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Research Article

An Efficient K_2CO_3-Promoted Synthesis of 1-Bromo-2-aryloxyethane Derivatives and Evaluation of Larval Mortality against *Aedes aegypti*

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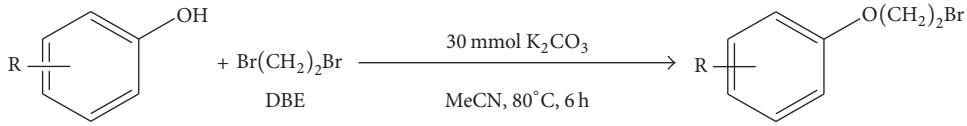
The influences of reaction parameters on the etherification of phenols to obtain 1-bromo-2-aryloxyethane derivatives were evaluated. The compounds were prepared by direct etherification of phenols with 1,2-dibromoethane using anhydrous K_2CO_3 and acetonitrile as solvent reaction, at 80°C, in a reaction time of 6 h. Under these conditions, excellent yields (71%–94%) were obtained, with low yields of secondary products. The anhydrous K_2CO_3 was recycled by simple filtration, dried in vacuum, and reused. The compounds were characterized by conventional spectral data (MS and NMR). Larvicidal activity results showed a 100% larval mortality after 24-hour exposure to the compound *1-(2-bromoethoxy)-2-phenylbenzene*.

1. Introduction

Generally, the synthesis of chemical compounds is associated with expensive and unfriendly environmental procedures. These disadvantages have become a challenge for chemists, transforming these methodologies into simple procedures, easy implementation, and low environmental impact, with the purpose of obtaining organic compounds with potential applications. In this context, the synthesis of organic compounds including aromatic rings in their structure has been widely reported in the literature. The compounds with aromatic substructure have been reported to show a broad spectrum of pharmaceutical, agricultural, and chemical engineering applications and are scaffolding reagents for synthetic organic chemistry [1–6]. They are also ubiquitous structural units in biologically important molecules such as cyclooxygenase and β-galactosidase inhibitors and anticancer porphyrins [7]. A large number of them can be used as adhesives, herbicides, fungicides, and fire retardant [1, 8, 9].

For the preparation of ethers, one of the main aromatic derivatives, a variety of procedures have been developed over recent years. Some methods include intramolecular etherification using $InCl_3$ [10], reductive etherification of aldehydes photocatalyze [11], and modifications to conventional Williamson synthesis [12], the most appropriate method for the preparation of symmetrical and unsymmetrical ethers, which involves treating a halide with an alkoxylated derivative or by direct mixture of a halide with KOH solid [13].

Particularly, 1-bromo-2-aryloxyethane derivatives have been prepared from phenols and 1,2-dibromoethane, employing different bases and solvents, and include Na_2CO_3/glycerol,



Scheme 1: K_2CO_3-promoted synthesis of 1-bromo-2-aryloxyethane derivatives.

KOH/butanone, K_2CO_3/MeCN [14], Bu_4NBr/toluene [15], NaOH/Bu_4NBr [16], NaOH/H_2O [17], K_2CO_3/butanone [18], K_2CO_3/DMF [19], and NaH/EtOH [20], among other modifications to the classical Williamson ether synthesis.

The use of synthetic organic compounds as alternative sources of insecticidal/larvicidal agents in the fight against the dengue, Zika, and chikungunya vector-borne diseases has become inevitable. In this context, the relevant bioactivity of these bromo-derivative compounds aroused our interest in synthesizing several compounds and screening them for *Aedes aegypti* larval mortality. In continuation of our work, we prepared twelve 1-bromo-2-phenoxyethane derivatives (Scheme 1, Table 4), optimizing one of the classical methods described in the literature [21–25], and then studied the larval mortality of *A. aegypti* (Table 5).

2. Materials and Methods

2.1. General. Chemicals were purchased from Aldrich, Fluka, and Merck chemical companies and were freshly used after purification by standard procedures (distillation and recrystallization). All the reactions were monitored by TLC on percolated silica gel plates (254 mm). Flash column chromatography was performed with 230- to 400-mesh silica gel. The yields were calculated from pure products. All the products were identified by comparison of physical data (mp, TLC, NMR, and mass spectra) with those reported or with those of authentic samples prepared by the respective conventional methods using sulfuric acid as catalyst.

