SUGGESTION MECHANISMS OF SYNTHESIS A NOVEL CHIRAL COMPOUND: (*R*) AND (*S*)-1-(2-BENZYLOXY-3-METHOXYPHENYL)-2,2,2-TRICHLOROETHYL BENZENESULFONATE

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Abstract: A novel chiral compound was synthesized from the reaction between the new benzimidazole, 2-(2-benzyloxy-3-methoxyphenyl)-1*H*-benzimidazole **8** and benzenesulfonyl chloride **9** in dry dichloromethane DCM at 45ºC for 10 hr in the presence of 4-*N*,*N*-dimethyl aminopyridine DMAP **12** as a catalyst was expected to obtain 2-(2-benzyloxy-3-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-benzimidazole, **10**. Unfortunately, a novel chiral compound (*R*) and (*S*) 1-(2-benzyloxy-3-methoxyphenyl)-2,2,2-trichloroethyl benzenesulfonate **11** was obtained as a single crystal (59% yield) with melting point of 58.4°C. We suggest preliminary mechanisms of the formation of **11** by two ways: a) It is formed benzimidazolide ion **13** that is attacked from benzene sulfonic acid **15**, which is hydrolyzed from **9** to form *N*-(2-aminophenyl)-2-(benzyloxy)-3-methoxybenzimidine benzenesulfonate **17**, or b) that benzimidazole **8** is hydrolyzed to its basic compound benzyl *o*-vanillin **18**, which it attacks the 4-(dimethylamino)-1-(phenylsulfonyloxy) pyridinium chloride **21** to form (2-(benzyloxy)-3-methoxyphenyl) (phenylsulfonyloxy) methylium ion **22**. However, the mechanism of this reaction still is under investigation.

Keywords: Benzimidazole; Benzimidazolide ion; benzenesulfonyl chloride; Benzenesulfonic acid; 4-*N*,*N*-Dimethyl aminopyridine; (*R*) and (*S*)-1-(2-Benzyloxy-3-methoxyphenyl)-2,2,2-trichloroethyl Benzenesulfonate.

Introduction

Between 1977 and 1980, Gill's teams were synthesized three novel compounds **1–3**, which they distinguished by a new bulky functional group as a *p*-toluene sulphonate ester. Two of those derivatives showed as (*R*) and (*S*) enantiomers **2** and **3**, while **1** showed as (*S*) configuration (Begley *et al*., 1978; Gill *et al*., 1979; Figure 1).

