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An Overview of Synthetic Approaches towards of Nitration of α-Tetralones

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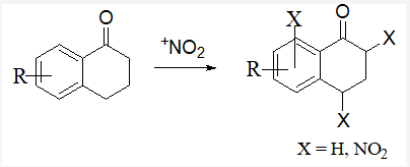
Abstract

The 1-tetralone scaffold and its derivatives are not only important as pharmacological agents but these also serve as precursors for natural products and compounds of medicinal importance. The easiest way to introduce a substituent on an aromatic as well as aliphatic system is nitration. Once introduced, the $–NO_2$ group can be easily replaced by a wide range of functional groups. The review aims to highlight strategies for nitration of substituted and unsubstituted 1-tetralone which led to introduction of NO_2 functionality at various positions.



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Introduction

The 1-tetralone 1, a readily available bicyclic ketone with aliphatic as well as aromatic ring,is an economical, inexpensive andvaluable precursor for the construction of a number of natural products and compounds of medicinal importance.[1-16] A derivative of 1-tetralone, 4, 7-dimethyl-6-methoxy-1-tetralone, is the fundamental structure of Aristelegone A, a natural product used in Chinese Traditional Medicines.[17] 4-hydroxy- 1-tetralone is one of the secondary metabolites isolated from Ampelocera edentula. This tetralone derivative has antileishmanial[18] and anti diabetic properties.[19]

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4-Hydroxy-1-tetralone is an important structural component of several natural products like catalponol, isocatalponol, isoshinanolone and palmarumycin CP4.[20] 4, 8-dihydroxy-1-tetralone is one of the secondary metabolites isolated from endophytic Aspergilli. This secondary metabolites has been found to exhibit antifungal activity against Alternaria alternata, Alternaria solani, Botrytis cinerea, Candida albicans, Colletotrichum gloeosporioides, Fusarium solani, Fusarium oxysporum f. sp. Niveum, Fusarium oxysporum f. sp. Vasinfectum, Gibberella saubinettii.[21]

Chalcones derivatives of 1-tetralones have been screened for a wide range of biological activities including anticancer, antifungal, and antibiotic properties.[22,23]

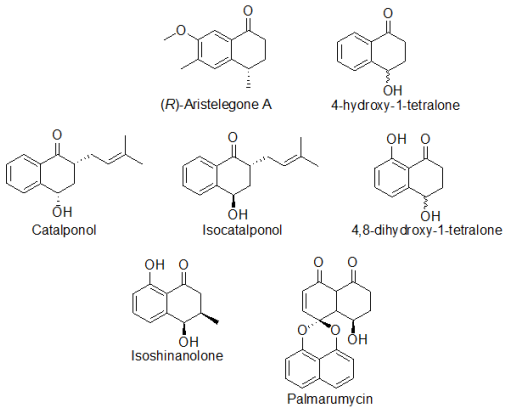


Fig. 1: Natural products with basic skeleton of 1-tetralone

Considering the involvement of 1-tetralone as structural unit of a number of natural products and compounds of medicinal importance, this substrate is of special interest and therefore preparation of its derivatives is of prime importance. Nitration is a very simple and efficient way of bringing a variety of subsituents on aliphatic as well as aromatic system by means of Sand meyer sequence.

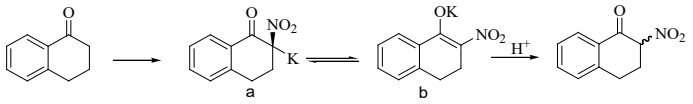
Different approaches have been reported for nitration of 1-tetralone that results in introduction of NO_2 group at different positions of the tetralone nucleus. For convenience, various strategies concerning nitration of 1-tetralone have been categorized as follows:

Direct Nitration of 1-Tetralone
Nitration on aliphatic ring
Nitration on α-carbon
Nitration on C-4
Nitration of aromatic nucleus

