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Synthesis of 8-Methoxy-1-Tetralone

Ajoy K. Banerjee[1], Liadis Bedoya[1], Alexis Maldonado[1], Lisbeth Mendoza[1], Elvia V. Cabrera[2,3]

[1]Chemistry Center, Venezuelan Institute of Scientific Research (IVIC), Caracas, Venezuela

[2]Faculty of Chemical Engineering, Central university of Ecuador, Quito. Ecuador

[3]Molecules and Functional Materials Research group (MoleMater), Quito, Ecuador

Correspondence: Ajoy K. Banerjee, Chemistry Center, Venezuelan Institute of Scientific Research (IVIC), Cascaras. Venezuela. E-mail: aabanerje@gmail.com

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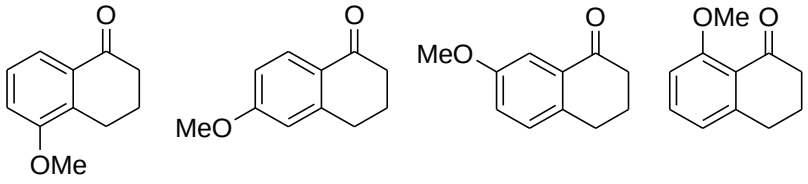
Abstract

Several methods have been developed for the synthesis of 8-methoxy-1- tetralone **4**. The applications of some named organic reactions can be observed during the synthesis of tetralone **4.** Attempts have been made to achieve the direct conversion of 5-methoxy-1-tetralone into the tetralone **4.** The method for the ring expansion of tertiary cyclobutanol **30** catalyzed by silver salts has proved useful to obtain the title tetralone **4.**

Keywords: 8-methoxy-1-tetralone, condensation, bromination, cyclization, Eaton's reagent

1. Introduction

The substituted 1-tetralones e.g. 5-methoxy **1**, 6-methoxy **2** and 7-methoxy **3** (**Fig 1**) which are commercially available have played an important role in the synthesis of (Poon et al., 2008) natural and non-natural products.



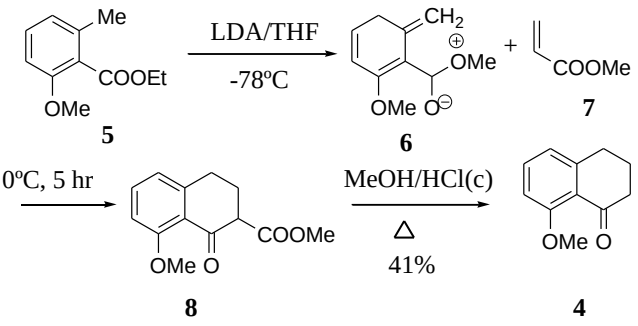
1 **2** **3** **4**

Figure 1. Substituted methoxy 1-tetralone

8-methoxy-1-tetralone **4,** unlike the mentioned tetralones, though available in commerce is very expensive (Sigma-Aldrich). Tetralone **4** has been utilized (Yang et al., 2008) as starting material for the synthesis of ARQ-501 (β -lapchone) human blood metabolites and for the synthesis of some of CYP27A1 (employed for the treatment of vitamin D deficiency) (Aboraia et al., 2010). In addition the tetralone **4** has been used for the synthesis (Miyashite et al., 2003) of antitumor antibiotic (±) spiroxin C. Due to the several uses of the tetralone **4** as starting material for the synthesis of organic compounds, many synthetic approaches have been developed to obtain the tetralone **4**. The computational studies indicate that the 5-, 6-, and 7-methoxy-1-tetralone are energetically favored over 8-methoxy-1 tetralone by 20-40 KJ mol^{-1}. Thus it is concluded that the low availability of 8-methoxy-1-tetralone **4** is due to electronic and steric requirements resulting from the repulsion occurring between the carbonyl oxygen atom and the bulky methoxy substituent (Matos et al., 2009). Some selected syntheses of 8-methoxy-1-tetralone **4** are described below.

