Synthesis of 8-Methoxy-1-Tetralone

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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.

![Figure 1. Substituted methoxy 1-tetralone](image)

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 acetooacetate, (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 dimethyl sulfate 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°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°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-tolumide 13 is lithiated in tetrahydrofuran (THF) to form the lithio species 13a (Scheme 4) which on treatment with vinylsilane 14 (R5=H) at -78°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-tolumamides 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-tolumamide, 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-tolumamides are prepared by the direct lithiation of the corresponding methoxy-substituted N,N-diethylbenzamides with Mel 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.

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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 et al. 2010). The synthetic route is depicted in Scheme 6.

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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 (Chidambaram & 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 (NaBH₄CN) and hexamethylphosphoramide (HMPA) undergoes detosylation (Hutchins et al., 1977) and affords the tetral 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](image.png)

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 (AgNO₃) in presence of an oxidant (K₂S₂O₈) 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](image.png)

**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 K₂S₂O₈ (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](image.png)

**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 (AgNO₃) has displayed better catalytic activity than other silver salts such as AgF, AgOAc, AgOTf and AgBF₄.

The other oxidants (oxone, mCPBA, tBuOOH, H₂O₂ etc) except K₂S₂O₈ are inefficient for redox cycles. Among the solventes examined, the biphasic solution dichloromethane [DCM: water (H₂O) (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).
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 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 CF3. 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](image)

Bromination of the ester 47 with N-bromosuccinimide (NBS) in dichloroethane (DCE) at 80ºC 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 vinlyacetic 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 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 valuable comments during the preparation of manuscript. Tech. Bedoya for typing the manuscript. All authors read and approved the final manuscript.

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