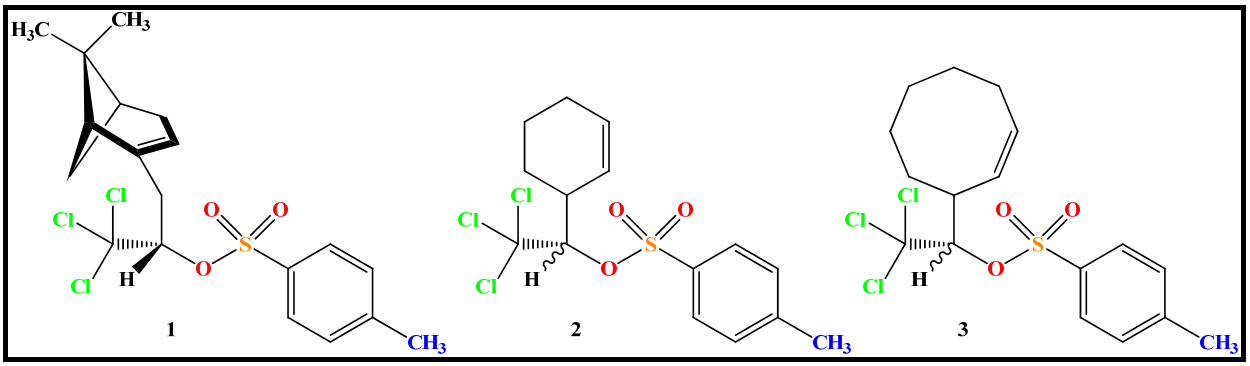
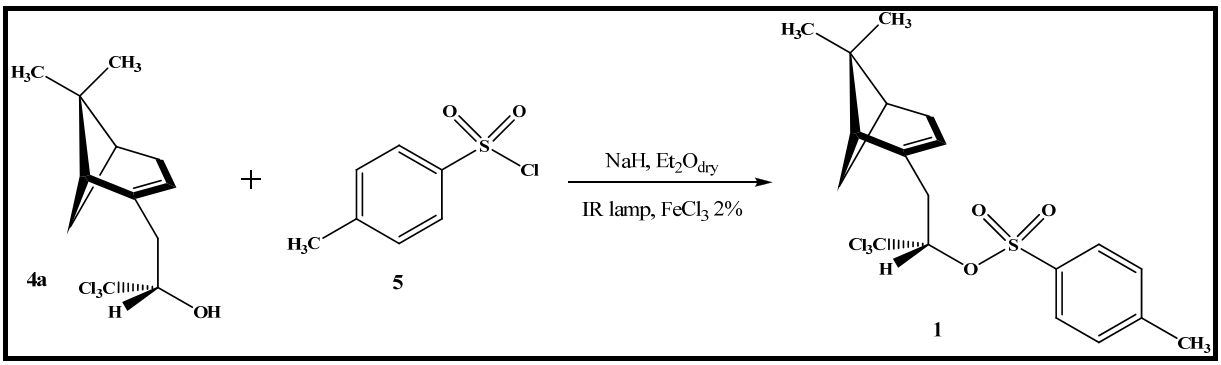
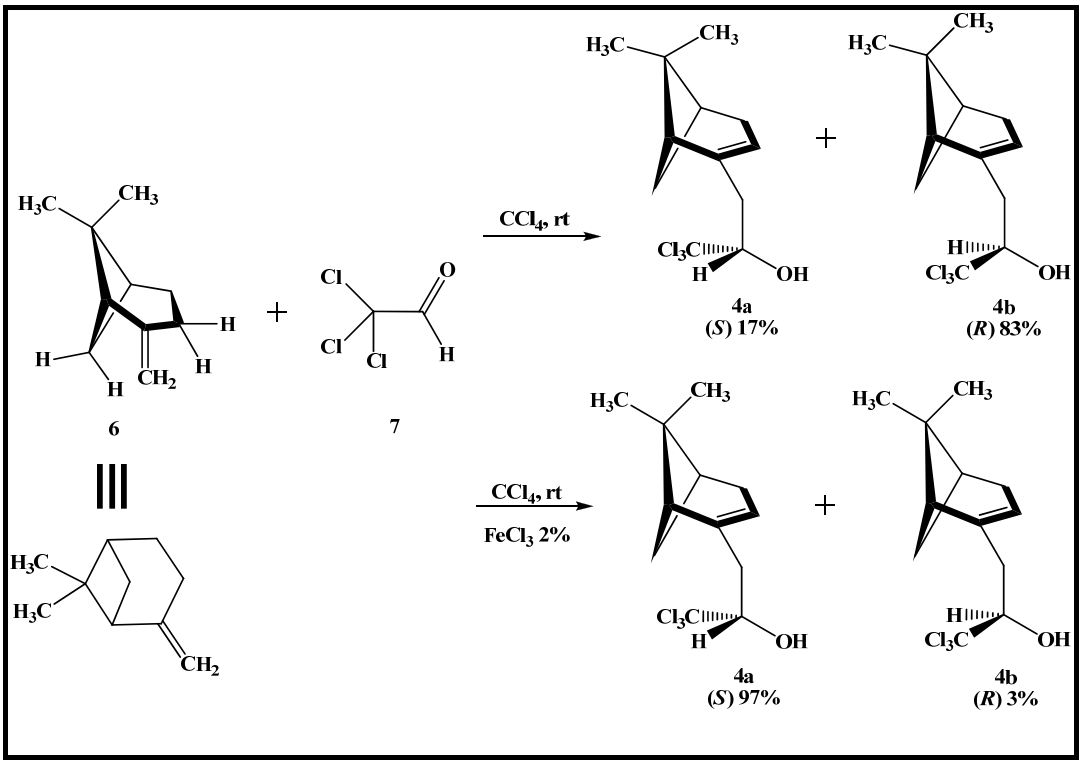


Figure 1: *p*-Toluene sulphonate esters **1–3** (Begley *et al*., 1978; Gill *et al*., 1979).

Those derivatives were formed by the reaction of **4a** with toluene-*p*-sulphonyl chloride or tosyl chloride **5** (Scheme 1). Compound **4** was formed as enantiomers (*S*) **4a** and (*R*) **4b** with ratio 17:83 by the addition of (–)-(1*S*, 5*S*)-pin-2(10)-ene **6** to chloral **7**, while the ratio was enhanced in the presence of $FeCl_3$ 2% as a bulky Lewis acid catalyst to 97:3, respectively, which were confirmed by ^{1}H and ^{13}C NMR experiments and X–ray analysis, (Begley *et al*., 1978; Gill *et al*., 1979; Scheme 2). Derivatives **2** and **3** were synthesized as enantiomers (*R*) and (*S*) from the reaction of cyclohex-1-ene and cycloocta-1-ene with **5**, respectively (Figure 1).