2.2. Characterizations. Melting points were determined using Thermo Scientific Fluke 51 II, model IA 9100 melting point apparatus, and are reported as uncorrected. The ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Bruker Ultra Shield instrument 400 MHz model, using $CDCl_3$ as solvent; chemical shifts are expressed in δ units with Me_4Si (TMS) as the internal standard.

2.3. K_2CO_3 Reuse. Stability tests of anhydrous K_2CO_3 were carried out running four consecutive experiments, under the same reaction conditions. After each test, the solid was separated from the reaction mixture by filtration, washed with acetonitrile (2 × 2 mL), dried under vacuum, at 120°C, for 5 h, and then reused (Table 3).

2.4. General Procedure for 1-Bromo-2-aryloxyethane Derivatives. The compounds were synthesized according to Scheme 1. A suspension of phenol (10 mmol), 1,2-dibromoethane (50 mmol), and anhydrous K_2CO_3 (30 mmol) in dry acetonitrile (50 mL) was stirred at 80°C for 6 h. The reaction mixture was filtered, and the K_2CO_3 was recovered, reactivated (in vacuum at 120°C, 5 h), and the solvent was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using petroleum ether as eluent to give the product as a solid (Scheme 1, Table 4).

1-(2-Bromoethoxy)-benzene [22, 23] (Entry 1). mp: 33-34°C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.29–7.26 (m, 2H), 6.95–6.92 (m, 3H), 4.26–4.23 (t, J = 3.6 Hz, 2H), 3.61–3.58 (t, J = 3.6 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ: 158, 129.5, 121.4, 114.8, 67.8, 29.1. MS *m/z* (I): 202 (50, M^{+2}), 200 (48, M^+), 109 (97), 107 (100), 94 (60), 77 (29), 65 (38), 51 (22), 39 (52).

1-(2-Bromoethoxy)-4-bromobenzene [25] (Entry 2). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.44–7.41 (m, 2H), 6.84–6.81 (m, 2H), 4.31–4.28 (t, J = 6 Hz, 2H), 3.63–3.60 (t, J = 6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 157.2, 132.7, 116.3, 113.7, 68.0, 29.1.

1-(2-Bromoethoxy)-4-phenylbenzene [21, 23] (Entry 3). mp: 112-113°C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.47–7.43 (m, 4H), 7.30–7.24 (m, 3H), 6.89–6.87 (dd, J = 8.5–1.5 Hz, 2H), 4.25–4.21 (t, J = 6.3, 2H), 3.56–3.51 (t, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 157.6, 140.6, 134.6, 128.7, 128.3, 126.8, 126.6, 115.1, 68.1, 29.1. MS *m/z* (I): 278 (46, M^{+2}), 276 (49, M^+), 183 (12), 170 (36), 169 (100), 153 (7), 142 (8), 141 (61), 109 (12), 107 (12).

1-(2-Bromoethoxy)-2-iodobenzene [23] (Entry 4). mp: 49-50°C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.79–7.75 (d, J = 8.0 Hz, 1H), 7.42–7.39 (dd, J = 8.0–1.5 Hz, 1H), 7.30–7.25 (dd, J = 8.0–1.5 Hz, 1 H), 6.80–6.76 (d, J = 8.0 Hz, 1H), 4.32–4.29 (t, J = 6.6 Hz, 2H), 3.68–3.64 (t, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 156.7, 139.6, 129.4, 123.3, 112.8, 86.9, 69.1, 28.5. MS *m/z* (I): 328 (71), 326 (72), 233 (6), 220 (56), 219 (52), 203 (11), 191 (23), 109 (95), 107 (100).

1-(2-Bromoethoxy)-2-nitrobenzene [22, 23] (Entry 5). mp: 49-50°C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.82–7.79 (dd, J = 8.4–1.8 Hz, 1H), 7.56–7.52 (dd, J = 8.0–1.5 Hz, 1H), 7.13–7.07 (m, 2H), 4.44–4.40 (t, J = 6.2 Hz, 2H), 3.69–3.66 (t, J = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 151.4, 140.3, 134.0, 125.5, 121.3, 115.4, 69.7, 28. MS *m/z* (I): 247 (10), 245 (10), 139 (23), 122 (26), 109 (100), 107 (90).