Synthesis of 1-tetralones from Nitro-Precursors
Oxidation of tetralin
Intramolecular acylation of nitro-substitutedprecursors

Direct Nitration of 1-Tetralone
Nitration on Aliphatic Ring
A number of 2- and/or 4-substituted 1-tetralone derivatives are prevalent in natural as well as in synthetic motifs[24-27] however, introducing a substituent at these positions of 1-tetralone is difficult as well as low yielding due to unstable nature of the product as well as the tendency of tetralone to undergo aromatization.[28,29]

2-nitro-1-tetralones could be synthesized by treating 1-tetralone with *dl*- as well as *d*- or *l*-2-octyl nitrates in presence of potassium ethoxide. The resulting potassium salt was optically inactive.Immediate acid workup resulted in free 2-nitro-1-tetralone which was also optically inactive. The reaction was carried out at 0°C, 22°C and 40°C but temperature appeared to have no effect on optical activity of the product. The authors believe that the reason for the optical inactivity of nitro product was due to existence of potassium salt of 2-nitro-1-tetralone in the form of b.[30] This method is of little significance from synthetic point of view since the yield of product was quite low.

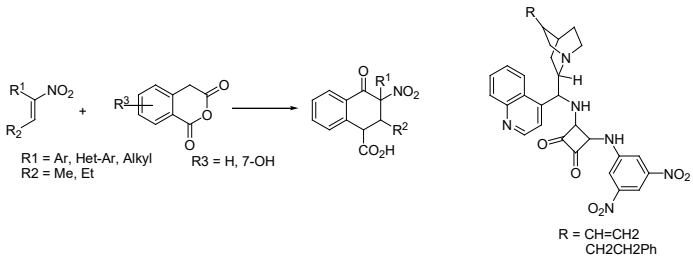


Reagent and conditions: ***dl-/d-/l*-2-octylnitrate, EtOK, 20 min, 40°/22°/0°C, Et_2O**

Scheme 1: Study of effect of temperature on synthesis of 2-nitro-1-tetralone

The 2-nitro-1-tetralone was synthesized by Feuer *et al.,* from 1-tetralone in reasonable yield by employing alkyl nitrates (R: Et, Pr, Bu, amyl) and potassium alkoxides in presence of non-alcohlic solvents (Et_2O, THF, toluene, hexane). The presence of alcohol was found to be detrimental for the product; even small amount of alcohol was reported to result in 2.5-5% reduction of product yield. The reaction worked well at low temperature (-30°C) conditions. For R: amyl in presence of ^tBuOK, 1-tetralone afforded potassium salt of 2-nitro derivative in 46.2% yield which after acidification to pH of 3.0 resulted in 2-nitro-1-tetralone.[31]

Chiral tetra-substituted 2-nitro-1-tetralone was synthesized by Nath *et al.,* in significant yields via enantioselective Tamura cycloaddition reaction of α-branched nitro-olefins with homophthalic anhydride in the presence of cinchonidine derived squramide as chiral catalyst. Best enantiomeric excess (ee) of 88% was observed with Et_2O as solvent. Interestingly, the use of 4Å molecular sieves (MS) was observed to influence the ee of product depending upon the nature of substituent on nitro olefins. With certain substituents, the use ofMS led to an increase of ee while in others the use of the same resulted in significant reduction of ee (scheme 2).[32]

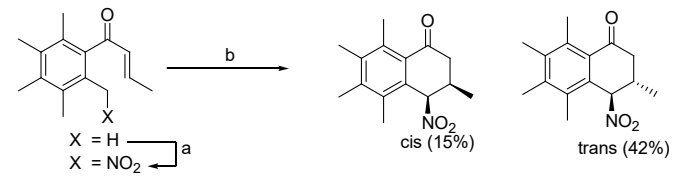


Reagent & Conditions: 10 mol% catalyst, 4Å molecular sieve, 25°C, Et_2O, 36 h.