2. Synthesis of 8-Methoxy-1-Tetralone by Tarnchompoo, Thebatanounth and Thebtaranounth.

Thebtaranounth and collaborators (Tarnchompoo et al., 1986) have devised an interesting approach for the synthesis of tetralone **4.** The synthetic details are described in the **Scheme 1**. Treatment of ethyl 6-methoxy-2-methyl benzoate **5** (Hauser & Pogany, 1980) with lithium diisopropylamide in THF generates the anion **6** (Hauser et al., 1980). The tandem Michael addition-Dieckmann condensation (Kodpinid et al., 1984) of the anion **6** with methyl acrylate **7** forms the bicyclic ester **8** which without purification is hydrolyzed and decarboxylated by heating with methanolic conc. hydrochloric acid overnight to obtain the tetralone **4** in 41% yield (**Scheme 1).**

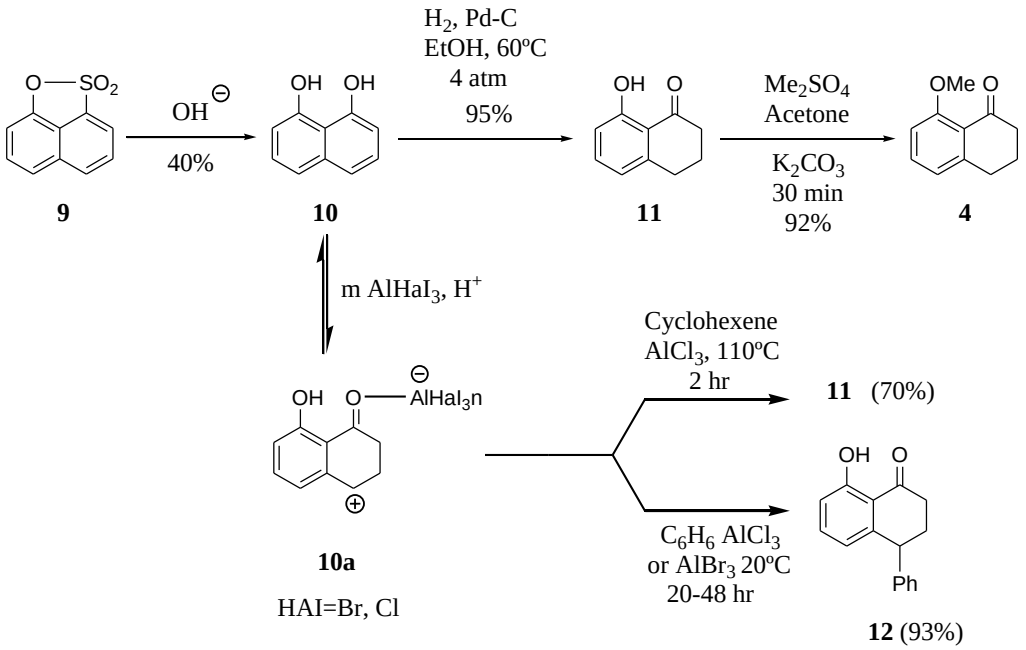


Scheme 1. Synthesis of 8-methoxy-1-tetralone **4** by Tranchompo et al

The noteworthy aspect of the synthesis is the intelligent use of the tandem Michael- Dieckmann condensation to obtain the bicyclic ester **8**. The present synthesis deserves the following comments : (a) the synthesis of the starting material **5** requires five steps [(i) condensation of crotonaldehyde and ethyl acetoacetate, (ii) intramolecular cyclization with acid , (iii) bromination, (iv) aromatization, (v) methylation] and thus the synthesis of the tetralone **4** involves 8 steps; (b) the methyl acrylate has a tendency to undergo polymerization and thus should be purified before use; (c) the procedure for isolation of tetralone is laborious. The synthetic approach is attractive but not suitable for the gram scale preparation of the tetralone **4.**

3. Synthesis of 8-Hydroxy-1-Tetralone by Kaye, Matthews and Scala. Synthesis of 8-- Methoxy-1-Tetralone by Bilger, Demerseman and Royer

