Table 2. The results presented in Tables 1 and 2 indicate microwave heating leads to the rapid formation of aryloxypropanolamines.

TABLE 2. Reaction Conditions and Yields of 1-Aryloxy-3-alkylamino-2-propanols (**4**)

Ar	R	Microwave Oven Power (watt), and Time	Yield (%)	Hydrochloride mp. (°C)	lit. mp. (°C)
3-$CH_3C_6H_4$	*i*-Pr	30w. for 40 min., then 60w. for 10 min.	85	118-120	119-121[5]
4-Cl-3-$CH_3C_6H_3$	*i*-Pr	30w. for 30 min.	79	142-144	142-143[5]
1-Naphthyl	*i*-Pr	30w. for 30 min.	67	158-161	161-162[5]
1-Naphthyl	*t*-Bu	30w. for 25 min.	89	176-179	178-180[6]

EXPERIMENTAL SECTION

The microwave-promoted reactions were carried out in a focused microwave digester (monomode system) Prolabo Maxidigest MW 350 equipped with a mechanical stirrer placed in the reaction tube. IR spectra were recorded on a Specord M-80 Carl Zeiss spectrometer, and ^1H NMR spectra, on a Varian Gemini 200MHz instrument in a $CDCl_3$ solution with TMS as internal standard. Gas chromatography was performed on a Chrompack CP 9002 gas chromatograph.

Typical Procedures. Aryloxyglycidyl Ethers (2).- To a powdered mixture of 11 g of anhydrous potassium carbonate, 0.8 g of sodium hydroxide, and 0.6 g of tetrabutylammonium bromide (TBAB), 0.02 mole of the appropriate phenol was added and mixed thoroughly with 2.76 g (0.03 mole) of epichlorohydrin. The solid mixture was placed in the reactor tube and irradiated with mechanical stirring as indicated in Table 1. Upon cooling, the mixture was dissolved in water (100 mL) and extracted with ethyl ether (3 x 70 mL), the etheral extract was washed with water until neutral and dried over anhydrous magnesium sulfate. The aryloxyglycidyl ethers left upon evaporation of the solvent were purified by distillation under reduced pressure.Their purity was checked by GC and their structure was confirmed by IR and ^1H NMR spectra.

1-Aryloxy-3-alkylamino-2-propanols (4).- A mixture of 10 mmoles of the aryloxyglycidyl ether and 16 mmoles of the appropriate alkylamine was mixed with 3 g of silica gel (Merck, Kieselgel 60 for column chromatography, < 230 mesh) and placed in a microwave oven. The reaction mixture was stirred during the reaction carried under conditions specified in Table 2. Upon cooling to room temperature, the mixture was extracted with ethyl ether (3 x 50 mL), dried over magnesium sulfate,

and evaporated to dryness. The crude products were dissolved in ethyl acetate and precipitated as their hydrochlorides by addition of conc. hydrochloric acid.

REFERENCES

1. H. S. Bevinakatti and A. A. Banereji, *J. Org. Chem.*, **56,** 5372 (1991) and references cited therein.

2. Y. Wang and Y. Jiang, *Synth.Commun.*, **22**, 2287 (1992); D. Abenhaim, E. Diez-Barra, A. de la Hoz, A. Loupy and A. Sanchez-Migallon, *Heterocycles,* **31**, 793 (1994); E. Diez-Barra, A. de la Hoz, A. Loupy and A. Sanchez-Migallon, *J. Heterocyclic Chem.,* **31**,1715 (1994); R. Deng, Y. Wang and Y. Jiang, *Synth. Commun.*, **24**, 111(1994); *ibid.*, **24**, 1917 (1994); D. Barbry, C. Pasquier and C. Faven, *ibid.*, **25**, 3007 (1995).

3. J.-X. Wang, M. Zhang, Z. Xing and Y. Hu, *ibid.*, **26**, 301 (1996).

4. H. Jullien, A. Petit and C. Merienne, *Polymer,* **37**, 3319 (1996).

5. H. Schulz, *Pharmazie,* **23**, 240 (1968).

6. *Ger. Pat.* 1,236,523; *Chem. Abstr.*, **67**, 64046 (1967).

7. J. Pitha, J. Milecki, T. Czajkowska and J. W. Kusiak, *J. Med. Chem.*, **26,** 7 (1983).

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FACILE SYNTHESES OF *p*-(DICYANOMETHYLENE)BENZOQUINONES

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The redox properties of quinones possessing electron-withdrawing substituents have elicited interest in these compounds as electron transport materials in organic photo-conductors.[1] A number of *bis*(dicyanomethylene) compounds (e.g., 7,7,8,8-tetracyano-quinodimethane) have been synthesized from 1,4-cyclohexanediones by the Knoevenagel reaction with malononitrile, followed by oxidation of the resulting product.[2] In contrast, the condensation of 1,4-benzoquinones with malononitrile proceeds *via* a Michael addition at the α-position; subsequent oxidation gives 3-dicyanomethyl-1,4-benzoquinone.[3] When 1,4-benzoquinones sterically hindered at 2,6-position such as **1b**, are condensed with malononitrile and piperidine as catalyst, the product **2b** reacts with the anion of malononitrile at the 7-position; subsequent elimination of HCN affords predominantly 4-tricyanovinylphenol.[4] The