Scheme 2: Synthetic strategies for synthesis of 2-nitro-1-tetralone

Nitration on C-4

Keumi *et al.,* synthesized polysubstituted -nitro-1-tetralones via regioselective nitration of methyl substituted alkenoylbenzenes by using HNO_3 and Ac_2O. This transformation afforded 2-(nitromethy1)alkenoylbenzenes. The nitromethyl group present ortho to α,β-unsaturated system acts as a Michael donor and undergoesintramolecular Michael addition in presence of a base to afford 4-nitro-1-tetralones (scheme 3).[33]

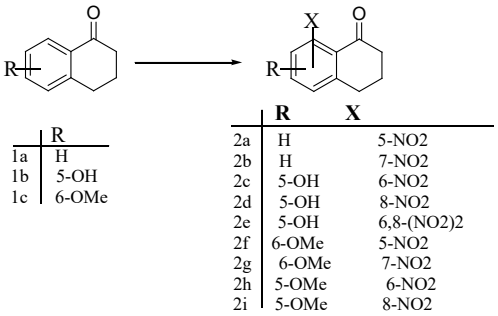


Reagent & conditions: a) HNO3, Ac2O, 0°C, 2 h; b) DBU, DCM, rt, 24 h

Scheme 3: Nitration at C-4 position of aliphatic ring of 1-tetralone

Nitration of Aromatic Nucleus

Nitration on aromatic ring is one of the most employed strategies for the functionalization of aromatic systems in synthetic chemistry. A number of strategies and reagents have been employed for nitration of 1-tetralone. In general, it has been observed that direct nitration is often low yielding. The findings of various researchers indicate that the use of alcohol as solvent proves to be detrimental for the nitration product. The reaction works well at low temperature (-30°C) conditions.[31] It has also been observed that longer exposure to acid mixture decreases the yield sharply; also effective stirring is important for the reaction, the absence of which leads to formation of side products.[34]



	R
1a	H
1b	5-OH
1c	6-OMe

	R	X
2a	H	5-NO2
2b	H	7-NO2
2c	5-OH	6-NO2
2d	5-OH	8-NO2
2e	5-OH	6,8-(NO2)2
2f	6-OMe	5-NO2
2g	6-OMe	7-NO2
2h	5-OMe	6-NO2
2i	5-OMe	8-NO2

Scheme 4: Nitration on aromatic ring of 1-tetralone

Ferry *et al.,* carried out successful synthesis of 7-nitro-1-tetralone by utilizing H_2SO_4 and fuming HNO_3 as nitrating mixture. The drop-wise addition of pre-chilled nitrating mixture was carried out over a time period of 20 min at/or below 0°C. Longer addition times and/or prolong acid exposure were observed to result in decreased product yield. After commencement of addition, the reaction was stirred for 20 min and precipitation of product was induced by pouring in ice water. The gummy paste thus formed was allowed to stand overnight during that time the paste hardened. The recrystallization from either afforded pure product with reduced yield of 25% (table 1, entry 1).[34]

Zhang *et al.,* utilized H_2SO_4/ HNO_3 for nitration of 1-tetralone at -15°C→ ambient. The reaction was completed in 45 minutes and yielded 7-nitro-1-tetralone in 55% yield and the 5-nitro isomer in 26% yield (table 1, entry 2).[35]

The slow addition of fuming HNO_3 to 1-tetralone below 8°C followed by ice treatment of the reaction mixture afforded 7-nitro tetralone as the exclusive product (table 1, entry 3).[36]

Nitration of 1-tetralone with triflouroacetic anhydride (TFAA) and ammonium nitrate in cooling mixture (comprising of ice/NaCl) afforded 7-nitro in 58% yield. Dichloromethane (DCM)was employed as solvent for the reaction (table 1, entry 4).[37]