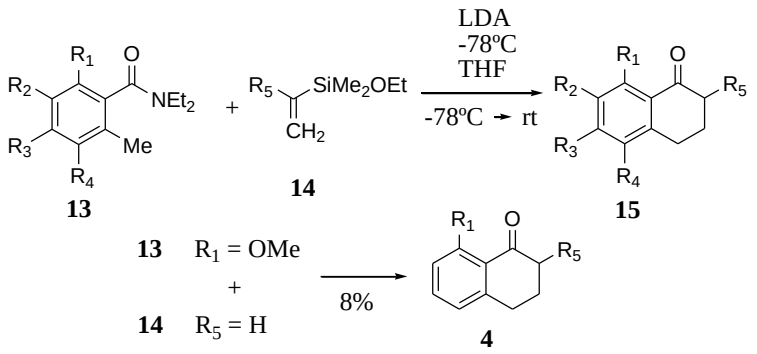
8-methoxy-1-tetralone **4** has also been prepared (Bilger et al., 1987) by methylation of 8-hydroxy-1-tetralone **11** (**Scheme 2**) with dimethylsulfate in acetone and anhydrous potassium carbonate. 8-hydroxy -1-tetralone **11** can be obtained (Kaye et al., 1964) by the hydrogenation of the naphthalene 1,8-diol **10** in absolute ethanol with palladium –charcoal (Pd-C, 10 %) .The naphthalene 1,8-diol **10** is commercially available and also has been prepared (Poirier et al., 1996) by stirring in an argon atmosphere naphthosultone **9** suspended in a melted mixture of sodium hydroxide and potassium hydroxide about 30 min. It is worthwhile to mention that naphthalene -1,8-diol **10** if heated with 5-fold molar aluminium chloride in a pressure tube at 110^{O}C (oil bath temperature) (Zhu & Koltunov, 2016) affords the 8-hydroxy-1-tetralone **11** (**Scheme 2**). The diol **10** smoothly reacts with benzene at room temperature in the presence of aluminium chloride or aluminium bromide to give 8-hydroxy-4-phenyl-1-tetralone **12** in 93% yield. The diol **10** on treatment with aluminium chloride forms the electrophilic species **10a** as key intermediate (**Scheme 2**) which produces the tetralones **11** and **12** respectively according to the experimental condition as depicted in **Scheme 2**.



Scheme 2. Synthesis of 8- methoxy-1-tetralone and 8-hydroxy-1-tetralone

4. Synthesis of 8-Methoxy-1- Tetralone by Date, Watanabe and Furukawa

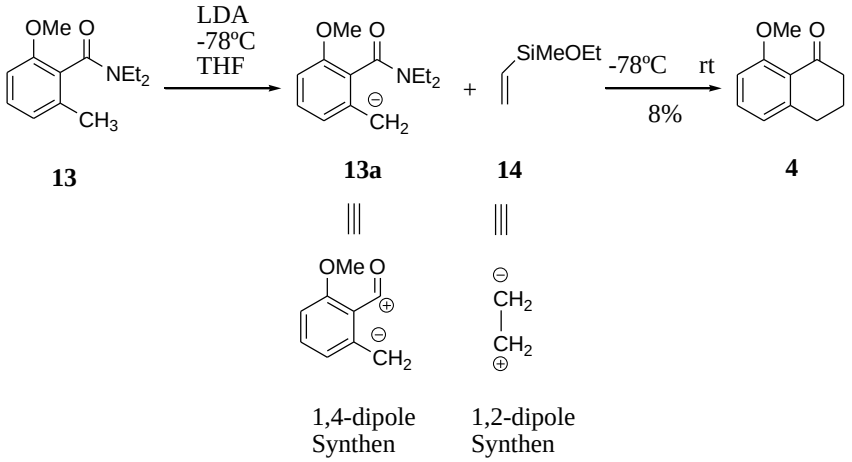
It has been reported (Date et al., 1990) that various methoxy substituted *ortho*-tolumide **13** can be made to react with ethoxy substituted vinylsilanes **14** in presence of LDA at -78^{O}C to yield the substituted 1-tetralone **15** in moderate yield. The general objective has been shown in **Scheme 3.**



Scheme 3. Synthesis of 8-methoxy-1-tetralone from the reaction of *ortho*-tolumide and vinyl silanes by Date, Watanabe and Furukawa

The compound **13** (**R1=OMe, R2=R3=R4 = H**) reacts with vinylsilanes **14** (**R5=H**) to yield the tetralone **4** in 8% yield. N,N-diethyl *ortho*-toluamide **13** is lithiated in tetrahydrofuran (THF) to form the lithio species **13a** (**Scheme 4**) which on treatment with vinylsilane **14** (R5=H) at -78^{O}C yield the tetralone **4.**

