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Improvement and simplification of synthesis of 3-aryloxy-1,2-epoxypropanes using solvent-free conditions and microwave irradiations. Relation with medium effects and reaction mechanism

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Abstract—Some 3-aryloxy-1,2-epoxypropanes, interesting as potential synthons in β-adrenergic receptor antagonists preparation, were obtained in excellent yields (65–96% within 2–17 min) by microwave activation (monomode system) using solid–liquid solvent-free phase transfer catalysis (PTC). The best results for the O-alkylation of some phenols with epichlorohydrin were obtained using TBAB and $NaOH/K_2CO_3$ (1:4 mol/mol) as phase transfer catalyst and more acceptable basic system, respectively. These new procedure is compared with classical methods. Significant specific microwave effect (non-purely thermal) was evidenced in all cases. They were discussed in terms of reaction medium and mechanism, taking into account the variations in polarity of the systems.

1. Introduction

During last 10 years our interest in an efficient and economical technology for the preparation of some organic synthons has promoted the research in the field of microwave irradiation.[1–3] The use of such non-conventional reaction conditions reveals several features like: a short reaction time compared to conventional heating, ease of work-up after a reaction, and reduction in the usual thermal degradation and better selectivity.[4–5] In recent years some important reviews, concerning study of microwave assisted organic reactions, have been published.[6–7]

Generally, interpretation of microwave enhancements in organic synthesis is now well-demonstrated and fully acknowledged.[8] Their interpretation lies in a consideration of the concept of dielectric polarization[9] and, more precisely, *dipolar polarization*, which is at the origin of microwave heating due to the alignment of polar molecules along an electromagnetic field. As microwaves consist in an alternating electric field of high frequency (ν=2450 MHz, λ=12.2 cm), inversion in the dipole orientation at each alternance results in the stirring and friction of molecules, inducing energy dissipation into internal homogenous heating. Among other physical phenomena concerned in dielectric polarization, *ionic polarization* can be involved. It results in the separation of positive and negative charges induced by the electromagnetic field. Therefore, this phenomenon can also be considered in the acceleration of organic synthesis under microwave irradiation after the generation of more reactive species by ionic dissociation.

In this work, we want to check this second hypothesis as a possible cause, like dipolar polarization effects, of microwave enhancement. For this purpose we assume that the acceleration observed previously[10] in the case of O-alkylation reactions of some phenols with epichlorohydrin, could also have consequences for the reaction selectivity. In previous paper we reported preliminary results for O-alkylation of some selected phenols **1c**,**f**,**g**,**j** with epichlorohydrin by microwave irradiation under solid–liquid solvent-free phase transfer catalysis.[10] The aim of this work was to reproduce some of these reactions in classical conditions (aqueous solution of NaOH) and in solvent-free conditions under microwave irradiation (MW) or classical heating (Δ). These conditions were extended to another case of phenols such as: **1a**–**b**,**d**–**e**,**h**–**i** (Scheme 1). It is important to note that the alkylation of phenols to give aromatic ethers is well known (Williamson reaction). However, in classical conditions the reaction time is very long. The phase transfer catalysis technique[11,12] under classical heating[13] or microwave irradiation[14] has been successfully applied to the Williamson ether synthesis. Concerning 3-aryloxy-1,2-epoxypropanes

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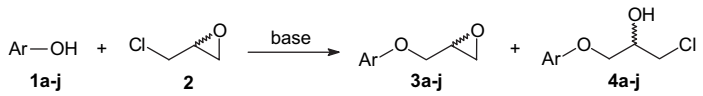


Scheme 1. **Ar**=**a**: C_6H_5–, **b**: 2-CH_3–C_6H_4–, **c**: 3-CH_3–C_6H_4–, **d**: 4-CH_3–C_6H_4–, **e**: 4-Cl–C_6H_4–, **f**: 3-CH_3–4-Cl–C_6H_3–, **g**: 1-naphthyl-, **h**: 2-CH_3O–C_6H_4–, **i**: 2,6-Cl–C_6H_3–, **j**: 2-CN–C_6H_4.

3, the simplest and more popular method for their preparation consist in one-step O-alkylation of the suitably substituted phenol **1** with epichlorohydrin **2** in the presence of base (Stephenson procedure).[15] Generally, in all procedures described, the epichlorohydrin is used in a significant excess and the reaction is carried out in an aqueous solution of a base (NaOH, KOH, K_2CO_3, etc.) or in an organic solvent containing pyridine or piperidine.[16,17] Concerning chemical industry and high scale, only last methods were used.[16i,j] Depending on the substituent position or nature in the phenol **1**, it takes 6–20 h at reflux or 24–26 h at room temperature to complete the reaction. It is important to note that, these classical methods can suffer from some inconvenience due to moderate isolated yields (50–70%), moderate purity of products and poor reaction selectivity (1-chloro-3-aryloxypropan-2-ols **4** were formed in an important amount as non-suitable by-product[15,16a]). Some from these inconvenience may be limited by addition of the phase transfer catalyst (e.g. benzyltriethylammonium chloride) to the aqueous solution of base (K_2CO_3, etc.).[16a,h,k,n,17a,i,r] However, as described by Bevinakatti and Banerji,[16h] the acceptable reaction rates, selectivities and isolated yields of product **3** were obtained, in PTC procedures, only by using very high concentrations of the base.

We have sought to develop a general method of the O-alkylation of phenols **1a–j** with epichlorohydrin **2**. Such a procedure should retain the convenience of PTC methods but should be free from some limitations related to PTC systems and much faster. Therefore, we decided to explore the use of microwave heating under solvent-free phase transfer catalysis (PTC) conditions.

2. Results and discussion

The conditions for O-alkylation of various phenols **1a–j** with epichlorohydrin **2** were optimized according to the conventional scheme described in the literature (Scheme 1). In the first time, one selected classical procedure was tested, in term of conversion, selectivity and isolated yield. In second time, the same reactions were performed in non-classical conditions by using solid–liquid PTC catalysis under microwave irradiation or classical heating. Concerning all method tested, the effects of nature and position of the substituent on the phenyl ring were evaluated on conversion, selectivity and isolated yield of suitable product **3**.

2.1. Classical conditions

Generally, it is always difficult to anticipate the best choice of classical method for the preparation, in high scale, of 3-aryloxy-1,2-epoxypropanes **3**. On the other hand, for these compounds, the correlations between nature or position of substituent on the aromatic ring and conversion, selectivity or reaction yield were newer evaluated. In a first series of experiments, the efficiency of known classical procedure described by Biniecki,[17g] for O-alkylation of various phenols with epichlorohydrin, was investigated. For this purpose, various phenols **1a–i** were treated, at reflux, with 1.26 equiv of epichlorohydrin in an aqueous sodium hydroxide (Scheme 1).

The reactions were performed in high scale (0.19 mol of phenol and 0.24 mol of epichlorohydrin) and monitored by GC. The 3-aryloxy-1,2-epoxypropanes **3** were separated by silica gel column chromatography from the corresponding 1-chloro-3-aryloxypropan-2-ols **4**, which were formed as by-products. The main results are given in Table 1.