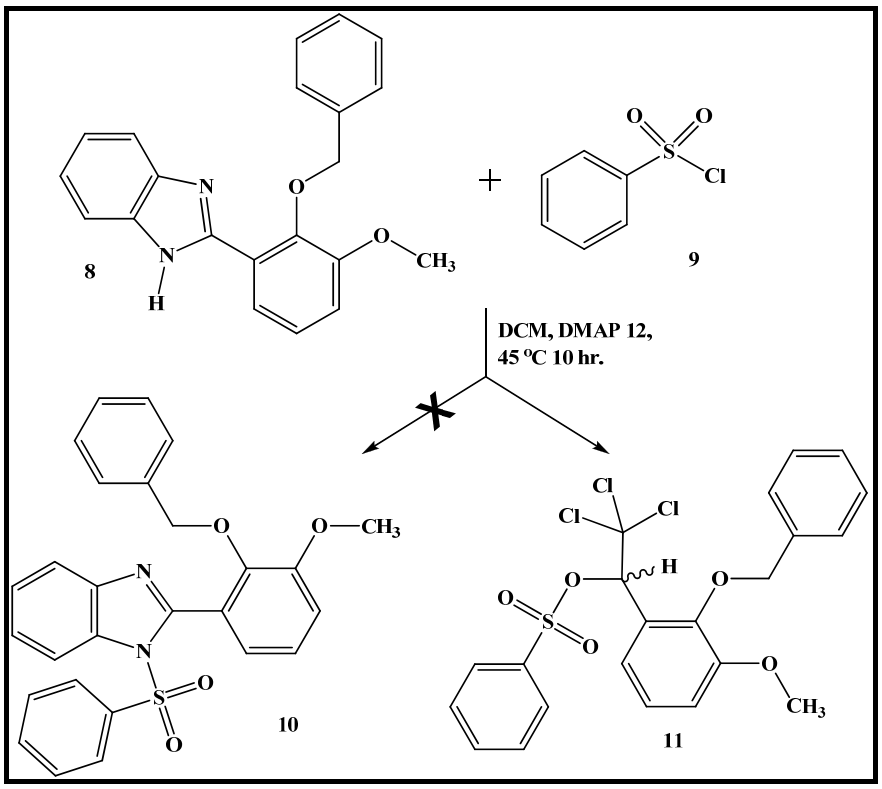


Scheme 1: Derivative **1** was prepared by (Begley *et al*., 1978)



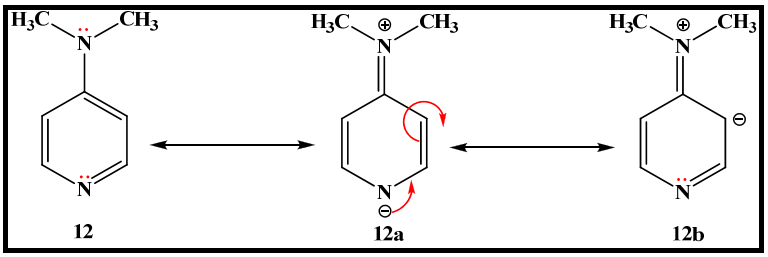
Scheme 2: Gill *et al*. method to prepare derivative of **4** (Gill *et al*., 1979)

In 2007, a novel chiral compound (*R*) and (*S*) 1-(2-benzyloxy-3-methoxyphenyl)-2,2,2-trichloroethyl benzenesulfonate **11** was obtained from the reaction between the new benzimidazole, 2-(2-benzyloxy-3-methoxyphenyl)-1*H*-benzimidazole **8** and benzenesulfonyl chloride **9** in dry dichloromethane DCM at 45ºC for 10 hr in the presence of 4-*N*,*N*-dimethyl aminopyridine DMAP **12** as a catalyst. This reaction was expected to obtain 2-(2-benzyloxy-3-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-benzimidazole, **10** but it is formed **11** (Al–Douh *et al*., 2007; Al–Douh, 2012; Scheme 3).