Mahana *et al.,* employed HNO_3 in AcOH as nitrating mixture for nitration of 5-hydroxy-1-tetralone. The authors have reported the reaction both at room temperature as well as under refluxing conditions. When the reaction was carried out at room temperature, 6-nitro isomer was isolated as major product in 47% yield while 6,8-nitro-1-tetralone was isolated in 19% yield (table 1, entry 5). the same reaction when carried out under refluxing conditions afforded 6-nitro, 8-nitro and 6,8-dinitro isomers in 21, 48 and 9% yields respectively (table 1, entry 6).[38]

Ryu *et al.,* synthesized nitro-substituted 5-methoxy-1-tetralones as precursors for transient receptor potential VI (TRPVI) antagonists. The authors reported nitration of 5-methoxy substituted 1-tetralone by employing$Cu(NO_3)_2$ / Ac_2O in Et_2O used as a solvent. Reaction was carried out by stirring at room temperature followed by filtration through celite. The reaction yielded 6-nitro and 8-nitro-6-methoxy-1-tetralones in 1:1 yield after flash column chromatography (table 1, entry 7).[39]

Devkota *et al.,* synthesized nitro derivatives of 6-methoxy-1-tetralones as precursors for water soluble amino acid conjugates. The authors carried

out nitration by HNO_3 and AcOH in presence of Ac_2O used as solvent; the reaction was initially stirred at 0°C for 20 min followed by stirring at ambient temperature for 20 h. Reaction work up and chromatographic purification afforded 5-nitroproduct in 33% yield (table 1, entry 8).[40]

6-methoxy-5-nitro-1-tetralone and its 7-nitro isomer have the potential to serve as precursors for tubulin binding ligands. These ligands were synthesized by Pinney *et al.,* by carrying out nitration of 6-methoxy-1-tetralone in acetone by stirring to which was added H_2SO_4/HNO_3 at 0°C. The reaction was completed in 6 hours and after workup and column chromatographic purification, the 7-nitro and 5-nitro isomers were isolated in 30 & 35% yields respectively (table 1, entry 9).[41]

Table 1 summarizes the details of different methodologies for the nitration of unsubstituted and substituted 1-tetralone.

Table 1: Comparison of different strategies for syntheses of nitro-1-tetralone

Substrate		Reagent (eq to substrate)	Solvent	Time	Temp	Product(%Yield)
1	1a	H_2SO_4 (4.8), HNO_3*fuming* (2)	-	45 min	0°C	**2b*** (25)[34]
2	1a	H_2SO_4 (4.4), HNO_3 (1.2)	-	45 min	-15-0°C	**2a** (26), **2b** (55%)[35]
3	1a	HNO_3 *fuming* (23)	-	30 min	0-8°C	**2b** (major)[#36]
4	1a	TFAA (1.7), NH_4NO_3 (1.05)	DCM	18 h	-15-0°C	**2b** (58% approx) [37]
5	1b	HNO_3 (71) /AcOH (28)	AcOH	45 min	reflux	**2c** (21%), **2d** (48%), **2e** (9%)[38]
6	1b	HNO_3 (7.1) /AcOH (28)	AcOH/H_2O (10:1)	45 mn	rt	**2c** (47), **2d** (19) [38]
7	1d	$Cu(NO_3)_2$ (1) /Ac_2O (10.5)	Et_2O	3 h	rt	**2i** (46%), **2j** (42%) [39]
8	1c	HNO_3 (2), AcOH (1.5), Ac2O (17.5)	-	21 h	0°C - rt	**2f** (33%)*[40]
9	1c	H_2SO_4 (3.3) / HNO_3 (3.5)	Acetone	6 h	0°C	**2f** (35), **2g** (30)[41]

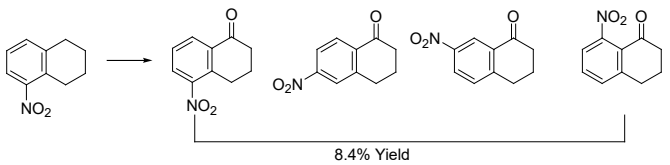
*Isolated yield after chromatographic purification; [#]% yield has not been reported; TFAA: trifloroacetic anhydride

Synthesis of 1-Tetralones from Nitro-Precursors

The direct nitration of substituted and unsubstituted 1-tetralones is associated with low product yields, as evident from table 1. Therefore some alternate attempts have also been reported by a number of researchers that involved indirect preparation of substituted and unsubstituted nitro-1-tetralone.

