

Synthesis Involving Metals

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INTRODUCTION

A wide spectrum of synthetic methods have been used towards the synthesis of isocoumarins and 3,4-dihydroisocoumarins⁹¹. A number of new methods⁹²⁻¹⁰² are being developed and reported each year. Some of these methods provide the isocoumarins directly whereas others lead to the 3,4-dihydroisocoumarins. Some of the most important, high yield methods applicable to the synthesis of a large number of these compounds are mentioned below.

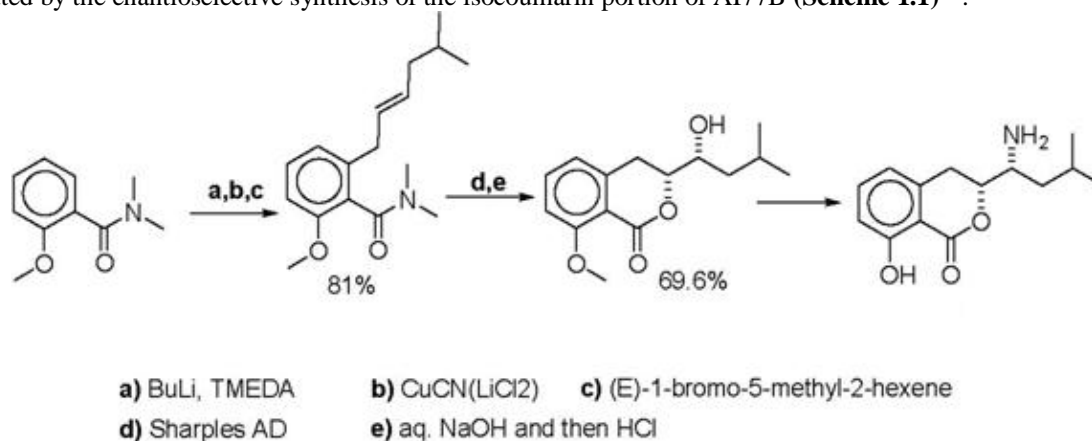
Literature reveals that isocoumarins and 3,4-dihydroisocoumarins have been extensively prepared by such methods, involving metallation at specific position like lithiation, silylation and thallation etc.

METHODS INVOLVING METALLATION AT SPECIFIC POSITION

- 2.1 Lithiation Reaction
- 2.2 Silylation Method
- 2.3 Thallation-olefination of Arenes
- 2.4 Palladium catalyzed method
- 2.5 Iridium catalyzed method
- 2.6 Rhodium-Catalyzed Oxidative Coupling of Benzoic Acids with Alkynes via Regioselective C-H Bond Cleavage
- 2.7 Mercury catalyzed method

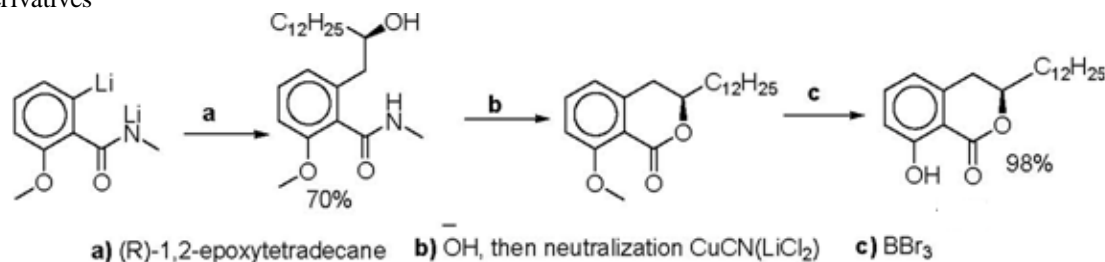
2.1 Lithiation Reaction

Benzoic acid derivatives are important precursors of isocoumarins. Among the methods available for introducing a β -functionalized carbon substituent *ortho* to the carboxyl group, those involving *ortho*-metallation of the benzene ring have enjoyed a great popularity. This approach has been thoroughly reviewed¹⁻³. Summarizing the general concepts, carboxylic acid derivatives suitable for promoting *ortholithiation*⁴⁻⁵ are tertiary amides (4,4-dimethyl)oxazolin-2-yl group and secondary amides. Lithiated tertiary amides are readily and generally *ortho*-lithiated using *s*-butyllithium and tetramethylethylenediamine, but their reaction with alkylating agents other than methyl iodide gives low yields because of a poor nucleophilicity. Allylation of lithiated tertiary benzamides has however been accomplished in high yields by previous transmetalation to a magnesium or (better) to a copper derivative; the allyl group thus introduced has been converted to the β -hydroxyalkyl group required to complete the lactone ring in the conditions of the acid hydrolysis of the benzamide, leading to racemic 3,4-dihydroisocoumarins directly, apparently without the possibility of isolating the intermediate allylbenzoic acids; alternatively, asymmetric hydroxylation of the double bond followed by treatment with acids has been used to obtain 3,4-dihydroisocoumarins with a high degree of enantiomeric purity, as demonstrated by the enantioselective synthesis of the isocoumarin portion of AI77B (Scheme 1.1)⁶⁻⁹.