The results presented in Table 1 clearly show that the conditions described by Biniecki were sligthly acceptable, concerning selectivity and isolated yield of suitable product **3**. It is important to note that, for all phenols tested **1a–i**, the arylglycidyl ethers **3** were formed as major product with moderate yields (yield of **3**=58–76%). On the other hand, the quantities of non-suitable by-product **4**, determined in the reaction mixture by GC analysis, were important (10–32%, yield of **4**=5–23%). Generally, we observe a notable effect of the phenyl-ring substituent in terms of reaction time (94–99% conversion within 5–12 h). Concerning selectivity, the values of ratio **3**:**4** depend only slightly on the nature and position of the phenyl-ring substituent. In fact, the values of ratio **3**:**4** were only slightly different when the electronic effects of the substituent changed (e.g.: 76:24 for 4-CH_3–C_6H_4–, 70:30 for 2-CH_3O–C_6H_4–, 68:32 for 4-Cl–C_6H_4–). Concerning 1-naphthol **1g**, the value of ratio **3**:**4** was notably higher (ratio **3**:**4**=90:10) than in all other cases. Finally, we note that when the reaction conversion

Table 1. Reaction of epichlorohydrin **2** with several phenols **1a–i** by using aqueous solution of NaOH at reflux[a]

Phenol **1**	Ar	Time (h)	Conv. (%)[b,c]	Ratio **3**:**4**[d]	Yield of **3** (%)[e]	Yield of **4** (%)[e]
a	C_6H_5–	5	98	80:20	69	14
		10	99	85:15	75	7
b	2-CH_3–C_6H_4–	7	97	68:32	58	18
		14	99	75:25	66	13
c	3-CH_3–C_6H_4–	11	98	70:30	63	19
		19	99	78:22	77	16
d	4-CH_3–C_6H_4–	6	98	76:24	70	16
e	4-Cl–C_6H_4–	7	97	68:32	61	22
f	4-Cl–3-CH_3–C_6H_3–	12	96	82:18	65	11
g	1-Naphthyl	6	94	90:10	69	5
h	2-CH_3O–C_6H_4–	7	98	70:30	68	23
i	2,6-Di-Cl–C_6H_3–	8	>99	81:19	76	10

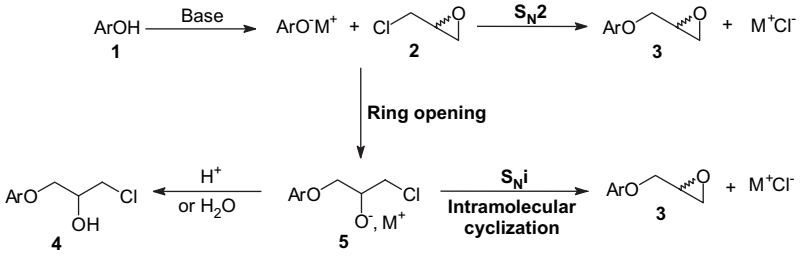
[a] Conditions: **1a–i** (0.19 mol), epichlorohydrin **2** (0.24 mol) in 100 mL of aqueous solution of NaOH (0.24 mol) under reflux.
[b] Determined by GC and ^{1}H NMR.
[c] Complement to 100% conversion is an unreacted substrate phenol.
[d] Determined by GC and ^{1}H NMR.
[e] Yields calculated after purification and separation by chromatography on silica gel 60.

was 97–98%, the further prolongation of the reaction time produce only slight increase in the yield of product **3** and as a consequence the yield of non-suitable by-product **4** decreased. For example, in the case of phenol **1a**, the isolated yield of **3a** increase from 69 to 75% when the reaction time was prolonged from 5 to 10 h, but in this case the yield of corresponding chloroalcohol **4** was decreased from 14 to 7%. This last observations can justify our thesis that in the reaction mixture exists permanent competition of two different mechanisms (Scheme 2) *mechanism 1*=the direct nucleophilic substitution (S_N2) of phenate ion (ArO^-) on epichlorohydrin **2** with destruction of C–Cl bond and *mechanism 2*=the ring opening of epichlorohydrin **2** with ArO^- followed by intramolecular cyclization (S_Ni) of corresponding alcoholate **5** formed in situ.

2.2. Non-classical conditions

In second series of experiments, the O-alkylations were performed by mixing selected phenol **1**, the solid base, the solid phase transfer catalyst [tetrabutylammonium bromide (TBAB)], and the liquid alkylating agent epichlorohydrin **2**, without any organic solvent in the relative amounts indicated in the Tables 2 and 3. All reactions were performed under atmospheric pressure by using microwave irradiation (MW, power=60 W) or classical heating in a thermostated oil bath (Δ). The microwave irradiations were carried out using a monomode Synthewave 402 Prolabo reactor[18] fitted with an infrared detector to measure the temperature throughout the reaction. The interest of a monomode reactor lies in its focalization of the electromagnetic waves using an accurately proportioned waveguide, which allows a homogeneous distribution of the field. It can be used with a low emitted power and therefore produces a high energetic yield. The use of such an apparatus was shown to lead to considerable improvements in organic synthesis at very low emitted powers and with a good temperature homogeneity. In order to check for the possible intervention of specific (not purely thermal) effects of microwaves (such as those that might be due to a different temperature increase profile, better temperature homogeneity, or modifications of the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$), reactions were performed with the two activation methods, microwave irradiation (MW) and classical heating (Δ), keeping the reaction time, final temperature and pressure the same. In control experiments performed by using microwave irradiation and classical heating, it was shown that the reaction did not proceed in the absence of phase transfer catalyst (TBAB) and base within the reaction time indicated in the Tables 2 and 3, concerning all bases and phenols tested. The temperature of sample was measured in each experiment immediately upon termination of the microwave exposure. Reference reactions were then carried out at this temperature with conventional heating. In all cases of reactions performed by using microwave irradiation, the ^{1}H NMR, IR and GC analyses revealed that the reaction product was pure 3-aryloxy-1,2-epoxypropane **3** and not mixture of **3** and **4**. The main results are given in Tables 2 and 3.

2.2.1. Effect of the base. The effect of the base nature on the selectivity, conversion and reaction yield of some O-alkylation reactions is well documented in the literature. Therefore, in a first series of experiments, the influence of the base nature on the selectivity, conversion and reaction yield



Scheme 2.

Table 2. Reaction of epichlorohydrin **2** with phenol **1f** by using different solid bases under focused microwave irradiation (MW) or classical heating (Δ)[a]

Entry	Base	Relative amounts **1f/2**/TBAB/(base)	Activation mode[b]	Temp (°C)[c]	Time (min)	Conv. (%)[d,e]	Ratio **3f**:**4f**[d]	Yield of **3f** (%)[f]	Yield of **4f** (%)[f]
1	NaOH	1/1.5/0.1/(1)	MW	105	5	65	100:0	51	—
			Δ	105	5	20	65:35	9	6
2	K_2CO_3	1/1.5/0.1/(4)	MW	108	5	20	100:0	16	—
			Δ	108	5	9	75:25	5	2
3	$NaOH/K_2CO_3$	1/1.5/0.1/(1:4)	MW	110	5	99	100:0	81	—
			Δ	110	5	56	85:15	36	8
4	$NaOH/Al_2O_{3basic}$	1/1.5/0.1/(1:4)	MW	112	7	28	100:0	21	—
			Δ	112	7	8	95:5	5	—
5	$NaOH/Ca(OH)_2$	1/1.5/0.1/(1:4)	MW	114	15	70	97:3	64	—
			Δ	114	15	23	69:31	10	5

[a] Conditions: **1f** (20 mmol), epichlorohydrin **2** (30 mmol), TBAB (2 mmol), solid base as presented in the table, under atmospheric pressure, without solvent under microwave irradiation (power=60 W) or classical heating in a thermostated oil bath.
[b] Incident emitted power all along the reaction.
[c] Temperature at the end of the microwave irradiation (MW) or classical heating (Δ).
[d] Determined by GC and ^{1}H NMR.
[e] Complement to 100% conversion is an unreacted substrate phenol.
[f] Yields calculated after purification and separation by chromatography on silica gel 60.