The mode of cyclization of **13** and **14** has been depicted in **Scheme 4.** The 1,4- dipole synthon combines with 1,2-dipole synthon to yield the tetralone **4**. In conclusion it can be said that the lithiated *ortho*-toluamides and related compounds behave as 1,4-dipole synthons in the reaction with vinylsilanes to afford various 1-tetralone derivatives in a one-pot tandem Michael addition-cyclization process. The use of *ortho*-toluamide, vinyl silane and LDA in the proportion of 2.0:2.1:1.0 is necessary to obtain a good yield of the tetralone. Instead of LDA, sec-BuLi or tetramethylethylene diamine (TMEDA) has also been used. The methoxy-substituted *ortho*-toluamides are prepared by the direct lithiation of the corresponding methoxy-substituted N,N-diethylbenzamides with MeI under the standard *ortho*-lithiation conditions (Narasimhan & Mali, 1983; Watanabe et al., 1984).



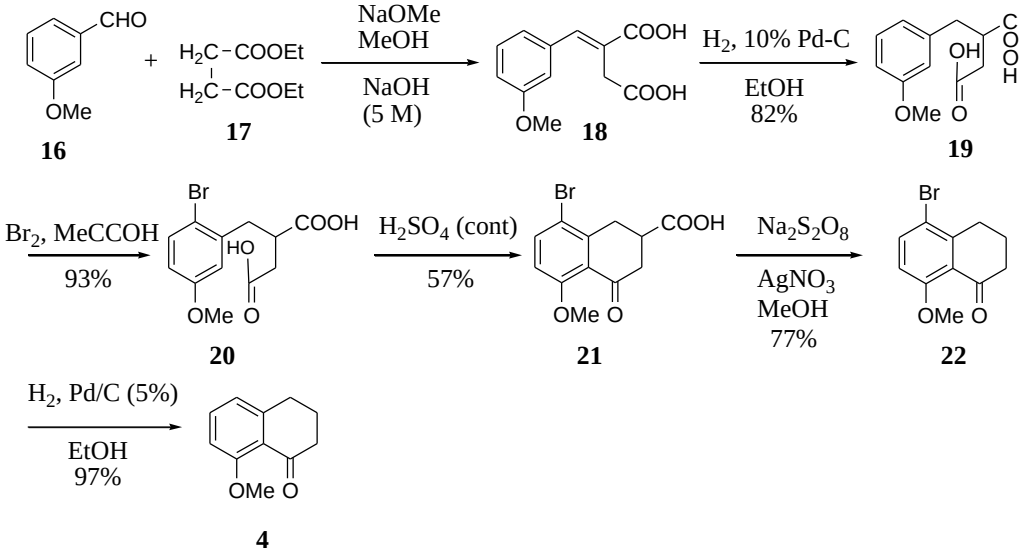
Scheme 4. Mechanism of the transformation of tolumide to tetralone

5. Synthesis of 8-Methoxy-1-Tetralone by Cabrera and Banerjee

A simple synthesis of 8-methoxy-1-tetralone has also been developed (Cabrera & Banerjee, 2010). The synthetic details are described in **Scheme 5**.

The condensation of m-methoxy benzaldehyde **16** with ethyl succinate **17** yields the reported (Yanagi et al., 2001) acid **18** which on catalytic hydrogenation produces the acid **19.** The bromination of **19** furnishes the bromoacid **20** which undergoes cyclization with conc. sulfuric acid to afford 3 –carboxy bromo tetralone **21**. The tetralone **21** is subjected to decarboxylation (Fristadt et al., 1983) by heating with a mixture of sodium persulfate and silver nitrate in acetonitrile to obtain the bromo tetralone **22** which is converted into the desired tetralone **4** by catalytic hydrogenation. The present