Scheme 3: Synthetic route towards the compound **11** (Al–Douh, 2012)

Additionally, DMAP **12** was greatly facilitated acylation of hindered alcohols with carboxylic acid anhydrides (Steglich and Hofle, 1969; Steglich, and Hofle, 1970; Hofle and Steglich, 1972; Hofle, *et al*., 1978), which it is considered the most effective acylation catalyst comparing to other familiars derivatives (Hassner, *et al*., 1978), including, **12** is faster 20,000 times than pyridine in acylation (Hofle, *et al*., 1978). The resonance of **12** showed the localization of the pair of electron in nitrogen atom when it is sharing with the double bonds of the pyridine ring, which it has to share with other nitrogen atom, to localized the negative charge in *ortho* and *para* positions of tertiary amine (Scheme 4).



Scheme 4: The resonance of **12** (Hassner, *et al*., 1978).

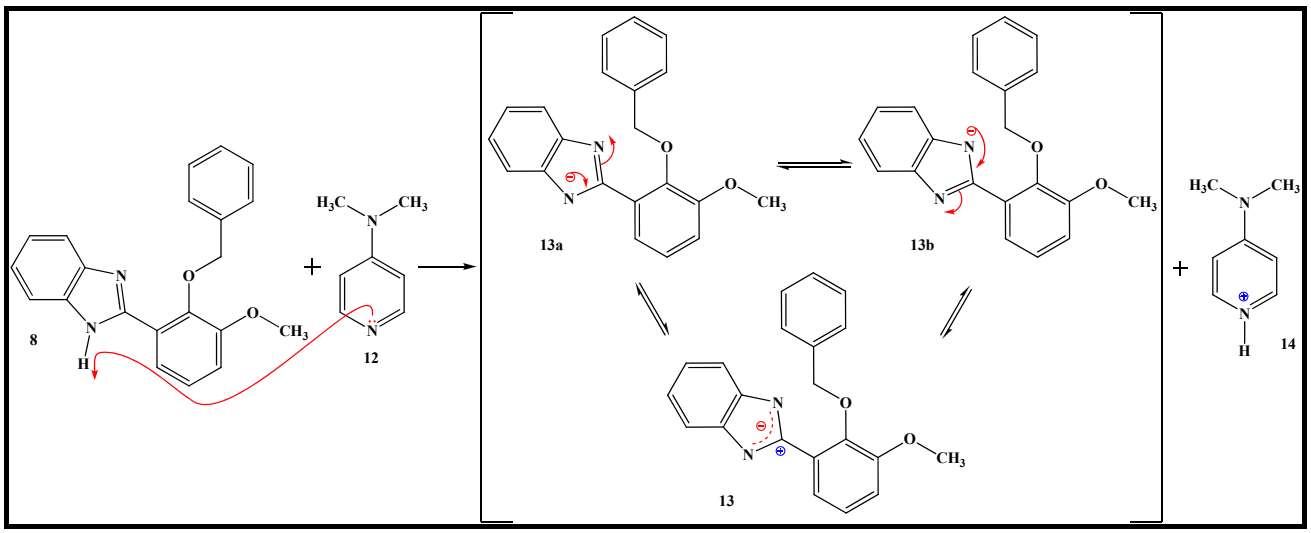
In our previous work, we have been reported the synthesis of **11** and confirmed by FTIR, HRMS, X–Ray crystallography (Al–Douh *et al*., 2007), 1D and 2D NMR spectroscopy (Al–Douh, 2012). The mechanism of this reaction was unknown. Therefore, we suggest of preliminary mechanisms of the formation of **11** by two ways:

Catalytic Protonation Mechanism (CPM):

This mechanism has four steps.

The first step in CPM:

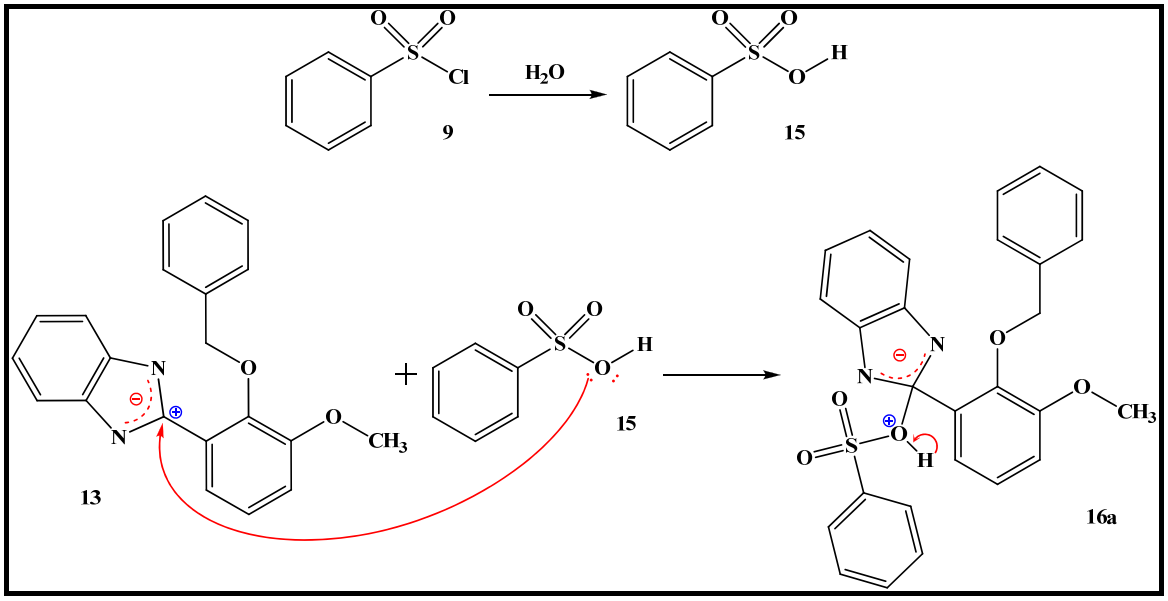
This step is started by the formation of benzimidazolide ion **13** as an intermediate, which it is formed from the reaction between the benzimidazole **8** and the catalyst DMAP **12**. The pair of electron of nitrogen atom in the pyridine ring of **12** attacked that proton in the tertiary amine of **8** to form two an ionic intermediate structures **13a** and **13b** and unstable protonated ion 4-*N*,*N*-dimethyl aminopyridinium ion **14** (Scheme 5). It is called benzimidazolide ion step.



Scheme 5: The formation of the benzimidazolide ion **13**.

The second step in CPM:

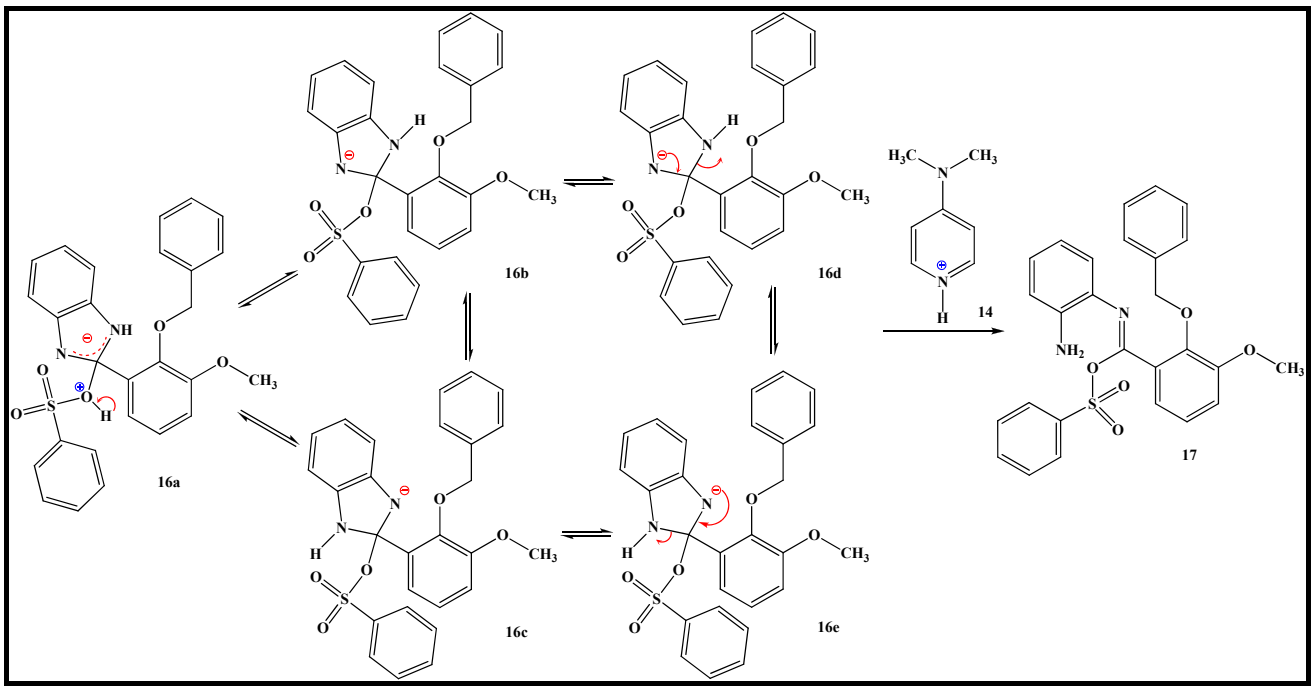
On the other hand, benzene sulfonic acid **15** is formed from **9** by hydrolysis, then, the benzimidazolide ion **13** is nucleophilic attacked from **15** to form *N*-(2-aminophenyl)-2-(benzyloxy)-3-methoxybenzimidine benzenesulfonate **17**, through an intermediate **16** (Scheme 6). This step called hydrolyzed step.