Table 3. Reaction of epichlorohydrin **2** with several phenols **1a–i** by using of solid–liquid solvent-free phase transfer catalysis under microwave irradiation (MW) or classical heating (Δ)[a]

Entry	Phenol **1**	Ar	Activation mode[b]	Temp[c] (°C)	Time (min)	Conv. (%)[b,c]	Ratio **3**:**4**[d]	Yield of **3** (%)[e]	Yield of **4** (%)[e]
1	**a**	C_6H_5–	MW	113	6	99	100:0	90	—
			Δ	113	6	48	76:24	31	10
2	**b**	2-CH_3–C_6H_4–	MW	110	7	96	95:5	89	2
			Δ	110	7	38	83:17	26	6
3	**c**	3-CH_3–C_6H_4–	MW	112	5	99	100:0	95	—
			Δ	112	5	50	66:34	29	15
4	**d**	4-CH_3–C_6H_4–	MW	110	7	98	95:5	87	4
			Δ	110	7	41	88:12	30	5
5	**e**	4-Cl–C_6H_4–	MW	113	11	95	99:1	68	—
			Δ	113	11	40	69:31	20	9
6	**f**	4-Cl–3-CH_3–C_6H_3–	MW	110	5	99	100:0	81	—
			Δ	110	5	56	85:15	36	8
7	**g**	1-Naphthyl-	MW	116	2	99	99:1	96	—
			Δ	116	2	55	76:24	38	12
8	**h**	2-CH_3O–C_6H_4–	MW	111	5	98	99:1	87	—
			Δ	111	5	36	66:34	19	10
9	**i**	2,6-Di-Cl–C_6H_3–	MW	110	12	96	100:0	65	—
			Δ	110	12	57	73:27	28	10
10	**j**	2-CN–C_6H_4–	MW	106	17	98	100:0	67	—
			Δ	106	17	33	80:20	20	5

[a] Conditions: **1a–i** (0.19 mol), epichlorohydrin **2** (0.24 mol) in 100 mL of aqueous solution of NaOH (0.24 mol) under reflux and atmospheric pressure.
[b] Determined by GC and ^{1}H NMR.
[c] Complement to 100% conversion is an unreacted substrate phenol.
[d] Determined by GC and ^{1}H NMR.
[e] Yields calculated after purification and separation by chromatography on silica gel 60.

of TBAB catalyzed O-alkylation of phenol **1f**, taken as model substrate, with epichlorohydrin was investigated. The reactions were carried out by employing dry powdered bases or basic systems such as: NaOH, K_2CO_3, NaOH/K_2CO_3 (1:4 mol/mol), NaOH/Al_2O_{3basic} (1:4 mol/mol), NaOH/$Ca(OH)_2$ (1:4 mol/mol). Concerning all reactions performed under microwave irradiation, it is important to note, that the power=60 W was sufficient to maintain the temperature at a limited imposed value 105–114 °C. The main results and the reaction conditions are presented in Table 2.

It can be clearly seen from Table 2, that it is possible to run the O-alkylation of phenol **1f** with epichlorohydrin **2** by microwave activation or classical heating using solid–liquid solvent-free phase transfer catalysis (PTC). Generally, for all bases the tested results of these reaction were significantly better in the case of microwave irradiation when compared to classical heating, concerning conversion, selectivity and the yield of isolated product **3f**. It also indicates the presence of a specific microwave effect (non-purely thermal) on the O-alkylation of phenol **1f** with epichlorohydrin **2**, conforming thus some conclusions already described in the literature for other types of reactions. In fact, for all the bases tested conversions of phenol **1f** as well as the isolated yields of suitable product **3f** were significantly higher under microwave irradiation when compared to classical heating, concerning the same conditions like: time, temperature and pressure. It is important to note that, all reactions performed by using microwave irradiation were totally selective and the suitable arylglycidyl ether **3f** was obtained as an unique product of the reaction (ratio **3f**:**4f**=100:0). As expected, the reaction performed by using NaOH/$Ca(OH)_2$ as basic system is not totally selective. In this case the traces of by-product **4f** were observed in the reaction mixture by GC analysis (ratio **3f**:**4f**=97:3). On the other hand, in the case of the reactions performed by using classical heating, the by-product **4f** was formed in an important amount (35, 25, 15, 5 and 31% for NaOH, K_2CO_3, NaOH/K_2CO_3, NaOH/Al_2O_{3basic} and NaOH/$Ca(OH)_2$, respectively).

Finally, we showed that the best conditions for O-alkylation of phenol **1f** with epichlorohydrin **2** were obtained by using the mixture NaOH/K_2CO_3 (1:4 mol/mol) as basic system, concerning microwave irradiation and classical heating. However, using of microwave irradiation result in both significantly higher conversion and isolated yield of product **3f** (conv. of **1a**=99% and yield of **3f**=81%) when compared to classical heating (conv. of **1a**=56% and yield of **3f**=36%), concerning the same conditions like: time (5 min), temperature (110 °C) and pressure. On the other hand, changing the base from pure NaOH (1 mol) or pure K_2CO_3 (4 mol) to the mixture of both bases cited NaOH/K_2CO_3 (1:4 mol/mol) produce high increase in the reaction rate (conversion increased from 65 and 20 to 99%, respectively) and isolated yield of **3f** (yield of **3f** increased from 51% and 16%–81%, respectively). Finally, changing the base from K_2CO_3 to Al_2O_{3basic} or to $Ca(OH)_2$ in the mixture with NaOH induces important decrease in the reaction rate and consequently in the isolated yield of product **3f**. In fact, we observe 70% of conversion within 15 min when the mixture of NaOH/$Ca(OH)_2$ was used under microwave irradiation at 114 °C. On the other hand, the use of NaOH in the mixture with basic Al_2O_3 at 112 °C under microwave irradiation results in only 28% of conversion within 7 min. Evidently, in both cases cited the results obtained under microwave irradiation were significantly better when compared to classical heating (8 and 23% conversion within 7 and 15 min, respectively).

2.2.2. Effects of nature and position of the substituent on the phenyl ring. Finally, in order to investigate the influence of the nature and position of the substituent on the phenyl ring various phenols **1a–j** were used as substrates

in O-alkylation with epichlorohydrin **2**. All reactions were carried out in the best conditions previously selected for phenol **1f**. In fact, tetrabutylammonium bromide (TBAB) and the mixture $NaOH/K_2CO_3$ (1:4 mol/mol) were used as phase transfer catalyst and basic system, respectively, concerning microwave irradiation (MW) and classical heating (Δ). The results are collected in Table 3.

The comparative analysis of the results presented in Table 3 clearly showed that, all reactions performed under microwave irradiation were totally (ratio **3**:**4**=100:0 and 99:1 for **1a**, **1c**, **1f**, **1i–j** and for **1e**, **1g–h**) or highly selective (ratio **3**:**4**=95:5 for **1b** and **1d**). On the other hand, we observe that the nature of the substituent on the phenyl ring produces an important effect on the conversion and isolated yield of product **3**. In fact, the excellent yields of product **3** were obtained (yield of **3**=87–95% within 96–99% conversion), when the substituent of phenol was an electron-releasing group (2-CH_3–, 3-CH_3–, 4-CH_3–, 2-CH_3O–). However, the yields of suitable product **3** were significantly lower when the substituent of the phenol was an electron withdrawing group such as: 4-Cl–, 2,6-di-Cl– or 2-CN– (yield of **3**=65–68% within 95–99% conversion). It is important to note that for all phenols **1a–j** tested the results of O-alkylation reaction with epichlorohydrin **2** were significantly better under microwave irradiation when compared to classical heating, concerning the same conditions like: time, temperature and pressure. Finally, the results summarized in Table 3 and Figures 1 and 2 indicates the presence of a specific microwave effect (non-purely thermal). Figure 1 shows the course of the conversion of selected phenols, **1a** and **1e**, under microwave irradiation (MW) and classical heating (Δ), with time. The reactions of **1a** and **1e** under MW irradiation lead to a nearly 100% conversion within 6 and 11 min, respectively, with a final temperature of 113 °C. Heating in an oil bath gave only 48 and 40% conversion, respectively, under similar conditions of temperature, reaction time and pressure. The temperature–time profiles for the reactions of **1a** and **1e** under MW irradiation and in an oil bath are shown in Figure 2. It is important to note that, under classical heating (Δ) the conversion of **1a** can be enhanced up to 63% by increasing the reaction time to 13 min (Fig. 1).