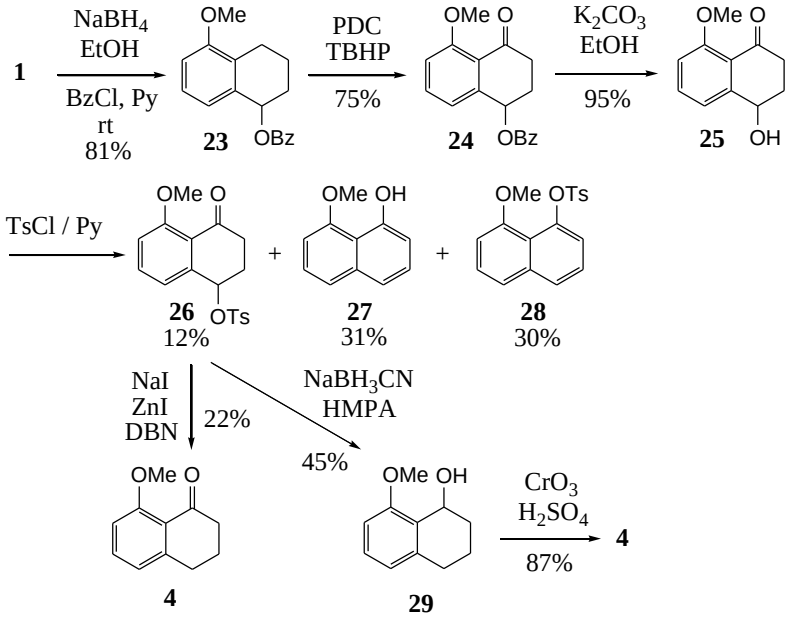
procedure involves eight steps and affords an overall yield of the tetralone **4** in 40% which is very similar to the yield (41%) reported (Tarnchompoo et al., 1986). The starting material of the present approach (Cabrera & Banerjee, 2010) is commercially available. Most of the intermediates are obtained in good yield.



Scheme 5. Transformation of 3-methoxybenzaldehyde into 8-methoxy-1-tetralone

6. Synthesis of 8-methoxy-1-tetralone by Banerjee, Bedoya, Adherian, Cabrera and Kariney

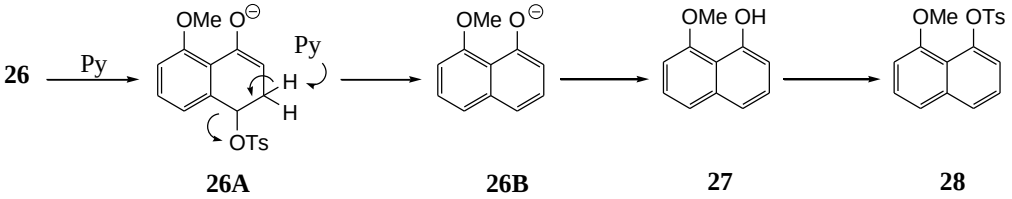
Banerjee and collaborators have reported the transformation of the 5 methoxy-1-tetralone **1** into the 8-methoxy-1-tetralone **4** (Banerjee etal. 2010). The synthetic route is depicted in **Scheme 6.**



Scheme 6. Transformation of tetralone **1** to tetralone **4**

The known alcohol (Banerjee et al., 2010) obtained by the metal hydride reduction of the tetralone **1** (Banerjee et al., 2004) on bezoylation yields the benzoyl derivative **23** which on oxidation (Chidambaran & Chandrasekaran, 1987) yields the tetralone **24**. The alcohol **25**, prepared by the alkaline hydrolysis of **24,** on tosylation with tosylchloride and pyridine yields the tosylate **26** (12%), the alcohol **27** (31%) (Sibi et al., 1986) and the tosylate **28** (30%). Detosylation of **26** attempted by heating with sodium iodide and zinc (Fujimoto & Tatsuno, 1976) in dimethoxyethane (DME) produces tetralone **4** in 22% yield. The tosylate **26** if heated with sodium cyanoborohydride ($NaBH_3CN$) and hexamethylphosphoramide (HMPA) undergoes detosylation (Hutchins et al., 1977) and affords the tetraol **29** (45%) which on oxidation with Jones reagent (Bowers et al., 1953) provides the tetralone **4** in 87% yield. The method involves

four steps and the yield of the tetralone is not very satisfactory. The mechanism of the formation of the products **27** and **28** from **26** is exhibited in **Scheme 7**.

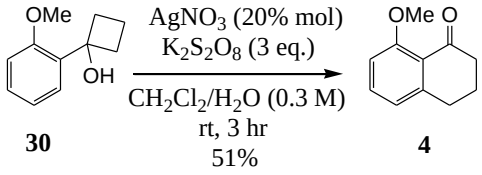


Scheme 7. Pyridine catalysed rearrangement of the tosylate

The tosylate **26** on treatment with pyridine forms the intermediate **26A** which generates the anion **26B** that produces naphthol **27** and the tosylate **28** respectively.