1-(2-Bromoethoxy)-2-phenylbenzene [22, 23] (Entry 6). mp: 70-71°C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.50–7.45 (dd, J = 8.4–1.5, 1H), 7.44–7.36 (m, 5H), 6.99–6.95 (dd, J = 7.5–1.5 Hz, 1H), 6.86–6.83 (d, J = 8 Hz, 2H), 4.15–4.11 (t, J = 6.3 Hz, 2H), 3.43–3.39 (t, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 155.0, 138.1, 131.5, 131.1, 129.6, 128.6, 127.9, 126.9, 121.9, 113.3, 68.6, 29.1. MS *m/z* (I): 278 (54), 276 (58), 183 (41), 169 (100), 153 (9), 141 (59).

1-(2-Bromoethoxy)-2-benzylbenzene [22, 23] (Entry 7). mp: 52–54°C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.14–7.06 (m, 7H), 6.88–6.84 (t, J = 7.3 Hz, 1H), 6.74–6.72 (t, J = 8 Hz, 1H), 4.18–4.14 (t, J = 6.2 Hz, 2H), 3.91 (s, 2H), 3.48–3.46 (t, J = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 155.9, 141.0, 130.7, 130.0, 129.1, 128.2, 127.4, 125.8, 121.3, 111.7, 68.0, 36.1, 29.3. MS *m/z* (I): 292 (48), 290 (268), 184 (16), 183 (100).

1-(2-Bromoethoxy)-2,4-dibromobenzene [22, 23] (Entry 8). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.55 (s, 1H), 7.26–7.23 (d, J = 2.6 Hz, 1H), 6.58–6.55 (d, J = 2.2 Hz, 1H), 4.46–4.42 (t, J = 6.2 Hz, 2H), 3.75–3.70 (t, J = 6.2 Hz, 2H). ^{13}CNMR (100 MHz, $CDCl_3$), δ: 152, 135, 131, 118.8, 114.4, 112.4, 67.4, 29.6.

1-(2-Bromoethoxy)-2-bromo-4-methylbenzene [25] (Entry 9). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.33–7.29 (d, J = 2.6 Hz, 1H), 7.18–7.14 (dd, J = 8.8–2.6 Hz, 1H), 6.74–6.77 (d, J = 8.8 Hz, 1H), 4.28–4.25 (t, J = 6.2 Hz, 2H), 3.65–3.60 (t, J = 6.2 Hz, 2H), 2.22 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$), δ: 152.3, 133.8, 132.6, 128.8, 114.4, 112.4, 69.4, 28.6, 20.1.

1-(2-Bromoethoxy)-2-bromo-4-chlorobenzene [22, 23] (Entry 10). ^{1}HNMR (400 MHz, $CDCl_3$), δ: 7.49–7.47 (d, J = 2.6 Hz, 1H), 7.18–7.13 (dd, J = 8.8–2.6 Hz, 1H), 6.75–6.72 (d, J = 8.8 Hz, 1H), 4.28–4.23 (t, J = 6.2 Hz, 2H), 3.63–3.60 (t, J = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 153.2, 133.1, 128.5, 126.6, 114.8, 112.9, 69.6, 28.8. MS *m/z* 318 (3), 316 (15), 314 (20), 312 (9), 209 (10), 208 (19), 206 (15), 179 (21), 177 (14), 109 (95), 107 (100).

2-(2-Bromoethoxy)-naphthalene [22, 23] (Entry 11). mp 91.5–92.0°C. ^{1}HNMR: (400 MHz, $CDCl_3$), δ: 8.30–8.25 (dd, J = 6.5–3.2 Hz, 1H), 7.79–7.76 (dd, J = 6.4–3.2 Hz, 1H), 7.49–7.42 (m, 4H), 6.78–6.74 (dd, J = 8.0–2.0 Hz, 1H), 3.36–3.33 (t, J = 6.5 Hz, 2H), 2.97–2.92 (t, J = 6.5 Hz, 2H). ^{13}CNMR (100 MHz, $CDCl_3$), δ: 156.0, 134.4, 129.3, 129.7, 127.7, 126.8, 126.5, 123.9, 118.1, 107.3, 67.9, 29.0. MS *m/z*: 252 (24), 250 (26), 157 (12), 144 (32), 143 (60), 116 (21), 115 (100), 109 (20), 107 (19).