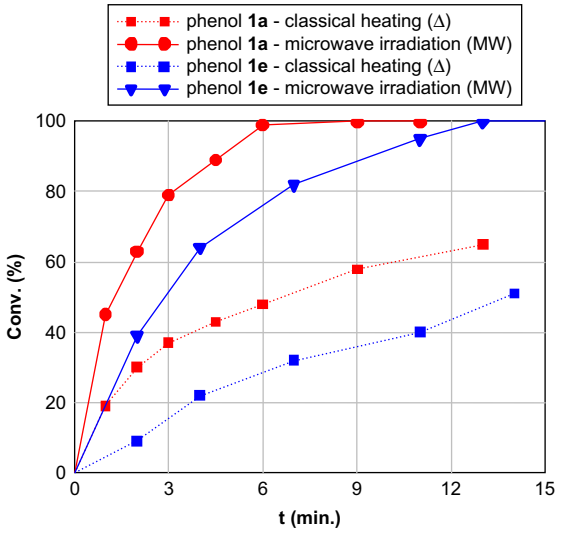


Figure 1. Conversion versus time for the reaction of epichlorohydrin **2** with phenol **1a** and **1e** by using of solid–liquid solvent-free phase transfer catalysis under microwave irradiation (MW) or classical heating in an oil bath (Δ).

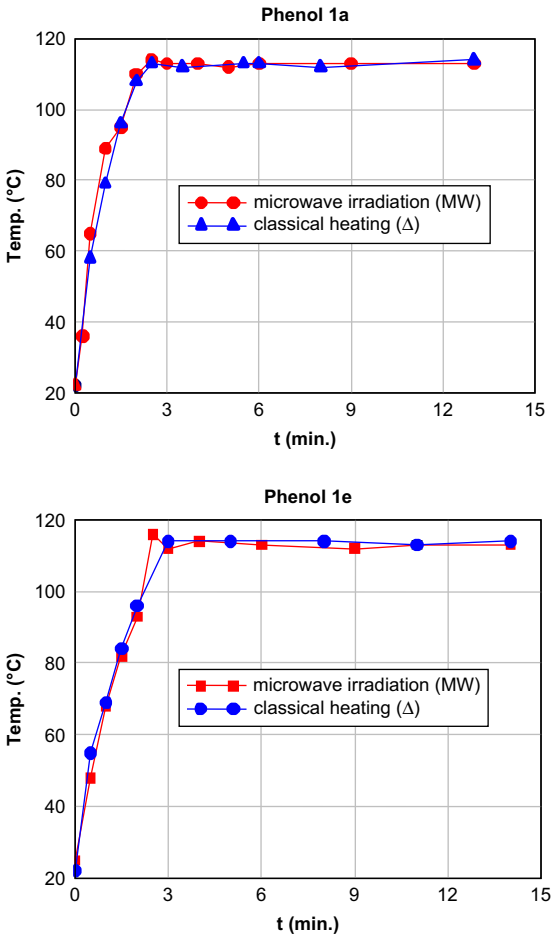


Figure 2. Thermal behaviour of the reaction mixture for phenols **1a** and **1e** under microwave irradiation (MW) and in an oil bath (Δ).

3. Effects according to reaction mechanism

Generally, microwave effects[19] result from material-wave interactions and, due to the dipolar polarization phenomenon, the greater the polarity of a molecule (such as the solvent) the more pronounced the microwave effect when the rise in temperature is considered. In terms of reactivity and kinetics, the specific effect has therefore to be considered according to the reaction mechanism and particularly with regard to how the polarity of the system is altered during the progress of the reaction. Specific microwave effects can be expected for the polar mechanism, when the polarity is increased during the reaction from the ground state (**GS**) towards the transition state (**TS**). The outcome is essentially dependent on the medium and the reaction mechanism. If stabilization of the transition state (**TS**) is more effective than that of the ground state (**GS**), this results in an enhancement of reactivity by a decrease in the activation energy ($\Delta G^{\neq}$) (Fig. 3). It is important to note that this decrease in the activation energy provoke direct increase in the rate constant (k) according to the Eyring equation:[19a]

$$k = A\exp(-\Delta G^{\neq}/RT).$$

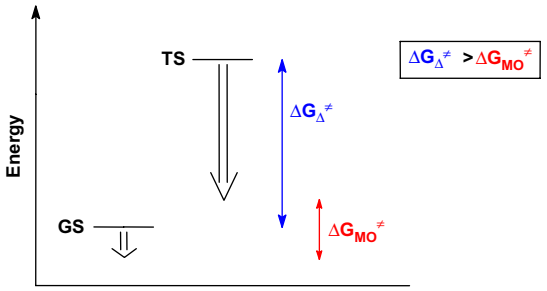
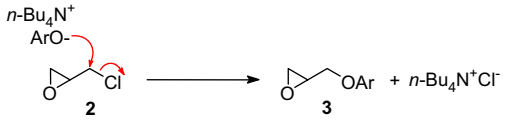


Figure 3. Relative stabilization of a more polar **TS** when compared to the **GS** (polar mechanism).

It is important to note that the reaction between any substituted phenol **1** and epichlorohydrin **2** may be considered as an *anionic bimolecular reaction involving neutral electrophile, which is epichlorohydrin* **2**. Generally, this case of reaction involve the reactivity of anionic species Nu^- associated as ion pairs having several possible structures with counterions M^+. The main results presented in Table 3 clearly show that the reaction between the phenate ion (ArO^-) and epichlorohydrin **2** reveals two competitive mechanisms (Schemes 3 and 4):

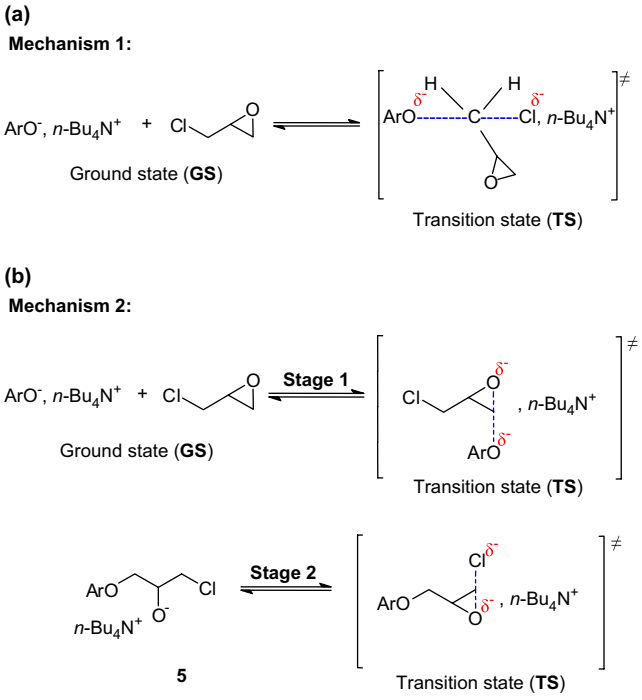


Scheme 3.

Mechanism 1. One-step nucleophilic substitution (mechanism S_N2) with cleavage of C–Cl bond (Scheme 3).

Mechanism 2. Ring opening of epichlorohydrin **2** with ArO^- (mechanism S_Ni) followed by intramolecular cyclization (S_Ni) of corresponding alcoholate **5**, containing one atom of chlorine in β-position, formed in situ (Scheme 4).

