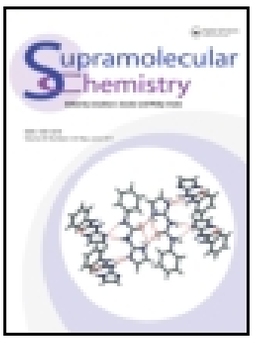

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Facile one-pot synthesis of aliphatic bridged diaryloxy compounds, cyclic and crown ethers under mild conditions

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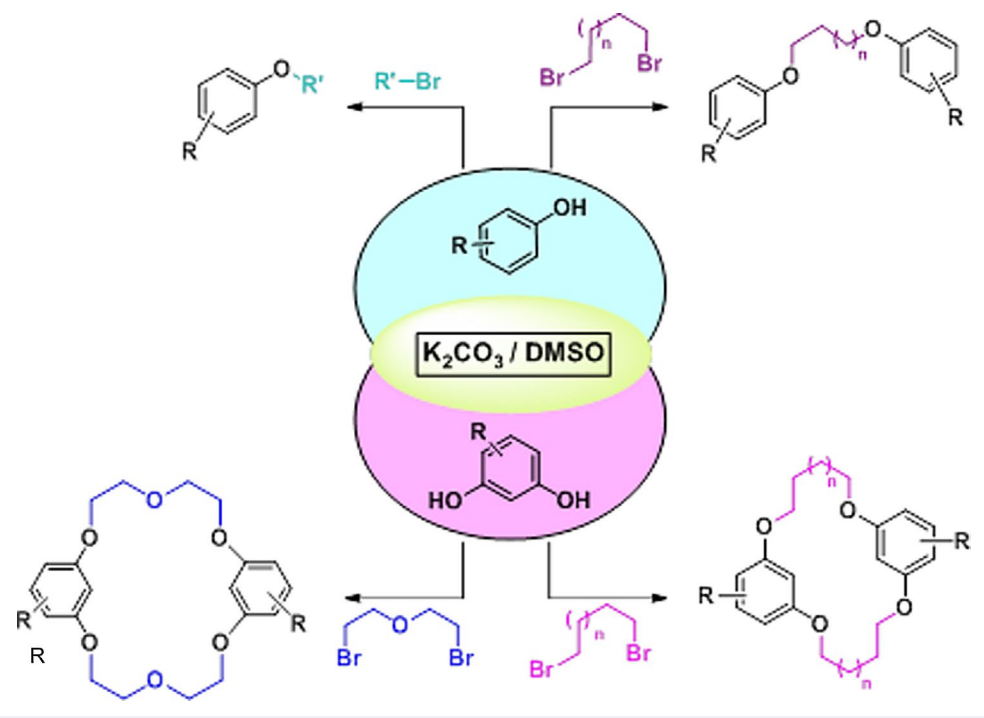
ABSTRACT

We report here the facile, room temperature, catalyst free, one pot synthesis of aliphatic bridged diaryloxy compounds, cyclic and crown ethers. Anhydrous potassium carbonate (K_2CO_3) as a mild base along with dimethyl sulfoxide generates the phenoxide ion which facilitates the nucleophilic substitution of bromoalkanes to yield the corresponding crown ethers.



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KEYWORDS
Crown ethers; cyclic ethers; aliphatic bridged diaryloxy compounds

Introduction

Aliphatic bridged diaryloxy compounds are used as important intermediates for the synthesis of various types of crown and thio crown ethers, (*1a–c*) polybenzoxazines, (*2*) basket handled porphyrin units etc. (*3a–b*) Cyclic and crown ethers have the ability to bind strongly to form the most stable complexes with the alkali metal and alkaline earth metals which contribute significantly to elucidate the host-guest and also the supramolecular chemistry. (*4a–d*) There is an excellent correlation of the stability of these complexes with the size of the cation and that of the cavity in the macrocyclic ligand. Crown ethers have also been used successfully for chiral recognition by selective binding to one of the enantiomers, thereby potentially providing a technique for optical resolution. (*4d*) Increasing the number of benzo substituents in a crown