Scheme 6: The hydrolysation of **9** and formation of **16**.

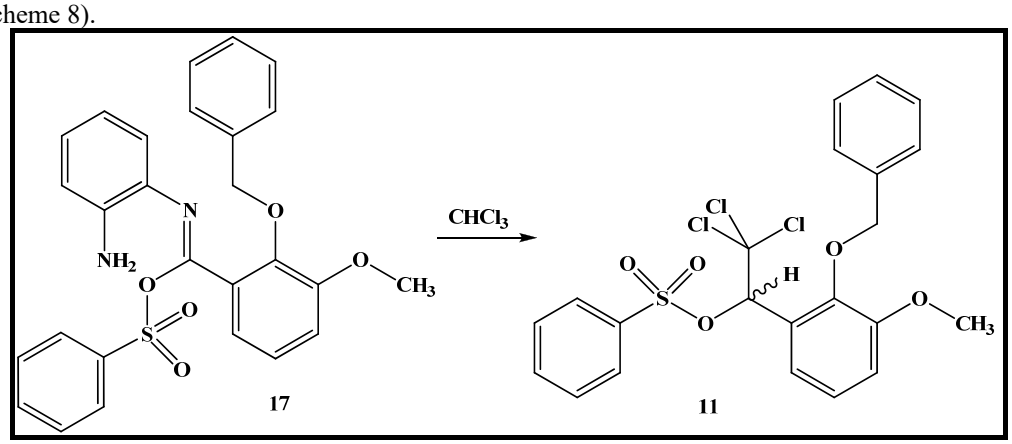
The third step in CPM:

This step is tautomerism step, which an intermediate **16a** was tautomerised when it losses proton to form both ions **16b** and **16c** that converted to both tautomer ions **16d** and **16e**, respectively, followed to form **17** in the presence of **14** (Scheme 7).



Scheme 7: The tautomerization of ion **16** to form **17**.

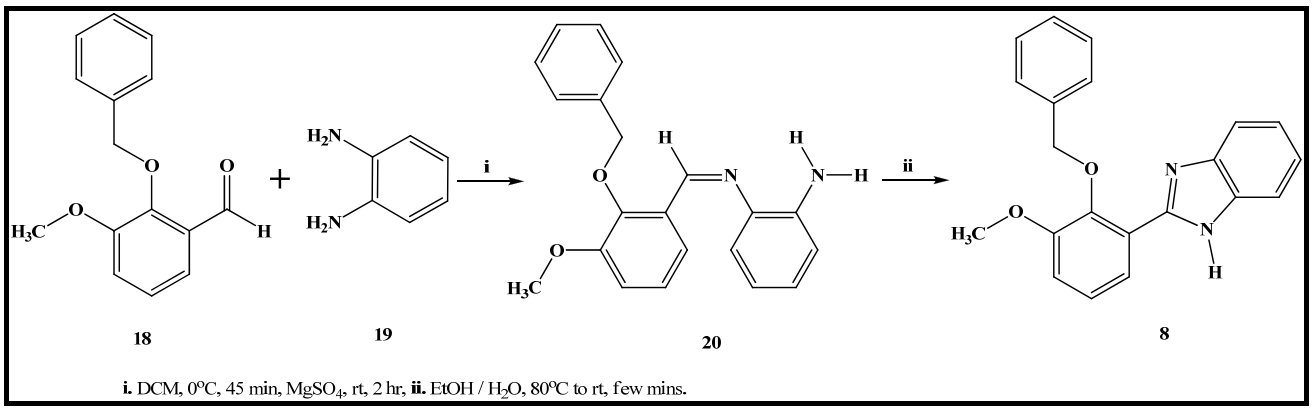
The fourth step in CPM:
This step unclear to convert **17** to **11**. It is deemed a free radical step carried **17** in the presence of $CHCl_3$ as a solvent to form **11** (Scheme 8).