In both cases of mechanism (Schemes 3 and 4), the ground-states (**GS**) were identical and composed, on the first hand, of an ion pair between anionic species as ArO^-, formed in situ, and counterions $n\text{-}Bu_4N^+$ coming from the phase transfer catalyst, and on the other hand, from epichlorohydrin **2**. The transition states (**TS**) were composed, in both cases of mechanism, of loose ion pairs in so far as they involve a charge delocalized anion possessing one atom of chlorine, thereby conferring an enhancement in polarity with respect to the ground state (in which the ion pairs are tighter) due to an increase in anionic dissociation as the more bulky product anion formed. As a consequence, specific microwave effects, directly connected to polarity enhancement were observed (Scheme 5a and b). It is important to note that in the case of O-alkylation reaction performed in two stages (under mechanism 2) the conversion and selectivity should be increased under microwave irradiation thanks to acceleration of both stages and we suppose that this acceleration is probably more important for second stage due to more marked localization of negative charge on the oxygen atom in the alcoholate **5**, which is the intermediate of this reaction.



Scheme 5.

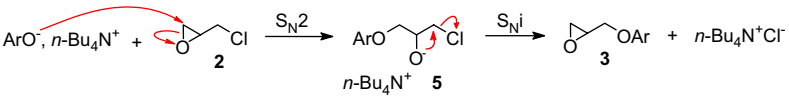
4. Conclusion

In this paper we present a general procedure to realize selective O-alkylation of diversely substituted phenols **1a–j**. High reaction selectivities and high isolated yields of corresponding 3-aryloxy-1,2-epoxypropanes **3a–j** were obtained using solvent-free phase transfer catalysis (PTC) coupled with microwave irradiation (MW). We have shown that the best conditions for O-alkylation were obtained using the mixture $NaOH/K_2CO_3$ (1:4 mol/mol) as basic system and tetrabutylammonium bromide (TBAB) as phase transfer catalyst. It is important to note that the results obtained under microwave irradiation were much better than those derived from classical methods described in the literature, concerning selectivity, conversion and yield of suitable product. Generally, our procedure is very mild, inexpensive and very easy to operate and can replace advantageously the classical ones.

5. Experimental

5.1. General methods

All the commercially available chemicals were obtained from Aldrich and Fluka. Solvents of analytical-grade quality were purchased from Lab Scan Ltd. and Aldrich.



Scheme 4.

5.2. Analytical methods

Microanalyses were performed by the Laboratoire Central de Microanalyse du CNRS, Gif sur Yvette, France. ^{1}H (200 or 250 MHz) and ^{13}C (50.23 or 62.9 MHz) NMR spectra were recorded on Bruker AC-200 or 250 spectrometer in $CDCl_3$ with TMS as an internal standard. Chemical shifts (δ) are given in parts per million. Gas chromatographic analyses were run on a 6000 Vega Series instrument equipped with a FID detector and Spectra-Physics SP 4290 integrator and an OV_1 column (12 m). The detector and the injector temperatures were set at 300 °C and 290 °C, respectively. Column temperature was programmed in the range 70–280 °C (10 °C min^{-1}) for **3a** and **4a**, and 100–280 °C (10 °C min^{-1}) for **3b–j**, and **4b–j**. The retention times (t_R/min) were as follows for 3-aryloxy-1,2-epoxypropanes: **3a**: 5.18; **3b**: 4.29; **3c**: 4.32; **3d**: 4.51; **3e**: 5.47; **3f**: 5.63; **3g**: 9.21; **3h**: 5.32; **3i**: 6.37; **3j**: 6.01 and were as follows for corresponding 1-chloro-3-aryloxypropan-2-ols: **4a**: 7.15; **4b**: 5.93; **4c**: 5.66; **4d**: 6.51; **4e**: 7.35; **4f**: 7.18; **4g**: 11.36; **4h**: 6.94; **4i**: 8.23; **4j**: 8.33. Column chromatography was performed on Merck silica gel 60 (230–400 mesh). TLC was carried out using glass sheets pre-coated with silica gel 60 F_{254} prepared by Merck. The reaction under microwave irradiations was performed in a monomode microwave reactor (Synthewave 402 from Prolabo), fitted with a stirring system and an IR temperature detector, which indicates the surface temperature.

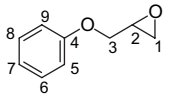
5.3. Typical O-alkylation procedure of phenols 1a–i with epichlorohydrin under classical conditions (aqueous solution of NaOH)

To a stirred solution of 9.6 g of sodium hydroxide (0.24 mol) in 100 mL of water, 0.19 mol of the phenol **1** (0.19 mol) was added. The solution was stirred for 15 min at room temperature and the alkylating agent, epichlorohydrin (0.24 mol, 22.2 g) was added. The final solution was stirred under reflux and monitored by thin layer chromatography (TLC). After the appropriate time (Table 1), the stirring was stopped and the reaction solution was extracted with diethyl ether (3×50 mL). The collected solutions were dried over anhydrous $MgSO_4$ and evaporated to dryness under reduced pressure. The crude mixture of two products, 3-aryloxy-1,2-epoxy-propane **3** and by-product 1-chloro-3-aryloxypropan-2-ol **4**, was separated by flash chromatography on silica gel with *n*-hexane/ethyl acetate (10:1 and 15:1 v/v, for phenol **1a–d**,**1g–h** and **1e–f**,**1i**, respectively) as the eluent.

5.4. Typical O-alkylation procedure for phenols 1a–j with epichlorohydrin using solvent-free phase transfer catalysis conditions (PTC) under microwave irradiation and classical heating

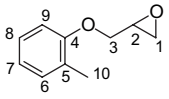
Into a Pyrex tube (2 cm diameter) were introduced 20 mmol of phenol **1**, 0.8 g (20 mmol) of powdered sodium hydroxide, 11.6 g (80 mmol) of anhydrous potassium carbonate and 0.6 g (2 mmol) of tetrabutylammonium bromide (TBAB). After stirring at room temperature during 2 min, 2.76 g (30 mmol) of epichlorohydrin was added. The reaction mixture was either introduced into the monomode microwave reactor (Synthewave 402 from Prolabo, power= 60 W) or in a thermostated oil bath for the times indicated in Tables 2 and 3. It is important to note that all reactions performed under microwave reactor or in an oil bath were agitated by using mechanical stirring. After cooling to room temperature, 100 mL of water was added to the reaction mixture to remove mineral salts and the obtained solution was extracted with diethyl ether (3×50 mL). The collected ethereal extract was washed with water and dried over anhydrous $MgSO_4$. Finally, the organic solution was evaporated to dryness under reduced pressure. The products, suitable 3-aryloxy-1,2-epoxypropane **3** and/or by-product 1-chloro-3-aryloxypropan-2-ol **4**, were purified by flash chromatography on silica gel with *n*-hexane/ethyl acetate (10:1 and 15:1 v/v, for phenol **1a–d**,**1g–h** and **1e–f**,**1i–j**, respectively) as the eluent. The purity of products was checked by GC analysis and their structure was confirmed by ^{1}H, ^{13}C NMR and MS spectra, IR data as well as micro-analyses. ^{1}H and ^{13}C NMR spectra of 3-aryloxy-1,2-epoxypropanes **3a–j** were identical with those presented in the literature. ^{1}H, ^{13}C NMR and MS spectra, IR data as well as micro-analyses of **3a–j** are as follows.