7. Synthesis of 8-Methoxy-1-Tetralone via Silver-catalyzed ring Expansion Procedure by Yu, Zhao, Liang, Bao and Zhu

Several tertiary cyclobutanols regardless of the electronic properties and steric hindrance of the substituents undergo ring expansion catalyzed by silver salts ($AgNO_3$) in presence of an oxidant ($K_2S_2O_8$) to yield 1-tetralone (Yu et al.2015). This finding has been utilized as depicted in **Scheme 8** for the synthesis 8-methoxy-1-tetralone **4** from the cyclobutanol **30**.

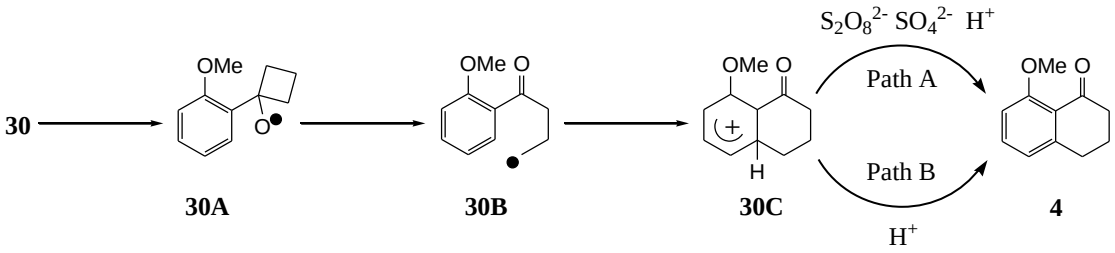


Scheme 8. Synthesis of 8-methoxy-1-tetralone via silver-catalyzed ring expansion

Mechanism of the reaction

A possible mechanism for the above mentioned transformation has been suggested in **Scheme 9.** The cyclobutoxy radical **30A**, formed from the single-electron oxidation of cyclobutanol (Yu et al., 2015; Ren et al., 2015) undergoes ring opening to afford radical **30B** which by intramolecular radical addition forms **30C.** Two possible path ways are proposed for the conversion of **30C** into the tetralone **4.**

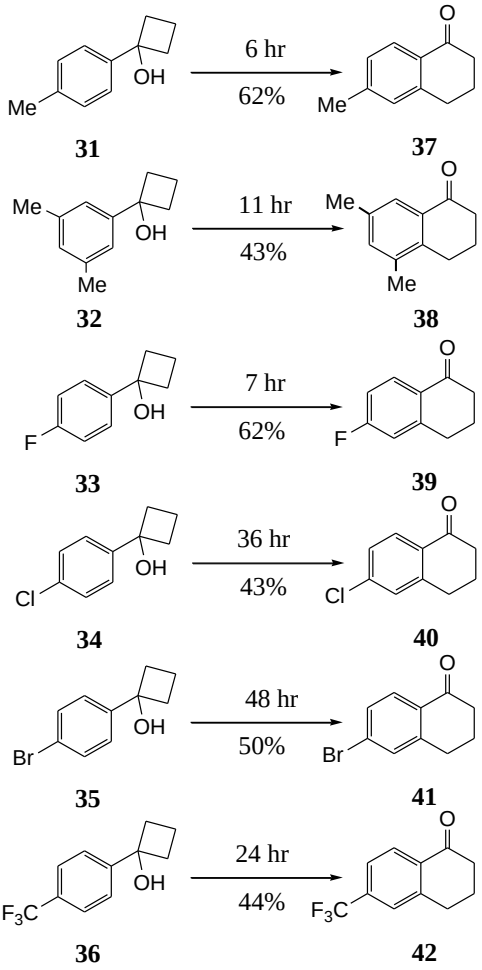
The first is the oxidation of **30C** by $K_2S_2O_8$ (**Path A**) and the second is the cleavage of the C-H bond of **30C** directly to dissociate a H-radical to yield the desired tetralone **4** (**Path B**). The combined experimental and computational studies indicate that the **Path B** is feasible mechanism in the formation of the desired tetralone **4.**



Scheme 9. Mechanism of the above mentioned transformation

The tertiary cyclobutanols can be prepared by the addition of various aryl Grignard reagents to cyclobutanones. Among various silver salts the silver nitrate ($AgNO_3$) has displayed better catalytic activity than other silver salts such as AgF, AgOAc, AgOTf and $AgBF_4$.