Oxidation of 5-Nitrotetralin

Biggs *et al.,* synthesized nitro substituted 1-tetralones as precursors for monoquaternary neuromuscular blocking agents. Nitro-1-tetralones were synthesized from tetralin. Nitration of tetralin yielded 5-nitro and 6-nitrotetralin which upon chromatographic purification afforded 5-nitrotetralin. The CrO_3 mediated oxidation of 5-nitrotetralin in presence of AcOH at 70-80C for over 2 hours afforded 5-nitro, 6-nitro 7-nitro and 8-nitro-1-tetralones after methanolic workup and fractional crystallization of the crude product with ligroin in an overall yield of 8.4% (scheme 5).[42]

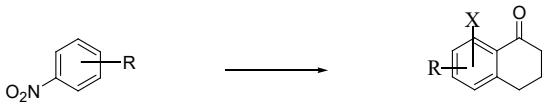


Scheme 5: Synthesis of nitro-1-tetralones via oxidation of 5-nitrotetralin

Intramolecular Acylation of Nitro-Precursors

In another method, 7-nitro-1-tetralone was synthesized via intramolecular acylation of *p*-nitro-*Y*-phenylbutyric acid in the presence of H_3PO_4 when heated at 120-125°C in an oil bath for 0.5 hoursusing toluene or anisole as solvent. This protocol leads for the formation of the nitro derivative as minor / side-product. The same protocol gave exceptional yields for p-methoxy- *Y* -phenylbutyric acid under identical conditions.[43]

The reaction of 4-(2-nitrobenzene)butyric acid with FSO_3H under refluxing conditions afforded 5-nitro and 7-nitro-1-tetralone in an overall yield of 68%. Refluxing 4-(2-nitrobenzene)butanonitrile with FSO_3H afforded 5-nitro-1-tetralone isomer as the exclusive product in 68% yield. Another way to obtain 5-nitro-1-tetralone as the exclusive product in good yield (81%) was to reflux 4-(2-nitrobenzene) butyric acid with FSO_3H in presence of super acid such as SbF_5.[44]



	R
3a	4- (CH2)3COOH
3b	3-CH(Et)COOH
3c	3-CH(Et)CN

	R	X
2a	H	5-NO2
2b	H	7-NO2
2c	5-OH	6-NO2
2d	5-OH	8-NO2
2e	6-OMe	5-NO2
2f	6-OMe	7-NO2

Scheme 6: Synthesis of nitro-1-tetralones via intramolecular acylation of nitroprecursors

Conclusion

1-tetralone is an important scaffold for a number of chemotherapeutic agents as well as a component of a number of natural products. Nitration of 1-tetralone has been reported by a number of different protocols; each with its own limitations. In this review various strategies for nitration of 1-tetralone have been critically evaluated. It has been observed, that the conditions of nitration vary depending upon the position on which NO_2 is desired to be introduced.

In general, the nitration at aliphatic as well as aromatic ring of 1-tetralone, give fruitful results under mild conditions (i.e., low temperature, slow rate of addition of nitrating agent, use of solvent). From the findings of all authors, it is evident that longer reaction time and high temperature conditions result in lower yields. Conversely, instead of using the conventional HNO_3/H_2SO_4 agent, the use of nitrate salts (as a source of nitronium ion) and use of fuming nitric acid afforded products in better yields.

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All authors contributed to obtain the data, to put forward the right questions and to find the replies to them, also to do a proof reading of the manuscript. We have all approved the final version of the manuscript.

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Conflict of Interest

The authors do not have any conflict of interest.

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