5.4.1. 3a: 1,2-Epoxy-3-phenoxypropane.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.74–2.81 (1H, dd, J_{gem}=4.89 Hz, J_{1-2}=2.70 Hz, H1), 2.80–2.91 (1H, m, H1′), 3.35–3.46 (1H, m, H2), 3.80–4.10 (1H, dd, J_{gem}=11.0 Hz, J_{3-2}=5.40 Hz, H3), 4.18–4.32 (1H, dd, J_{gem}=10.99 Hz, $J_{3'-2}$=2.99 Hz, H3′), 6.70–7.09 (3H, m, H5, H7, H9), 7.13–7.42 (2H, m, H6, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 44.36 (*C*H$_2$, Cl), 68.50 (*C*H$_2$, C3), 114.52 (C_{arom}, C5, C9), 120.99 (C_{arom}, C7), 130.41 (C_{arom}, C6, C8), 156.73 (C_{arom}, C4). IR (neat, cm^{-1}): 1245 cm^{-1}: C–O–C; Anal. Calcd for $C_9H_{10}O_2$ (150.17): C, 71.98; H, 6.71. Found: C, 71.91; H, 6.61. MS (electr. impact, 70 eV, *m*/*z*): $(M)^{+\bullet}$=150 (53), $(M-CH_2O)^+$=120 (13.6), $(M-C_2H_3O)^+$=107 (13), $(M-C_3H_4O)^+$=94 (64), $(M-C_3H_5O_2)^+$=77 (41.8), $(M-C_4H_5O_2)^+$=65 (31), $(M-C_6H_7O_2)^+$=39 (100). Colourless oil, bp=244–246 °C, $bp_{Lit.}$=245 °C.[20a]

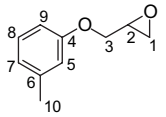
5.4.2. 3b: 1,2-Epoxy-3-(2-methylphenoxy)propane.



^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.26 (3H, s, H10), 2.72–2.84 (1H, dd, J_{gem}=4.96 Hz, J_{1-2}=2.61 Hz, H1), 2.85–2.95 (1H, m, H1′), 3.30–3.41 (1H, m, H2), 3.88–4.05 (1H, dd, J_{gem}=11.07 Hz, J_{3-2}=5.44 Hz, H3), 4.15–4.30 (1H, dd, J_{gem}=11.09 Hz, $J_{3'-2}$=3.04 Hz, H3′), 6.70–6.92 (2H, m, H7, H9), 7.05–7.20 (2H, m, H6, H8); ^{13}C NMR (50.23 MHz, $CDCl_3$, ppm): δ 16.13 (*C*H$_3$, Cl0), 44.56 (*C*H$_2$, Cl), 50.25 (*C*H, C2), 68.55 (*C*H$_2$, C3), 111.13 (C_{arom}, C9), 120.82 (C_{arom}, C7), 126.69 (C_{arom}, C8), 126.93 (C_{arom}, C5), 130.71 (C_{arom}, C6), 156.53 (C_{arom}, C4). IR (neat, cm^{-1}): 1240 cm^{-1}: C–O–C; Anal. Calcd for $C_{10}H_{12}O_2$

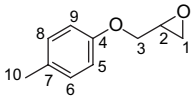
(164.20): C, 73.15; H, 7.36. Found: C, 73.02; H, 7.28. Colourless oil, bp=109–110 °C/0.2 mmHg.

5.4.3. 3c: 1,2-Epoxy-3-(3-methylphenoxy)propane.



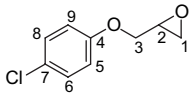
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.34 (3H, s, H10), 2.71–2.81 (1H, dd, J_{gem}=4.95 Hz, J_{1-2}=2.62 Hz, H1), 2.84–2.93 (1H, m, H1′), 3.31–3.43 (1H, m, H2), 3.83–4.01 (1H, dd, J_{gem}=11.10 Hz, J_{3-2}=5.36 Hz, H3), 4.13–4.28 (1H, dd, J_{gem}=11.13 Hz, $J_{3'-2}$=3.10 Hz, H3′), 6.76–7.92 (3H, m, H5, H7, H9), 7.18 (1H, m, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 21.63 (CH_3, Cl0), 44.61 (CH_2, Cl), 50.09 (*C*H, C2), 68.83 (CH_2, C3), 112.00 (C_{arom}, C9), 114.99 (C_{arom}, C5), 122.12 (C_{arom}, C7), 129.43 (C_{arom}, C8), 139.82 (C_{arom}, C6), 157.99 (C_{arom}, C4). IR (neat, cm^{-1}): 1244 cm^{-1}: $\overset{O}{C'-C}$; Anal. Calcd for $C_{10}H_{12}O_2$ (164.20): C, 73.15; H, 7.36. Found: C, 73.09; H, 7.24. Colourless oil, bp=112–113 °C/0.1 mmHg, $bp_{Lit.}$=112–115 °C/0.1 mmHg.[10]

5.4.4. 3d: 1,2-Epoxy-3-(4-methylphenoxy)propane.



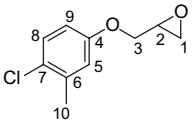
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.28 (3H, s, H10), 2.70–2.81 (1H, dd, J_{gem}=4.92 Hz, J_{1-2}=2.60 Hz, H1), 2.86–2.95 (1H, m, H1′), 3.28–3.40 (1H, m, H2), 3.85–4.02 (1H, dd, J_{gem}=11.02 Hz, J_{3-2}=5.59 Hz, H3), 4.12–4.22 (1H, dd, J_{gem}=11.04 Hz, $J_{3'-2}$=3.23 Hz, H3′), 6.77–6.89 (2H, m, H5, H9), 7.03–7.15 (2H, m, H6, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 20.42 (CH_3, Cl0), 44.70 (CH_2, Cl), 50.17 (*C*H, C2), 68.77 (CH_2, C3), 114.41 (C_{arom}, C5, C9), 129.88 (C_{arom}, C6, C8), 130.40 (C_{arom}, C7), 156.31 (C_{arom}, C4). IR (neat, cm^{-1}): 1245 cm^{-1}: $\overset{O}{C'-C}$; Anal. Calcd for $C_{10}H_{12}O_2$ (164.20): C, 73.15; H, 7.36. Found: C, 73.07; H, 7.26. Colourless oil, bp=121–126 °C/0.2 mmHg.

5.4.5. 3e: 1,2-Epoxy-3-(4-chlorophenoxy)propane.



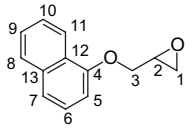
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.70–2.82 (1H, dd, J_{gem}=4.87 Hz, J_{1-2}=2.71 Hz, H1), 2.87–2.98 (1H, m, H1′), 3.29–3.45 (1H, m, H2), 3.80–4.01 (1H, dd, J_{gem}=11.02 Hz, J_{3-2}=5.77 Hz, H3), 4.15–4.30 (1H, dd, J_{gem}=11.00 Hz, $J_{3'-2}$=2.97 Hz, H3′), 6.80–6.95 (2H, m, H5, H9), 7.18–7.32 (2H, m, H6, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 44.53 (CH_2, Cl), 49.98 (*C*H, C2), 68.98 (CH_2, C3), 115.84 (C_{arom}, C5, C9), 126.02 (C_{arom}, C7), 129.31 (C_{arom}, C6, C8), 157.00 (C_{arom}, C4). IR (neat, cm^{-1}): 1240 cm^{-1}: $\overset{O}{C'-C}$; Anal. Calcd for $C_9H_9O_2Cl$ (184.62): C, 58.55; H, 4.91. Found: C, 58.41; H, 4.78; MS (electr. impact, 70 eV, *m/z*): $(M+2)^+$=186 (26), $(M)^{+\bullet}$=184 (73), $(M-CH_2O)^+$=154 (11.5), $(M-C_2H_3O)^+$=141 (21.7), $([M+2]-C_3H_4O)^+$=130 (26.5), $(M-C_3H_4O)^+$=128 (100), $(M-C_3H_5O_2)^+$=111 (26), $(M-C_4H_5O_2)^+$=99 (17.8). Yellowish oil, bp=110–114 °C/0.1 mmHg.