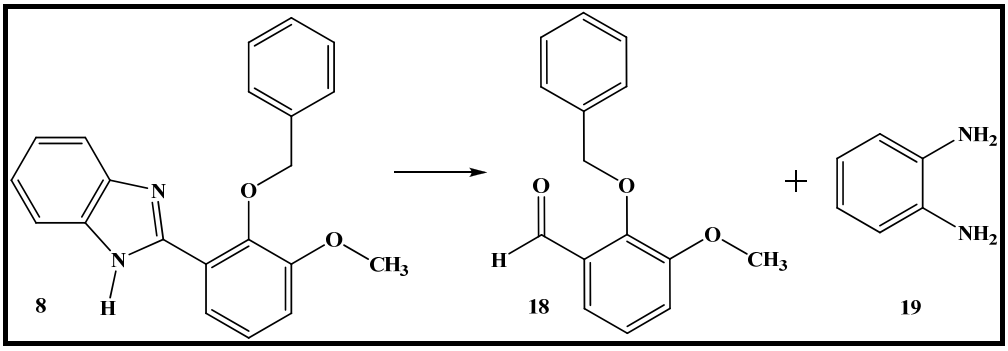
Scheme 8: The formation of **11**.

Hydrolysis Mechanism (HM):
This mechanism has three steps.

The first step in HM:
This is called the hydrolysis of benzimidazole step, which it is started by the hydrolysis of **8** to its raw materials benzyl-*o*-vanillin **18** and phenylenediamine **19** (Scheme 10), while the benzimidazole **8** was synthesized by the reaction between **18** and **19** in DCM at low temperature with other derivatives (Al–Douh, *et al*., 2006*a*,*b*; Al–Douh, *et al*., 2009; Al–Douh, *et al*., 2011; Scheme 9).



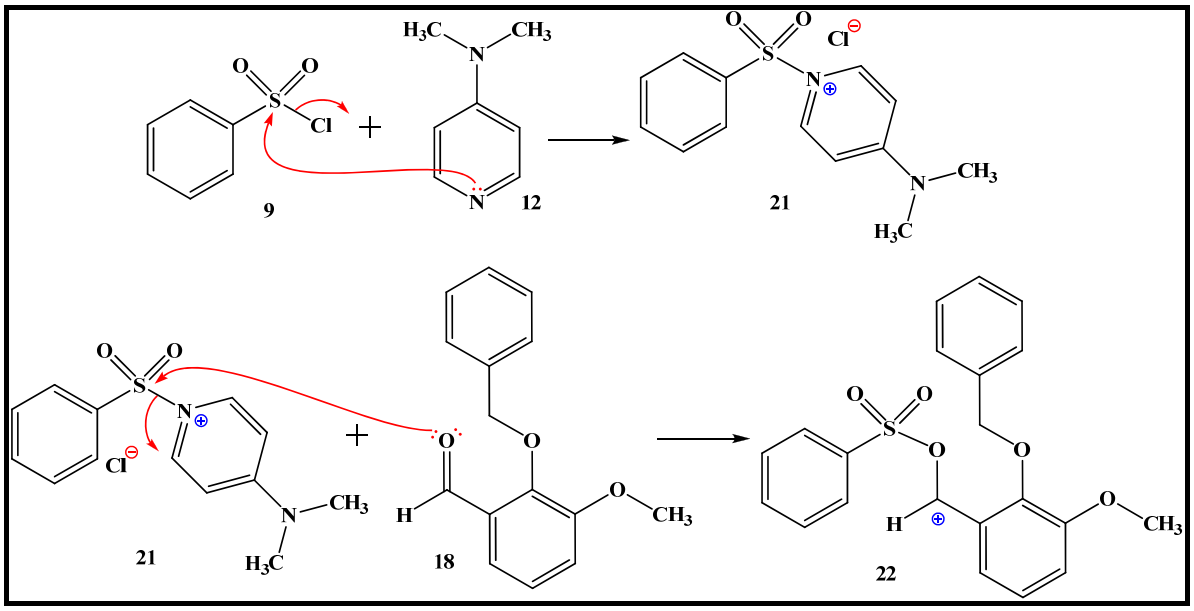
Scheme 9: The formation of **8**.



