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 –NO2 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 NO2 functionality at various positions.

Introduction
The 1-tetralone 1, a readily available bicyclic ketone with aliphatic as well as aromatic ring, is an economical, inexpensive and valuable 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 antileishmanial18 and anti diabetic properties.19
4-Hydroxy-1-tetralone is an important structural component of several natural products like catalponol, isocatalponol, isoshinanolone and palmarumycin CP4. 4, 8-dihydroxy-1-tetralone is one of the secondary metabolites isolated from endophytic Aspergillii. 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.

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

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 substituents 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 NO₂ 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-substituted precursors

**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 synthetic motifs 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.

2-nitro-1-tetralones could be synthesized by treating 1-tetralone with dl- as well as d- or l2-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. This method is of little significance from synthetic point of view since the yield of product was quite low.
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-alcoholic solvents (Et₂O, 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 BuOK, 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 \(\alpha\)-branched nitro-olefins with homophthalic anhydride in the presence of cinchonidine derived squaramide as chiral catalyst. Best enantiomeric excess (ee) of 88% was observed with Et₂O 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 of MS led to an increase of ee while in others the use of the same resulted in significant reduction of ee (scheme 2).\(^{32}\)

Nitration on C-4
Keumi et al., synthesized polysubstituted -nitro-1-tetralones via regioselective nitration of methyl substituted alkenoylbenzenes by using HNO₃ and Ac₂O. This transformation afforded 2-(nitromethyl)alkenoylbenzenes. The nitromethyl group present ortho to \(\alpha,\beta\)-unsaturated system acts as a Michael donor and undergoes intramolecular Michael addition in presence of a base to afford 4-nitro-1-tetralones (scheme 3).\(^{33}\)

Reagent and conditions: \(dl/d-l\)-2-octyl nitrate, EtOK, 20 min, 40°/22°/0°C, Et₂O

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

Reagent & Conditions: 10 mol% catalyst, 4Å molecular sieve, 25°C, Et₂O, 36 h.

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

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. 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.

Ferry et al., carried out successful synthesis of 7-nitro-1-tetralone by utilizing H₂SO₄ and fuming HNO₃ 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).

Zhang et al., utilized H₂SO₄/ HNO₃ 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).

The slow addition of fuming HNO₃ 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).

Nitration of 1-tetralone with trifluoroacetic 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).

Mahana et al., employed HNO₃ 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).

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 employingCu(NO₃)₂ / Ac₂O in Et₂O 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).

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$_2$O 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$_2$SO$_4$/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>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent (eq to substrate)</th>
<th>Solvent</th>
<th>Time</th>
<th>Temp</th>
<th>Product(%Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 1a</td>
<td>H$_2$SO$_4$ (4.8), HNO$_3$ fuming (2)</td>
<td>-</td>
<td>45 min</td>
<td>0°C</td>
<td>2b* (25)(^{34})</td>
</tr>
<tr>
<td>2 1a</td>
<td>H$_2$SO$_4$ (4.4), HNO$_3$ (1.2)</td>
<td>-</td>
<td>45 min</td>
<td>-15-0°C</td>
<td>2a (26), 2b (55%)(^{36})</td>
</tr>
<tr>
<td>3 1a</td>
<td>HNO$_3$ fuming (23)</td>
<td>-</td>
<td>30 min</td>
<td>0-8°C</td>
<td>2b (major)(^{9,36})</td>
</tr>
<tr>
<td>4 1a</td>
<td>TFAA (1.7), NH$_4$NO$_3$ (1.05)</td>
<td>DCM</td>
<td>18 h</td>
<td>-15-0°C</td>
<td>2b (58% approx) (^{37})</td>
</tr>
<tr>
<td>5 1b</td>
<td>HNO$_3$ (71) /AcOH (28)</td>
<td>AcOH</td>
<td>45 min</td>
<td>reflux</td>
<td>2c (21%), 2d (48%), 2e (9%)(^{38})</td>
</tr>
<tr>
<td>6 1b</td>
<td>HNO$_3$ (7.1) /AcOH (28)</td>
<td>AcOH/H$_2$O (10:1)</td>
<td>45 mn</td>
<td>rt</td>
<td>2c (47), 2d (19)(^{38})</td>
</tr>
<tr>
<td>7 1d</td>
<td>Cu(NO$_3$)$_2$ (1) /Ac$_2$O (10.5)</td>
<td>Et$_2$O</td>
<td>3 h</td>
<td>rt</td>
<td>2i (46%), 2j (42%)(^ {39})</td>
</tr>
<tr>
<td>8 1c</td>
<td>HNO$_3$ (2), AcOH (1.5), Ac2O (17.5)</td>
<td>-</td>
<td>21 h</td>
<td>0°C - rt</td>
<td>2f (33%)(^ {40})</td>
</tr>
<tr>
<td>9 1c</td>
<td>H$_2$SO$_4$ (3.3) / HNO$_3$ (3.5)</td>
<td>Acetone</td>
<td>6 h</td>
<td>0°C</td>
<td>2f (35), 2g (30)(^{41})</td>
</tr>
</tbody>
</table>

*Isolated yield after chromatographic purification; ^{40}\% 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 70-80°C 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$_3$PO$_4$ when heated at 120-125°C in an oil bath for 0.5 hours using 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$_3$H under refluxing conditions afforded 5-nitro and 7-nitro-1-tetralone in an overall yield of 68%. Refluxing 4-(2-nitrobenzene)butanamine with FSO$_3$H 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$_3$H in presence of super acid such as SbF$_5$.$^{44}$

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$_2$SO$_4$ 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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Conflict of Interest

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