Biphenyl-4,4′-di-(2-bromoethoxy) [21] (Entry 12). mp: 86-87°C. ^{1}HNMR: (400 MHz, $CDCl_3$), δ: 7.01–6.99 (d, J = 8.6 Hz, 4H), 6.77–6.74 (d, J = 8.6 Hz, 4H), 4.18–4.16 (t, J = 6.3 Hz, 4H), 3.55–3.51 (t, J = 6.3 Hz, 4H). ^{13}CNMR: (100 MHz, $CDCl_3$), δ: 156.5, 134.4, 124.9, 114.9, 68.0, 29.1. MS *m/z*: 416 (24), 414 (47), 412 (25), 307 (15), 305 (16), 291 (23), 289 (23), 198 (13), 153 (16), 152 (17), 141 (21), 115 (21), 109 (95), 107 (100).

2.5. Larval Toxicity Test. A laboratory-reared colony of *A. aegypti* larvae was used for the study of larval mortality (Table 5). From the stock solution, 2000 mg/L of each 1-bromo-2-aryloxyethane derivative was prepared with acetone. Hence, 0.25 mL of the compound was withdrawn and placed in a 250 mL glass beaker containing 99.75 mL of dechlorinated water and 20 individuals of third and fourth instar larvae. The control was setup by mixing 0.25 mL of acetone with 99.75 mL of dechlorinated water. At the tested concentration, two to five trials were made and each trial consisted of five replicates. The control mortalities were corrected by using Abbott's formula [26].

$$\text{Corrected mortality} = \frac{\text{Observed mortality in treatment} - \text{Observed mortality in control}}{100 - \text{control mortality}} \times 100,$$
$$\text{Porcent mortality} = \frac{\text{Number of dead larvae}}{\text{Number of larvae introduced}} \times 100. \quad (1)$$

3. Results and Discussion

The structural diversity of phenolic derivatives commercially available makes them attractive substrates for the preparation of aryl alkyl ethers. Transformation is accomplished via substitution reaction [27]. Herein, we report a simple, effective, easy workup procedure, with excellent yield under mild conditions, with the use and reuse of a soft promoter, environmentally friendly for the base-promoted preparation of halo-aryloxyethane derivatives.

Using the optimized conditions, phenol (10 mmol), 1,2-dibromoethane (50 mmol), anhydrous K_2CO_3 (30 mmol) at 80°C with 6 h of reaction time, and dry acetonitrile (50 mL), 12 substituted 1-bromo-2-aryloxyethane derivatives were prepared. In all the experiments, the desired products were obtained with high selectivity (Scheme 1, Table 4).

Optimal reaction conditions were examined employing phenol and 1,2-dibromoethane as test reaction substrate in acetonitrile as solvent. Without the presence of anhydrous K_2CO_3, no reaction was observed. First, the influence of the reaction temperature (20, 40, 60, and 80°C) on 1-bromo-2-phenoxyethane synthesis was tested (Table 1(a)). The tested experimental reaction conditions were phenol (10 mmol), 1,2-dibromoethane (50 mmol), anhydrous K_2CO_3 (30 mmol), 6 h of reaction time in acetonitrile (50 mL).

No reaction was observed at 20°C (entry 1, Table 1(a)). A temperature increase leads to a higher 1-bromo-2-phenoxyethane yield. For example, the yield of 1-bromo-2-phenoxyethane for a reaction time of 6 h at 40°C was only 29% (entry 2, Table 1(a)), whereas at 60°C the yields were 70% (entry 3, Table 1(a)). Finally, at 80°C the reaction yield was 85% (entry 4, Table 1(a)). After determining the temperature of the reaction, the effect of reaction time was studied to learn more about the substitution reaction. The reaction time was evaluated under the conditions described above at 80°C. Table 1(b) shows the changes in the yield of 1-bromo-2-phenoxyethane with reaction time over K_2CO_3. The yields of 1-bromo-2-phenoxyethane increased with the reaction time up to 6 h and then remained practically constant (ca. 90%,

Table 1: Effect of temperature (a) and time (b) on 1-bromo-2-phenoxyetane yield (%).

(a)

Entry	Temperature (°C)	Yield[a] (%)
1	20	—
2	40	29
3	60	70
4	**80**	**85**

(b)

Entry	Reaction time (h)[b]	Yield[a] (%)
1	3	48
2	**6**	**85**
3	9	86
4	12	87

[a]Isolated yield. [b]All at 80°C.

Table 2: Amounts of anhydrous K_2CO_3 (a) and 1,2-dibromoethane-DBE (b) for the direct substitution reaction of phenol to 1-bromo-2-phenoxyethane.