5.4.6. 3f: 1,2-Epoxy-3-(4-chloro-3-methylphenoxy)propane.



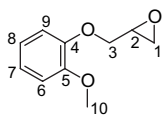
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.39 (3H, s, H10), 2.68–2.80 (1H, dd, J_{gem}=4.89 Hz, J_{1-2}=2.74 Hz, H1), 2.90–2.98 (1H, m, H1′), 3.33–3.47 (1H, m, H2), 3.78–4.03 (1H, dd, J_{gem}=11.06 Hz, J_{3-2}=5.69 Hz, H3), 4.12–4.29 (1H, dd, J_{gem}=11.01 Hz, $J_{3'-2}$=2.99 Hz, H3′), 6.69–6.94 (2H, m, H5, H9), 7.21–7.28 (1H, m, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 20.54 (CH_3, Cl0), 44.59 (CH_2, Cl), 53.17 (*C*H, C2), 68.76 (CH_2, C3), 113.23 (C_{arom}, C9), 116.96 (C_{arom}, C5), 127.00 (C_{arom}, C7), 129.64 (C_{arom}, C8), 137.46 (C_{arom}, C6), 156.24 (C_{arom}, C4). IR (neat, cm^{-1}): 1237 cm^{-1}: $\overset{O}{C'-C}$; Anal. Calcd for $C_{10}H_{11}O_2Cl$ (198.65): C, 60.46; H, 5.58. Found: C, 60.35; H, 5.49. Colourless oil, bp=120–121 °C/0.1 mmHg, $bp_{Lit.}$=119–123 °C/0.1 mmHg.[20b]

5.4.7. 3g: 1,2-Epoxy-3-(1-naphthoxy)propane.



^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.80–2.90 (1H, dd, J_{gem}=4.93 Hz, J_{1-2}=2.65 Hz, H1), 2.92–3.01 (1H, m, H1′), 3.42–3.55 (1H, m, H2), 4.03–4.18 (1H, dd, J_{gem}=11.07 Hz, J_{3-2}=5.61 Hz, H3), 4.32–4.45 (1H, dd, J_{gem}=11.08 Hz, $J_{3'-2}$=3.02 Hz, H3′), 6.75–6.87 (1H, m, H5), 7.34–7.61 (4H, m, H6, H7, H10, H11), 7.80–7.90 (1H, m, H9), 8.31–8.45 (1H, m, H8). ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 44.83 (CH_2, Cl), 50.20 (*C*H, C2), 69.89 (CH_2, C3), 104.05 (C_{arom}, C5), 119.80 (C_{arom}, C7), 120.85 (C_{arom}, C11), 125.10 (C_{arom}, C10), 125.48 (C_{arom}, C6, C12), 126.45 (C_{arom}, C9), 127.32 (C_{arom}, C8), 135.00 (C_{arom}, C13), 154.67 (C_{arom}, C4). IR (neat, cm^{-1}): 1248 cm^{-1}: $\overset{O}{C'-C}$; Anal. Calcd for $C_{13}H_{12}O_2$ (200.24): C, 77.98; H, 6.04. Found: C, 77.86; H, 5.92. Colourless oil, bp=148–149 °C/0.5 mmHg, $bp_{Lit.}$=145–149 °C/0.5 mmHg.[20c]

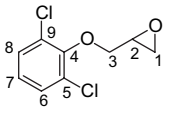
5.4.8. 3h: 1,2-Epoxy-3-(2-methoxyphenoxy)propane.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.67–2.82 (1H, m, H1), 2.83–2.98 (1H, m, H1′), 3.31–3.49 (1H, m, H2), 3.87 (3H, s,

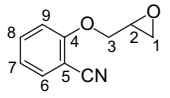
H10), 3.98–4.11 (1H, dd, J_{gem}=11.40 Hz, J_{3-2}=5.61 Hz, H3), 4.17–4.32 (1H, dd, J_{gem}=11.42 Hz, $J_{3'-2}$=3.58 Hz, H3′), 6.78–7.05 (4H, m, H6, H7, H8, H9). ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 44.92 (*C*H_2, Cl), 50.15 (*C*H, C2), 55.80 (*C*H_3, C10), 70.13 (*C*H_2, C3), 111.83 (C_{arom}, C6), 114.12 (C_{arom}, C9), 120.76 (C_{arom}, C7), 121.86 (C_{arom}, C8), 147.88 (C_{arom}, C5), 149.54 (C_{arom}, C4). IR (neat, cm^{-1}): 1245 cm^{-1}: C–O–C; Anal. Calcd for $C_{10}H_{12}O_3$ (180.20): C, 66.65; H, 6.71. Found: C, 66.53; H, 6.58. MS (electr. impact, 70 eV, *m*/*z*): $(M)^{+\bullet}$=180 (99.7), $(M-CH_2O)^+$=150 (11.8), $(M-C_2H_3O)^+$=137 (20.00), $(M-C_3H_4O)^+$=124 (48), $(M-C_3H_5O)^+$=123 (15.7), $(M-C_3H_6O)^+$=122 (21.8), $(M-C_3H_7O)^+$=121 (25), $(M-C_4H_7O)^+$=109 (100), $(M-C_4H_8O_2)^+$=92 (13), $(M-C_4H_7O_3)^+$=77 (83.10), $(M-C_5H_7O_3)^+$=65 (34.70), $(M-C_5H_8O_3)^+$=64 (25.90), $(M-C_5H_9O_3)^+$=63 (35.40), $(M-C_6H_8O_3)^+$=52 (87), $(M-C_6H_9O_3)^+$=51 (55.90). Yellowish oil, bp=110–114 °C/0.03 Torr, $bp_{Lit.}$=115–116 °C/0.03 Torr.[20d]

5.4.9. 3i: 1,2-Epoxy-3-(2,6-bischlorophenoxy)propane.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.68–2.75 (1H, dd, J_{gem}=4.90 Hz, J_{1-2}=2.57 Hz, H1), 2.86–2.95 (1H, m, H1′), 3.40–3.51 (1H, m, H2), 3.98–4.12 (1H, dd, J_{gem}=10.91 Hz, J_{3-2}=5.97 Hz, H3), 4.17–4.28 (1H, dd, J_{gem}=10.95 Hz, $J_{3'-2}$=3.69 Hz, H3′), 6.92–7.08 (1H, m, H7), 7.22–7.35 (2H, m, H6, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 44.59 (*C*H_2, Cl), 50.03 (*C*H, C2), 74.31 (*C*H_2, C3), 125.33 (C_{arom}, C7), 128.90 (C_{arom}, C6, C8), 129.34 (C_{arom}, C5, C9), 151.01 (C_{arom}, C4). IR (neat, cm^{-1}): 1247 cm^{-1}: C–O–C; Anal. Calcd for $C_9H_8O_2Cl_2$ (219.07): C, 49.34; H, 3.68. Found: C, 49.26; H, 3.56. Yellowish oil.