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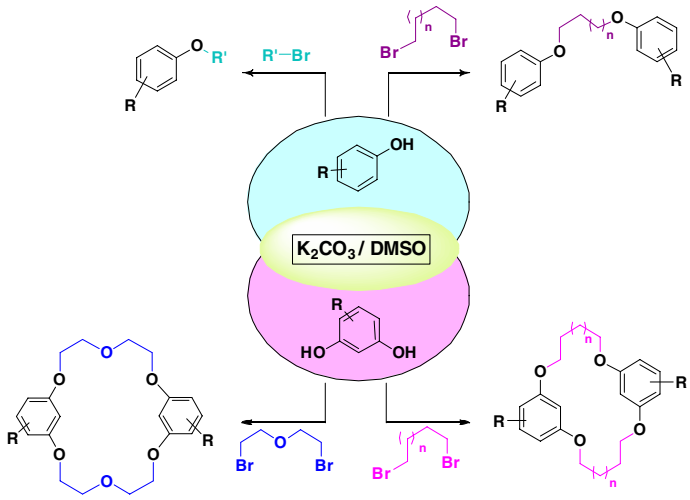


Scheme 1. (Colour online) Synthesis of alkyl aryl ether, aliphatic bridged diaryloxy compounds, crown ethers, cyclic ethers.

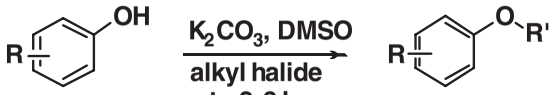
ether framework can significantly alter the properties of the ligand. Generally, adding benzo substituent will increase the rigidity of the crown ether framework and enhance its lipophilicity (*5*) but will decrease the basicity of the oxygen atoms attached to the aromatic rings. Several methods are reported in the literature for the synthesis of alkyl aryl ethers which are complementary to the traditional Williamson ether synthesis. Some of these involve the direct nucleophilic substitution of activated aryl halides, (*6a–d*) Cu (I)-catalysed cross-coupling of alkoxides with aryl halides (*7a–e*) and palladium-catalysed synthesis of protected phenols from aryl halides. (*8a–d*) Various catalytic and noncatalytic methods have been reported for the synthesis of the aliphatic bridged bisphenols, crown ethers, cyclic ethers and also for the protection of the phenols (Ar-OH), aromatics amines (Ar-NHR') and thiophenols (Ar-SH) which include the use of NaH/THF, TEGDT, (*9a*) CeO_2/KOH, DMSO, (*9b*) TBDMSCl/I_2, microwave, (*9c*) DMS, NaH/THF, (*9d*) K_2CO_3, KI, (*9*e) RX, KF, acetone, (*9*f) etc. All these methods, report the reactions at elevated temperatures, use of metals, multistep synthesis, long reaction times and the cumbersome work up of the reaction crude.

To overcome all these limitations we streamlined a facile, single-pot and noncatalytic synthesis of the alkoxy substituted aromatic compounds at ambient reaction conditions using K_2CO_3/DMSO. The developed method is equally applicable for the synthesis of the aliphatic bridged diaryloxy, oxy-bis-alkane diaryloxy compounds, cyclic and crown ethers and also for the protection of phenolic –OH and aromatic amines (Ar-NHR') by using the different alkyl halides (Scheme 1). The use of different dihalides with varying number of methylene groups was found to be the most convenient way for manipulating the ring size of the cyclic and crown ethers which can enhance their ability for the extraction of various types of the metal ions, mainly having the application for the extraction of radioactive elements (*10*). Also this strategy may be useful to reduce the steric interaction of the substituents present on the aromatic nucleus resulting into collapsing inside during the formation of the cyclic ring of the ether. All these substituents further may be used for the construction as the handles of the crown ethers like baskets for the porphyrin molecules (*11a–b*).