The other oxidants (oxone, mCPBA, tBuOOH, H_2O_2 ,etc) except $K_2S_2O_8$ are inefficient for redox cycles. Among the solventes examined, the biphasic solution dichloromethane [DCM: water (H_2O) (1 :1)] has proved effective for ring expansion. The other biphasic solution or only DCM does not provide successful result. This method has been utilized for the synthesis of several substituted tetralones **37-42** respectively from the cyclobutanols **31-36.** (**Scheme 10**).



Scheme 10. Transformation of cyclobutanol to tetralone

Both electron-rich and deficient tertiary cyclobutanols are converted into the corresponding tetralones in acceptable yields. With electron rich cyclobutanols shorter reaction time is required to complete the reaction. The substrate with electron - donating groups such as methoxy and methyl groups at p-position of the cyclobutanol undergoes smooth cyclization within few hours to yield the expected tetralone. Thus the cyclobutanol **31** forms tetralone **37** in good yield and the completion of cyclization takes place within few hours. The little influence of the steric hindrance of has been observed during the cyclization of cyclobutanols **32** and **30** to obtain the tetralones **38** and **4** respectively in modest yield. The halide **33** undergoes cyclization in few hours to yield tetralone **39** in good yield. The cyclizations of **34** and **35** are very sluggish and the tetralones **40** and **41** are obtained respectively in moderate yield. A moderate yield of the tetralone **42** has been obtained by cyclization of the cyclobutanol **36** with strong electron- withdrawing groups such as CF_3. In addition naphthyl substituted 1-tetralone and heterocycle fused tetralones have been prepared by this method. It is worthwhile to mention that the cyclopropanol under the similar reaction condition fails to provide the corresponding 1-indanone.

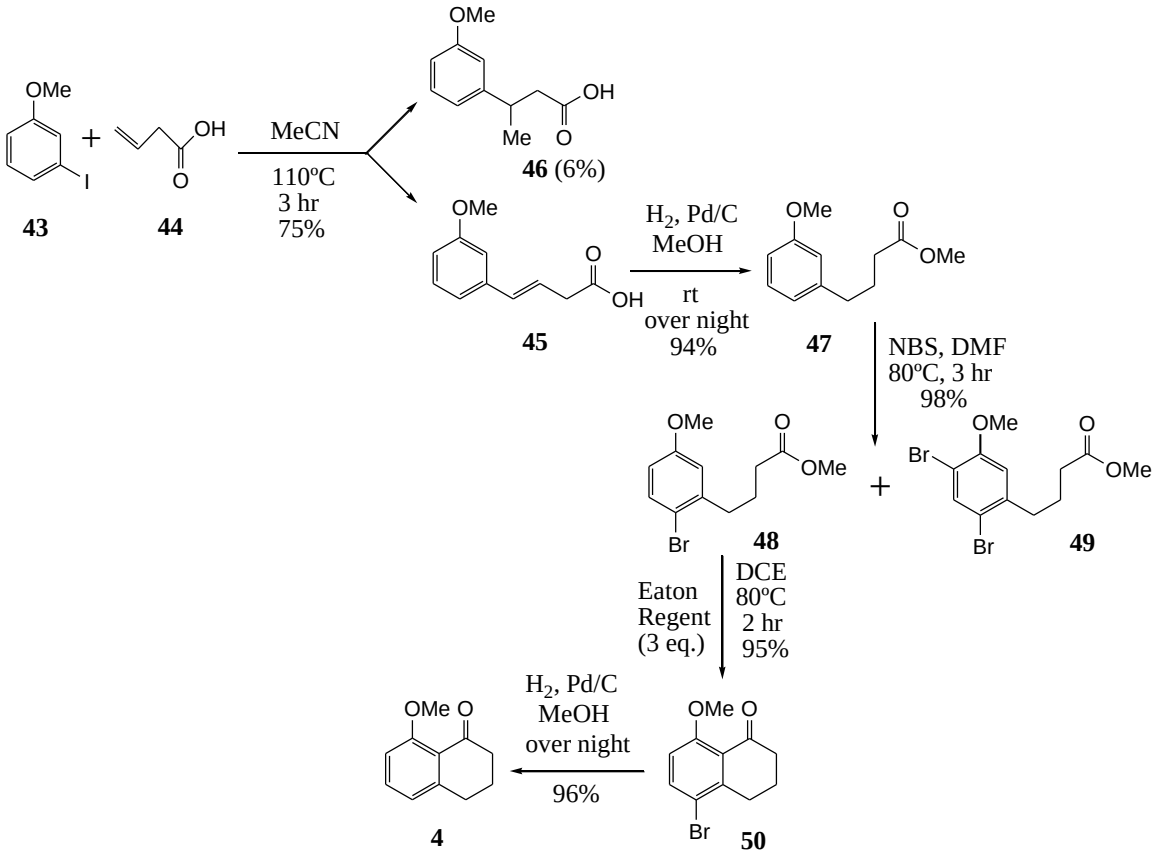
The present method is satisfactory for the synthesis of 1-tetralones but not very convenient because sometimes aryl or naphthyl substituted butanol are not easy to prepare. In addition the above mentioned tetralones can be prepared more conveniently by many other methods.