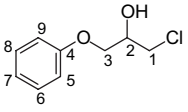
5.4.10. 3j: 1,2-Epoxy-3-(2-cyanophenoxy)propane.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.74–2.80 (1H, dd, J_{gem}=4.78 Hz, J_{1-2}=2.76 Hz, H1), 2.85–2.96 (1H, m, H1′), 3.28–3.46 (1H, m, H2), 3.10–4.18 (1H, dd, J_{gem}=11.12 Hz, J_{3-2}=5.76 Hz, H3), 4.17–4.48 (1H, dd, J_{gem}=11.13 Hz, $J_{3'-2}$=3.06 Hz, H3′), 6.98–7.39 (4H, m, H6, H7, H8, H9); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 43.28 (*C*H_2, Cl), 48.70 (*C*H, C2), 69.90 (*C*H_2, C3), 97.91 (C_{arom}, C5), 114.62 (C_{arom}, C9), 118.51 (CN, C10), 121.61 (C_{arom}, C7), 133.08 (C_{arom}, C6), 133.77 (C_{arom}, C8), 162.80 (C_{arom}, C4). IR (neat, cm^{-1}): 1245 cm^{-1}: C–O–C; Anal. Calcd for $C_{10}H_9NO_2$ (175.18): C, 68.56; H, 5.18; N, 8.00. Found: C, 68.43; H, 5.03; N, 7.92. Colourless oil, bp=128–129 °C/0.1 mmHg, $bp_{Lit.}$=124–127 °C/0.1 mmHg.[10]

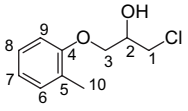
^{1}H NMR (and MS for **4a**) spectra, IR data as well as microanalyses of 1-chloro-3-aryloxypropan-2-ols **4a–j** are as follows.

5.4.10.1. 4a: 1-Chloro-3-phenoxypropan-2-ol.



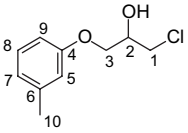
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.49 (1H, s, OH), 3.75 (2H, d, J_{1-2}=3.98 Hz, H1), 4.11–4.27 (3H, m, H2, H3), 6.67–6.98 (3H, m, H5, H7, H9), 7.08–7.35 (2H, m, H6, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_9H_{11}O_2Cl$ (186.64): C, 57.92; H, 5.94. Found: C, 57.85; H, 5.84. MS (electr. impact, 70 eV, *m*/*z*): $(M+2)^+$=188 (5.40), $(M)^{+\bullet}$=186 (18), $(M-CH_3OCl)^+$=119 (7.30), $(M-C_2H_3OCl)^+$=108 (5.90), $(M-C_2H_4OCl)^+$=107 (25.70), $(M-C_3H_4OCl)^+$=95 (24.50), $(M-C_3H_5OCl)^+$=94 (74), $(M-C_3H_6O_2Cl)^+$=77 (100), $(M-C_4H_5O_2Cl)^+$=66 (30), $(M-C_4H_6O_2Cl)^+$=65 (26). Colourless oil.

5.4.10.2. 4b: 1-Chloro-3-(2-methylphenoxy)propan-2-ol.



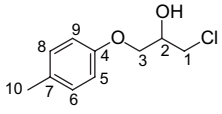
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.14 (3H, s, H10), 2.45 (1H, s, OH), 3.84 (2H, d, J_{1-2}=4.07 Hz, H1), 4.11–4.36 (3H, m, H2, H3), 6.77–6.90 (2H, m, H7, H9), 7.09–7.24 (2H, m, H6, H8). IR (neat, cm^{-1}): 3390 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{13}O_2Cl$ (200.66): C, 59.86; H, 6.53. Found: C, 59.79; H, 6.46. Colourless oil.

5.4.10.3. 4c: 1-Chloro-3-(3-methylphenoxy)propan-2-ol.



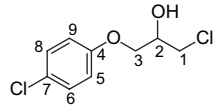
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.24 (3H, s, H10), 2.51 (1H, s, OH), 3.73 (2H, d, J_{1-2}=4.11 Hz, H1), 4.09–4.30 (3H, m, H2, H3), 6.63–6.78 (3H, m, H5, H7, H9), 7.10 (1H, m, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{13}O_2Cl$ (200.66): C, 59.86; H, 6.53. Found: C, 59.76; H, 6.50. Colourless oil.

5.4.10.4. 4d: 1-Chloro-3-(4-methylphenoxy)propan-2-ol.



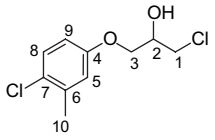
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.19 (3H, s, H10), 2.43 (1H, s, OH), 3.78 (2H, d, J_{1-2}=3.99 Hz, H1), 4.12–4.32 (3H, m, H2, H3), 6.70–6.90 (2H, m, H5, H9), 7.09–7.24 (2H, m, H6, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{13}O_2Cl$ (200.66): C, 59.86; H, 6.53. Found: C, 59.80; H, 6.45. Colourless oil.

5.4.10.5. 4e: 1-Chloro-3-(4-chlorophenoxy)propan-2-ol.



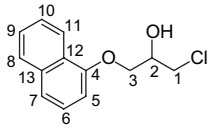
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.50 (1H, s, OH), 3.76 (2H, d, J_{1-2}=4.06 Hz, H1), 4.05–4.41 (3H, m, H2, H3), 6.78–6.89 (2H, m, H5, H9), 7.15–7.29 (2H, m, H6, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_9H_{10}O_2Cl_2$ (221.08): C, 48.90; H, 4.56. Found: C, 48.78; H, 4.50. Yellowish oil.

5.4.10.6. 4f: 1-Chloro-3-(4-chloro-3-methylphenoxy)-propan-2-ol.



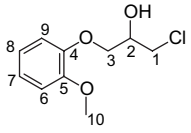
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.29 (3H, s, H10), 2.70 (1H, s, OH), 3.68 (2H, d, J_{1-2}=3.87 Hz, H1), 4.03–4.32 (3H, m, H2, H3), 6.53–6.79 (2H, m, H5, H9), 7.16–7.26 (1H, m, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{12}O_2Cl_2$ (235.11): C, 51.09; H, 5.14. Found: C, 50.95; H, 5.09. Yellowish oil.

5.4.10.7. 4g: 1-Chloro-3-(1-naphthoxy)propan-2-ol.



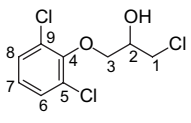
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.63 (1H, d, J=5.48 Hz, OH), 3.84 (2H, d, J_{1-2}=4.05 Hz, H1), 4.23–4.48 (3H, m, H2, H3), 6.68 (1H, m, H5), 7.26–7.71 (4H, m, H6, H7, H10, H11), 7.70–7.89 (1H, m, H9), 8.13–8.22 (1H, m, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{13}H_{13}O_2Cl$ (236.70): C, 65.97; H, 5.54. Found: C, 65.89; H, 5.44. Colourless oil.

5.4.10.8. 4h: 1-Chloro-3-(2-methoxyphenoxy)propan-2-ol.



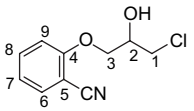
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.50 (1H, s, OH), 3.72 (2H, d, J_{1-2}=3.98 Hz, H1), 3.89 (3H, s, H10), 4.14–4.35 (3H, m, H2, H3), 6.71–7.10 (4H, m, H6, H7, H8, H9). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{13}O_3Cl$ (216.66): C, 55.44; H, 6.05. Found: C, 55.36; H, 5.91. Colourless oil.

5.4.10.9. 4i: 1-Chloro-3-(2,6-bischlorophenoxy)propan-2-ol.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.46 (1H, s, OH), 3.62 (2H, d, J_{1-2}=4.15 Hz, H1), 4.20–4.33 (3H, m, H2, H3), 6.89–7.06 (1H, m, H7), 7.19–7.31 (2H, m, H6, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_9H_9O_2Cl_3$ (255.53): C, 42.30; H, 3.55. Found: C, 42.21; H, 3.45. Colourless oil.

5.4.10.10. 4j: 1-Chloro-3-(2-cyanophenoxy)propan-2-ol.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.38 (1H, s, OH), 3.81 (2H, d, J_{1-2}=4.19 Hz, H1), 4.09–4.36 (3H, m, H2, H3), 6.80–7.31 (4H, m, H6, H7, H8, H9). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{10}O_2ClN$ (211.65): C, 56.75; H, 4.76. Found: C, 56.67; H, 4.66. Colourless oil.

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