(a)

Entry	Phenol/K_2CO_3 ratio	Yield[a] (%)
1	1 : 1	64
2	1 : 2	77
3	**1 : 3**	**85**
4	1 : 5	87

(b)

Entry	Phenol/DBE ratio	Yield[a] (%)
1	1 : 1	45
2	1 : 3	77
3	**1 : 5**	**85**
4	1 : 7	87

[a]Isolated yield.

Table 3: Effect of catalyst reuse cycles on 1-bromo-2-phenoxyethane yields (%).

Entry	Catalytic cycle	Yield[a] (%)
1	1	85
2	2	83
3	3	83
4	4	82

[a]Isolated yield.

Table 1(b), entries 3 and 4). These results mean that the rate of 1-bromo-2-phenoxyethane formation decreases with an increase in the reaction time.

Table 2(a) shows the effect of the amount of anhydrous K_2CO_3 and 1,2-dibromoethane on the yield of 1-bromo-2-phenoxyethane in the reaction. The experimental conditions were phenol (10 mmol) and 1,2-dibromoethane (50 mmol), with a reaction time of 6 h at 80°C in acetonitrile, with a variable amount of anhydrous K_2CO_3 (10, 20, 30, and 50 mmol). The yields increased from 64% to 85% when the amount of anhydrous K_2CO_3 increased from 10 to 30 mmol (Table 2(a), entries 1–3), and no significant changes were observed in the reaction yield with increased amount of anhydrous K_2CO_3 (2%) (87%, Table 2(a), entry 4). Thus 30 mmol of anhydrous K_2CO_3 is a suitable amount for performing this reaction.

The effect of the amount of 1,2-dibromoethane on the yield of 1-bromo-2-phenoxyethane in the reaction was evaluated (Table 2(b)), maintaining determined parameters and varying the amount of 1,2-dibromoethane (10, 30, 50, and 70 mmol). The yields increased from 45% to 85% when the amount of 1,2-dibromoethane increased from 10 to 50 mmol (Table 2(b), entries 1–3), and no relevant changes were observed in the reaction yield with increased amount of 1,2-dibromoethane (2%) (87%, Table 2(b), entry 4). Thus 50 mmol of 1,2-dibromoethane is a suitable amount for performing this reaction.

The reuse of the K_2CO_3 was investigated in the consecutive reaction of phenol and 1,2-dibromoethane in acetonitrile (Table 3). At the end of each run K_2CO_3 was removed, washed with acetonitrile, dried in vacuum at 120°C, and reused. The results are summarized in Table 3. K_2CO_3 was reused for three runs, and no appreciable loss of its activity was observed. The reaction yields under the same conditions were 85%, 83%, 83%, and 82% of 1-bromo-2-phenoxyethane, respectively.

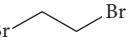
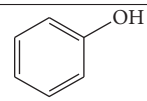
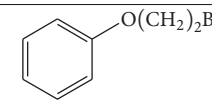
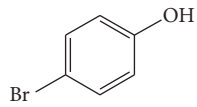
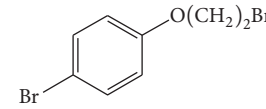
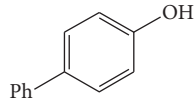
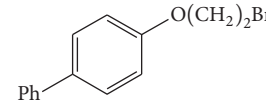
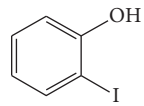
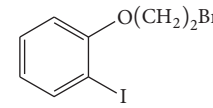
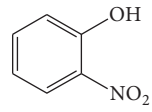
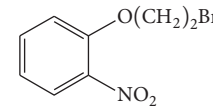
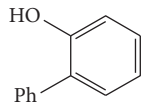
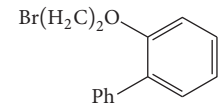
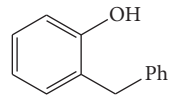
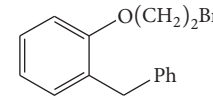
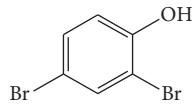
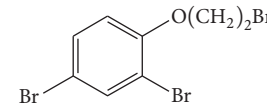
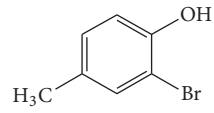
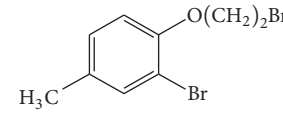
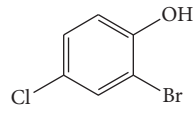
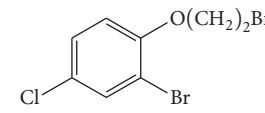
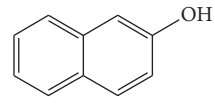
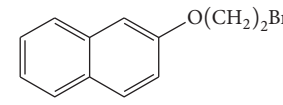
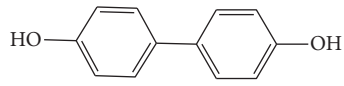
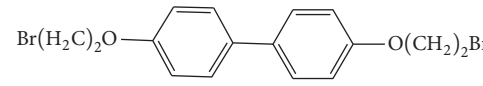
The present base-promoted substitution reaction is the *O*-alkylation of phenol process, which does not involve complex conditions and corrosive or transition metal catalysts. With the transition-metal-free method, no trace amounts of toxic transition-metals remain in the final target products after purification by the previous isolation procedures. Therefore, the present K_2CO_3-promoted method is environmentally friendly.