8. Synthesis of 8-methoxy-1-tetralona by Castillo-Rangel, Oscar Perez-Diaz, and Vasquez

An excellent approach (Castillo- Rangel et al., 2016) has been developed to improve the yield of the 8-methoxy-1-tetralone **4.** The synthetic route is exhibited in **Scheme 11.**

3-iodoanisole **43** is made to react with vinylacetic acid **44** via Heck coupling (Plevyak et al., 1979) to obtain 4-arylbutenoic acid **45** 10:1 (E/Z) mixture of isomers (determined by NMR spectroscopy) accompanied by a small amount (6%) of the isomeric 3-aryl-3-methylpropenoic acid **46.** The overnight catalytic hydrogenation of **45** in methanol at room temperature furnishes the 4-arylbutyric ester **47** in high yield. Attempts have been made to achieve the cyclization of

ester **47** with different Lewis acids and Eaton's reagent (phosphorous pentoxide in methane sulfonic acid) (Eaton et al., 1973) but unfortunately in all cases 6-methoxy-1-tetralone **2 is** recovered. The cyclization attempted with boron tribromide causes cleavage of the methyl ether and provides 6-hydroxy-1-tetralone in 60% yield.



Scheme 11. Synthesis of 8-methoxy-1-tetralone by Heck coupling

Bromination of the ester **47** with N-bromosuccinimide (NBS) in dichloroethane (DCE) at 80^{O}C yields the expected compound **48** along with a trace of dibrominated analogue **49** (6%). The cyclization of the compound **48** with Eaton's reagent produces bromo tetralone **50** whose transformation into the tetralone **4** has been accomplished by catalytic hydrogenation. The overall yield of tetralone **4** by the present procedure is 65%. The principle defect of the present procedure lies in the use of vinylacetic acid which is light sensitive, irritant and has a tendency to undergo polymerization. In addition of the above mentioned methods, other attempts have been made to obtain (Kumar, 1997; Huffman, 1959) the 8-methoxy-1-tetralone **4** but these approaches are very complicated and afford very poor yield and therefore the discussions of these approaches have been omitted.

9. Conclusions

It can be observed that several methods have been developed for the synthesis of 8-methoxy-1-tetralone. Some of these methods afford good yield but use reagents which are toxic, irritant and light sensitive. Several important organic reactions eg., Stobbe condensation, Heck coupling, tandem Michael addition-Dieckmann condensation etc have been utilized to achieve the synthesis of 8-methoxy-1-tetralone . The transformation of the commercially available diol **10** into the hydroxyl tetralone **11** by heating with aluminium chloride in cyclohexane is interesting which opens an easy route to the tetralone **4.** The rearrangement of the alcohol **25** with tosyl chloride and pyridine is noteworthy. The silver-catalyzed ring expansion of tertiary cyclobutanol **30** into tetralone **4** is very attractive.

We wish to mention here that recently tetralone scaffolds and their therapeutic applications have been reported (Gaumi et al., 2021; Sheng et al., 2022).

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Authors contributions

Prof Banerjee, Prof Cabrera and Dr. Mendoza were responsible for study design and revising the manuscript. Msc

Maldonado for some valuables comments during the preparation of manuscript. Tech. Bedoya for typing the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Informed consent

Obtained.

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The Publication Ethics Committee of the Canadian Center of Science and Education.

The journal's policies adhere to the Core Practices established by the Committee on Publication Ethics (COPE).

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Data sharing statement

No additional data are available.

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