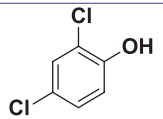
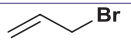
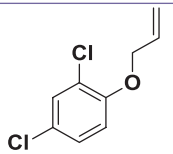
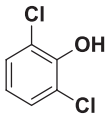
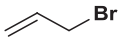
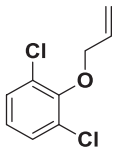
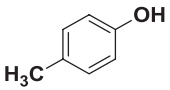
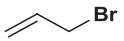
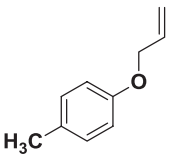
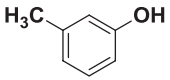
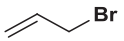
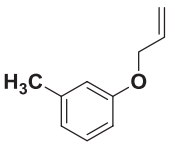
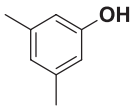
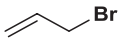
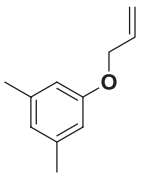
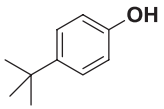
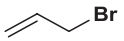
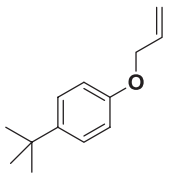
Results and discussion

In this work, alkylation of various substituted phenols was achieved at an ambient temperature through nucleophilic substitution involving different alkylating agents such as allyl, prenyl, benzyl bromides in presence of K_2CO_3/DMSO. The phenolic –OH was protected by alkyl, aryl, prenyl, benzyl protecting groups to form the corresponding aryl alkyl ethers (Table 1). Entries 1–16 in Table 1 show that phenol with various substituents reacts efficiently with all the three types of alkyl as well as benzyl bromides to give the corresponding ethers in 75–94% yields. It is very interesting to note that for resacetophenone containing two –OH groups, only the 4-position reacts to give the corresponding ethers in 81% and 82% yields, respectively (Table 1, entries 3–4), thus establishing the regeoselective alkylation. Regeoselectivity is possible due to the intramolecular hydrogen bonding between carbonyl oxygen and the phenolic–OH and its sterically hindered 2-position. The maximum yield of 92% was achieved in case of p-nitro phenol (Table 1, entry 5) due to the highest electron withdrawing ability of $–NO_2$ group at p-position. On the other hand, lower yields (75–79%) were obtained as expected, due to the electron donating effect of $–CH_3$ group (Table 1, entry 3–7). As compared to alkyl substituted phenols, chloro, acetyl, formyl and hydroxy substituted phenols gave much higher yield >80% which could be due to more pronounced electron withdrawing nature of functional

Table 1. Monoalkylation of substituted phenols.

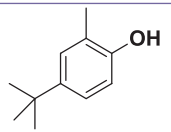
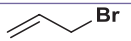
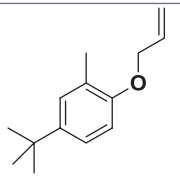
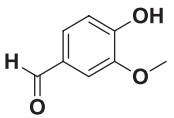
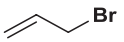
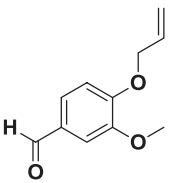
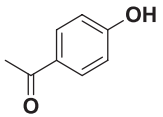
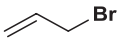
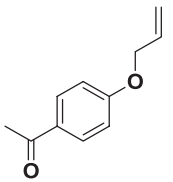
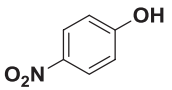
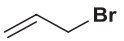
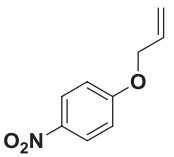
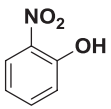
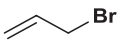
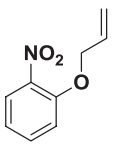
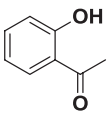
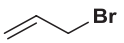
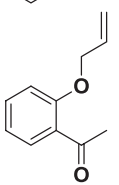
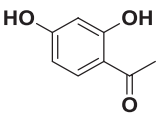
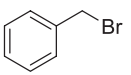
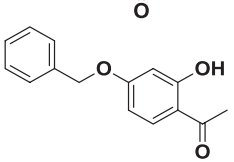