Scheme 10: The hydrolysis of **8**.

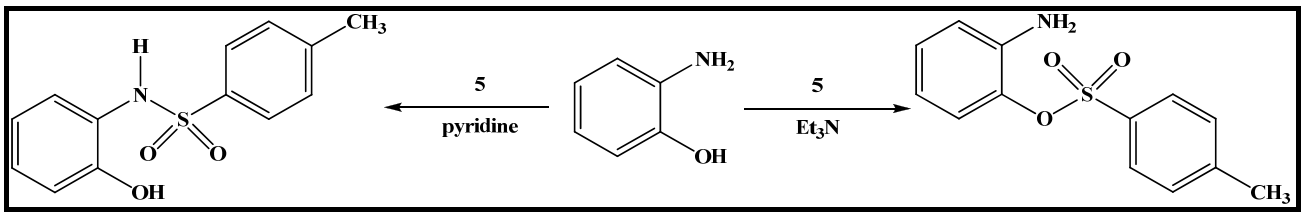
The second step in HM:

The benzosulphonyl chloride **9** is attacked by nucleophilic catalysis **12** to form the 4-(dimethylamino)-1-(phenylsulfonyloxy) pyridinium chloride **21**, then, the pair of electrons on the *O* atom in **18** attacked to form (2-(benzyloxy)-3-methoxyphenyl) (phenylsulfonyloxy) methylium ion **22** (Scheme 11). This step is called nucleophilic catalysis mechanism or two tetrahedral mechanisms (Smith, 2013).



Scheme 11: The formation of **22** from **18**.

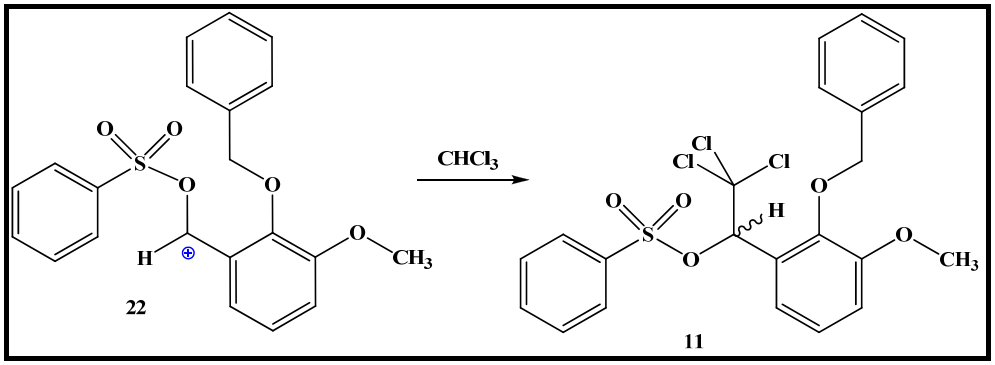
Kurita reported the selectivity tosylation by **5** of *o*-aminophenol in both pyridine and triethyl amine as solvents. The tosyl group was substituted in amino functional group in pyridine, while it was substituted in hydroxyl functional group in triethyl amine (Kurita, 1974; Scheme 12).



Scheme 12: The tosylation of *o*-aminophenol (Kurita, 1974).

The third step in HM:

This step also unclear to convert **22** to **11**. It is deemed a free radical step carried **22** in the presence of $CHCl_3$ as a solvent to form **11** (Scheme 13).



Scheme 13: The formation of **11** from cation **22**.

CPM *vs.* HM:

We expect CPM more than HM, in first step; ion **13** was strongly formed in benzimidazolide ion step than hydrolyzed step of **8** to **18** and **19**, whereas the hydrolyzed products from **8** to its raw compounds do not exist. On the other hand, compound **17** in steps two and three of CPM mechanism formed from ion **13** crossed tautomerised of **16**, while the methylium cation **22** will be formed from **18** as raw material if it was really hydrolyzed from **8** in HM mechanism. Both last steps in CPM and HM mechanisms to form **11** from **17** and **22** in the respective are unclear. It is believed that compound **11** is formed in the presence of $CHCl_3$. However, these steps need more studies to prove which one forms **11**.

Conclusion

In this work, both suggested mechanisms catalytic protonation mechanism **CPM** and hydrolysis mechanism **HM** to form a novel chiral compound (*R*) and (*S*) 1-(2-benzyloxy-3-methoxyphenyl)-2,2,2-trichloroethyl benzenesulfonate **11** were presented.

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