In general, under these reaction conditions 1-bromo-2-aryloxyethane derivatives are obtained with excellent yield and at shorter reaction time compared to data reported in the literature. The electronic effect of the aryl group was analyzed under the proposed reaction conditions. In this case, no effect of the substituents at the phenol on the reaction yields was observed (variable yields). Therefore, the electronic nature of the substrate phenols had no significant effect on the product yield of these reactions (Table 4).

Larval mortality of *A. aegypti* after the treatment with 1-bromo-2-aryloxyethane derivatives was evaluated. Table 5 lists the results of larval mortality of *A. aegypti* (III-IV instars) at 5 ppm and different times (1–24 h) for the compounds that showed activity.

Ten percent mortality was noted at 1 h following the treatment with 1-(2-bromoethoxy)-2-phenylbenzene (Tables 4 and 5, entries 6 and 8), whereas it increased to 30% at 6 h, 50% at 12 h, and 100% at 24 h for the treatment with only 1-(2-bromoethoxy)-2-phenylbenzene (Tables 4 and 5, entry 6). The treatment with 1-(2-bromoethoxy)-4-bromobenzene (Tables 4 and 5, entries 2 and 8) showed 30% of mortality at 24 h. The highest toxicity of

Table 4: Chemical structures and yield % of 1-bromo-2-aryloxyethane derivatives.

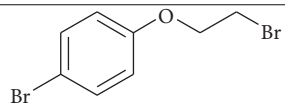
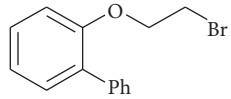
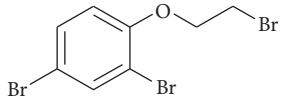
Entry DBE: 	Phenols	1-Bromo-2-aryloxyethane derivatives	Yields (%)
1			94
2			90
3			90
4			88
5			78
6			85
7			84
8			80
9			82
10			80
11			89
12			71

1-(2-bromoethoxy)-2-phenylbenzene (Tables 4 and 5, entry 6) is probably related to the precursor, *ortho*-phenylphenol [28], which is widely used as fungicide and antibacterial agent for commercial and consumer purposes. In this regard, the location of the phenyl group in *ortho* position and the 2-bromoethoxy radical promote activity and it could serve as a potential larvicidal agent, a possible alternative for controlling these vectors and their associated diseases [29, 30].

4. Conclusion

The described procedure for the synthesis of 1-bromo-2-aryloxyethane derivatives using anhydrous K_2CO_3 results in a useful alternative; the advantages of this methodology are operative simplicity, use of a reusable and noncorrosive solid base, soft reaction conditions, low reaction times, and good yields. The larval mortality was 100% at 24 h by the treatment with 1-(2-bromoethoxy)-2-phenylbenzene, which makes it an

Table 5: Larval mortality of *A. aegypti* after treatment with 1-bromo-2-aryloxyethane derivatives.

Entry	Compounds	% of larval mortality Time (h)				
		1	2	6	12	24
2		0	0	0	0	30
6		**10**	**30**	**30**	**50**	**100**
8		10	10	10	10	30

alternative for the control of *A. aegypti* larvae, suggesting that the location of the phenyl group in *ortho* position promotes activity in this compound.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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