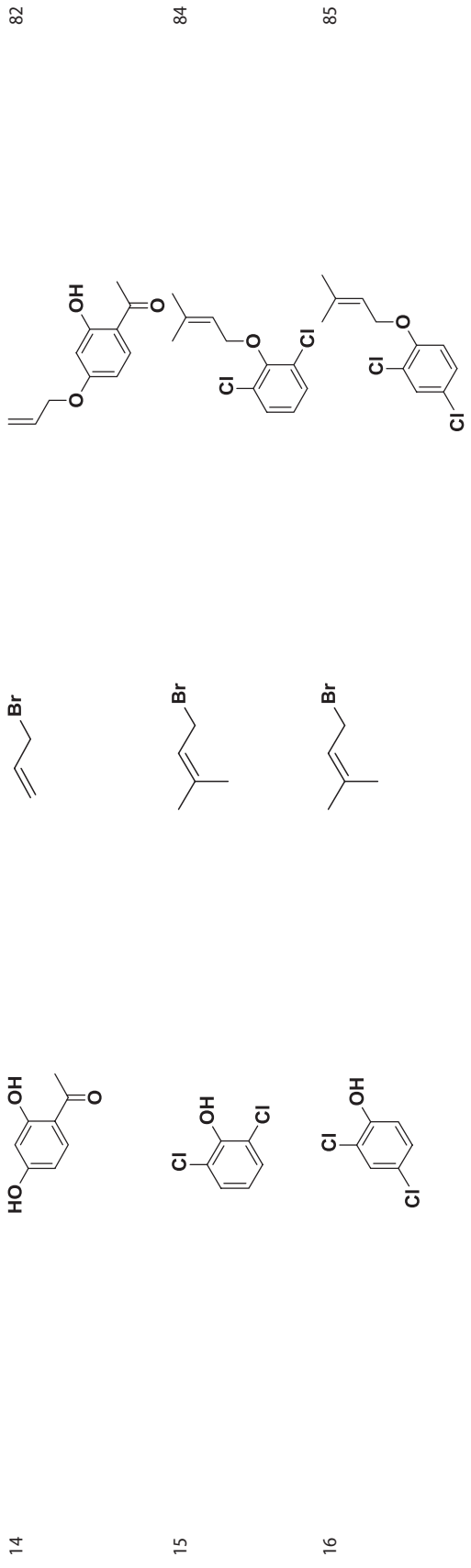
R'= alkyl, allyl, prenyl etc.

Entry	Reactant	Alkyl halide	Product	% Yield[b]
1				95
2				94
3				86
4				88
5				79
6				78

(*Continued*)

Table 1. (*Continued*)

Entry	Reactant	Alkyl halide	Product	% Yield[b]
7				75
8				93
9				91
10				92
11				94
12				89
13				81



[a]Reaction conditions: Phenol (1 mmol), dihaloalkane (1 mmol), anhydrous K_2CO_3 (1 mmol), DMSO (5 mL), Time (4–6 h).
[b]Yields of isolated products are reported.

groups present on the aromatic nucleus (Table, entry 1, 2 and 8, 9).

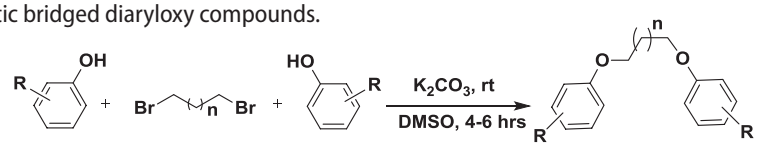
As a further extension of our methodology, synthesis of aliphatic bridged diaryloxy compounds with various substituents was achieved in excellent yields (86–92%), which serve as intermediates for the synthesis of the cyclic and crown ethers by reacting substituted phenols with dihaloalkanes like, 1,3-dibromopropane, 1,4-dibromobutane, 1-bromo-2-(2-bromoethoxy) ethane etc. (Table 2, entries 1–9). To start with, salicylaldehyde and the corresponding ketones (o-hydroxy acetophenone) were efficiently reacted with 1,3-and 1,4-dibromoalkanes to give more than 90% yield of the corresponding aliphatic bridged diaryloxy compounds having carbon atoms varying between 3 and 4 (Table 2, entries 1–6). Both ortho and para nitro phenols were also reacted with 1,4-dibromo butane to give excellent yields of the aliphatic bridged diaryloxy compounds (Table 2, entries 7, 8). Another alkylating agent such as 1-bromo-2-(2-bromoethoxy) ethane was chosen to react with orcinol (3,5-dimethyl phenol) in order to obtain oxybisalkane diaryloxy compound in 76% yield (Table 2, entry 9). N-alkylation was also attempted with acetanilide expecting that acidic proton attached to nitrogen could be easily substituted by the alkylating agent. On the contrary, the yield of the corresponding aliphatic bridged di-acetanilide compound achieved was less than 50% (Table 2, entry 10).

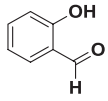
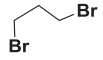
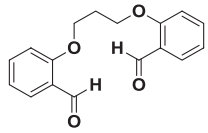
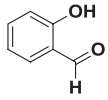
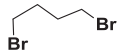
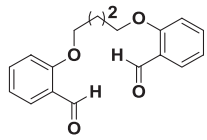
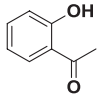
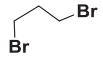
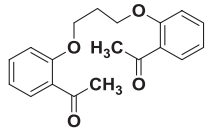
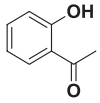
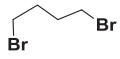
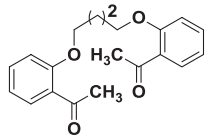
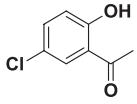
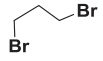
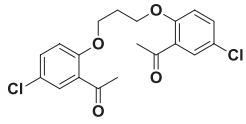
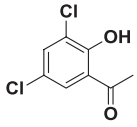
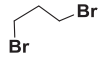
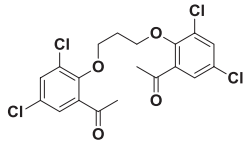
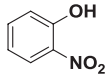
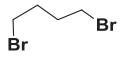
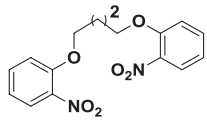
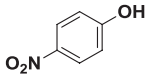
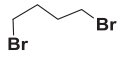
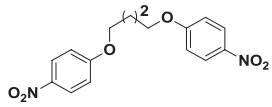
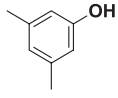
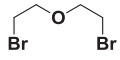
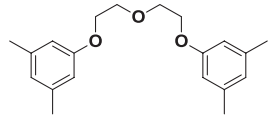
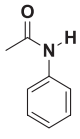
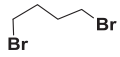
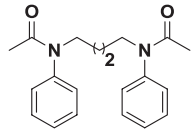
After the successful O-alkylation of the substituted phenols, N-alkylation of acetanilide and the synthesis of the aliphatic bridged diaryloxy compounds, our approach was further extended for one pot synthesis of cyclic and the crown ethers in which two moles of each substituted dihydroxy benzene and alkyl halide were used. The cavity size created during the synthesis of cyclic and crown ethers could be easily tailored by varying the ring size from sixteen to twenty atoms. Table 3, entries 1, 2 and 7 clearly demonstrate the efficient synthesis of cyclic ethers with varying cavity sizes by employing various dibromo alkanes such as 13-dibromopropane, 14-dibromobutane and 15-dibromopentane. Similarly, crown ethers were synthesised by reacting 1-(2,4-dihydroxyphenyl) propan-1-one with 1-bromo-2-(2-bromoethoxy) ethane at ambient conditions (Table 3, entries 3 and 6). Table 3, entries 4 and 5 show the examples of novel cyclic and crown ethers where, both the ketone groups attached to the benzene ring could collapse inside the ring cavity by using 1-(2,6-dihydroxyphenyl) ethan-1-one and the dihalo alkanes.

Experimental section

All chemicals and reagents were procured from commercial suppliers and used without further purification. The products were characterised using ^{1}H NMR, ^{13}C NMR

Table 2. Synthesis of aliphatic bridged diaryloxy compounds.

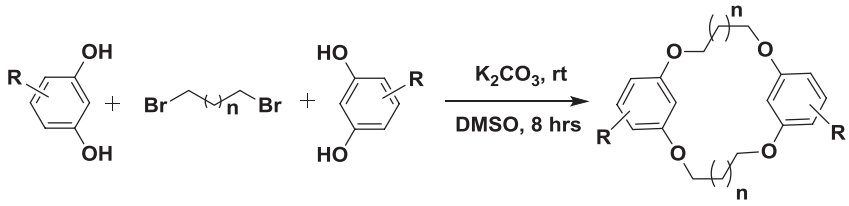


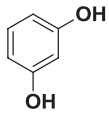
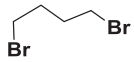
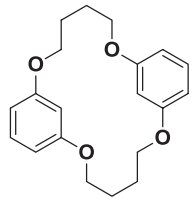
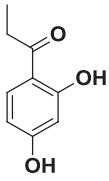
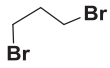
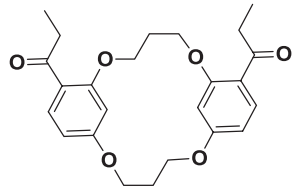
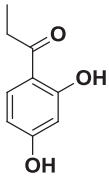
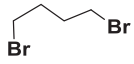
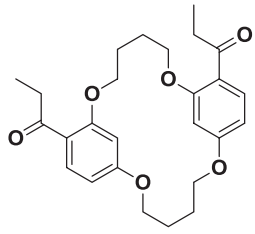
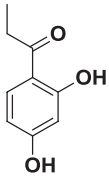
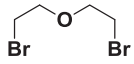
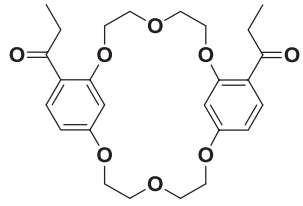
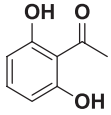
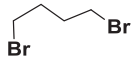
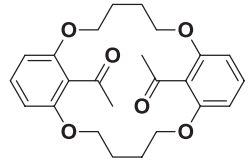
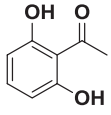
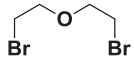
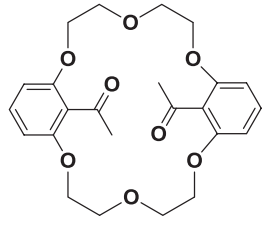
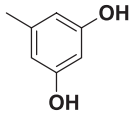
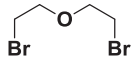
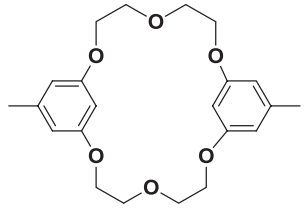
Entry	Reactant	Alkyl halide	Product	% yield
1				89
2				85
3				81
4				82
5				92
6				78
7				87
8				86
9				76
10				49

[a]Reaction conditions: Phenol (2 mmol), dihaloalkane (1 mmol), anhydrous K_2CO_3 (2 mmol), DMSO (10 mL), Time (4–6 h).
[b]Yields of isolated products are reported.

spectra. NMR spectrums of product were obtained using Bruker AC-200 MHz spectrometer with TMS as the internal standard. Column chromatography was performed on silica gel, Merck grade 60–120 mesh size. TLC was performed on 0.25 mm E. Merck precoated silica gel plates (60 F254).

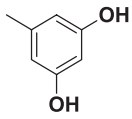
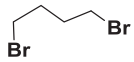
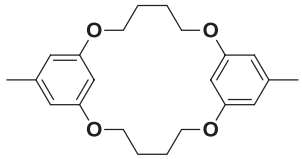
Table 3. Synthesis of cyclic and crown ethers.



Entry	Reactant	Alkyl halide	Product	% Yield[b]
1				74
2				78
3				76
4				72
5				82
6				80
7				78

(*Continued*)

Table 3. (*Continued*).

Entry	Reactant	Alkyl halide	Product	% Yield[b]
8				84

[a]Reaction conditions: Phenol (2 mmol), dihaloalkane (2 mmol), anhydrous K_2CO_3 (4 mmol), DMSO (10 mL) Time (6–8 h).
[b]Yields of isolated products are reported.

Typical procedure for synthesis of aliphatic bridged diaryloxy compounds (Table 1, entry 1)

To a solution of 2,4-dichloro phenol (1 mmol, 0.244 gm) in DMSO (10 mL), anhydrous potassium carbonate (1 mmol, 0.138 gm) was added in small portion and the solution was stirred continuously maintaining the inert atmosphere. To the above yellow coloured solution, 1,4-dibromo butane (1 mmol, 0.121 gm) was injected with syringe. The reaction mixture was stirred for 2 h. The completion of the reaction was monitored by TLC and reaction mixture was extracted with ethyl acetate (5 mL), washed two times with dil. HCl (2N) to neutralise the potassium carbonate. Finally the mixture was washed with ice cold water. The organic layer was treated with anhydrous sodium sulfate and evaporated under reduced pressure. A white coloured solid product was obtained which was further characterised by IR, NMR spectroscopy and HRMS technique.

Typical procedure for synthesis of aliphatic bridged diaryloxy compounds (Table 2, entry1)

To a solution of salicylaldehyde (2 mmol, 0.244 gm) in DMSO (10 mL), anhydrous potassium carbonate (2 mmol, 0.276 gm) was added in small portion and the solution was stirred continuously maintaining the inert atmosphere. To the above yellow coloured solution, 1,4-dibromo butane (1 mmol, 0.216 gm) was injected with syringe. The reaction mixture was stirred for 2–4 h. The completion of the reaction was monitored by TLC and reaction mixture was extracted with ethyl acetate (20 mL), washed two times with dil. HCl (2N) to neutralise the potassium carbonate. Finally the mixture was washed with ice cold water. The organic layer was treated with anhydrous sodium sulfate and evaporated under reduced pressure. A white coloured solid product was obtained which was further characterised by IR, NMR spectroscopy and HRMS technique.

Typical procedure for synthesis of cyclic ethers and crown ethers (Table 3, entry 5)

To a solution of 2,6-dihydroxy acetophenone (2 mmol, 0.304 gm) in DMSO (10 mL), anhydrous potassium carbonate (4 mmol, 0.552 gm) was added in small portions and the solution was stirred continuously maintaining the inert atmosphere. To the above yellow coloured solution, 1, 4-dibromo butane (2 mmol, 0.432 gm) was injected with syringe. The reaction mixture was stirred for 6–8 h. The completion of the reaction was monitored by TLC and the reaction mixture was extracted with dichloromethane (2 × 20 mL), washed two times with dil. HCl (2N) to neutralise the potassium carbonate. Finally, the mixture was washed with ice cold water. The organic layer was treated with anhydrous sodium sulfate and evaporated under reduced pressure. A colourless oily product was obtained which was further characterised by IR, NMR spectroscopy and HRMS techniques.

Conclusions

We have successfully demonstrated one pot method for the synthesis of some novel crown ethers, cyclic ethers (72–84%) and the aliphatic bridged diaryloxy and oxybisalkane diaryloxy compounds (82–90%) at ambient conditions using K_2CO_3/DMSO. Various types of substituted phenols and different dihalo alkane compounds were used for the synthesis of the aliphatic bridged diaryloxy compounds in one pot method which is very useful in the polymer chemistry applications for the synthesis of polybenzoxazines. The aliphatic bridge between the two phenol rings was very easily tailored by using dibromo propane, dibromo butane, dibromo pentane etc. Cyclic ethers and the crown ethers were also synthesised in one pot by varying the alkylating reagents (dibromo propane, dibromo butane, 2-bromo ethyl ether etc.). The ring size of the crown ether and the cyclic ethers can be further increased by the selection of the various dihalides which are known to be very suitable for the extraction of various types of metals including the radioactive elements and also for the resolution of the optical isomers. The carbonyl group attached to the phenols were shown to be easily collapsible inside the crown ether cavities, thereby minimising the steric interaction in the resultant compounds.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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