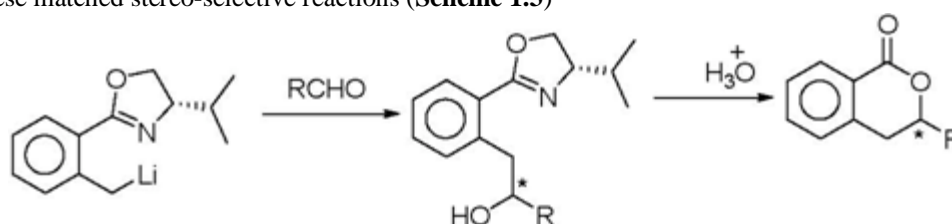
Scheme 1.1

Enantiomerically pure natural 3,4-dihydroisocoumarins have been obtained from lithiated secondary benzamides and homochiral epoxides. Coupling between lithiated secondary benzamides and epoxides belongs to the beginning of the anionic chemistry of aromatic compounds; unfortunately, yields are generally modest and N-alkylation can complicate the reaction¹⁰. Good yields have occasionally been reported though, as in the synthesis of the allergenic principle of *gingko biloba* (**Scheme 1.2**)¹¹ and of a variety of mellein derivatives¹²



Scheme 1.2

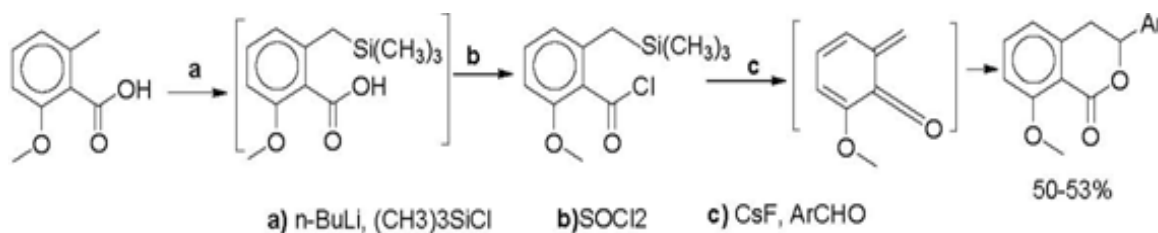
Lateral lithiation of (S)-4-isopropyl-2-(o-tolyl)oxazoline in diethyl ether followed by the reaction with aldehydes in the presence of TMEDA produced the addition products with stereoselectivities up to 84% de¹³. Utilization of TMEDA as a ligand is essential for the good selectivity. Rationale for the stereoselectivity is proposed based on ab-initio calculation of the lateral lithio species. The major (S,S)-products lactonized faster than the minor (S,R)-products to the corresponding 3,4-dihydroisocoumarins under acidic conditions. Thus, (3S)-3,4-dihydroisocoumarins were obtained in good optical purities up to 97% ee by sequential application of these matched stereo-selective reactions (**Scheme 1.3**)



Scheme 1.3

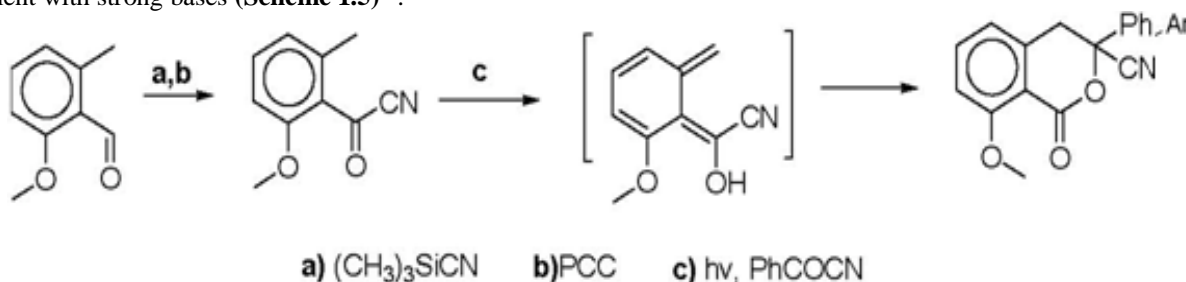
2.2 Silylation Method

Closely related to lithiation is the desilylation of 2-(trimethylsilylmethyl)-benzamides, which generates carbanions suitable for additions to aldehydes¹⁴. 2-(Trimethylsilylmethyl)benzoyl chlorides also undergo desilylation and addition to aldehydes to give dihydroisocoumarins through a concerted mechanism involving *ortho*-quinodimethanes rather than carbanions as reactive intermediates (**Scheme 1.4**)¹⁵.



(Scheme 1.4)

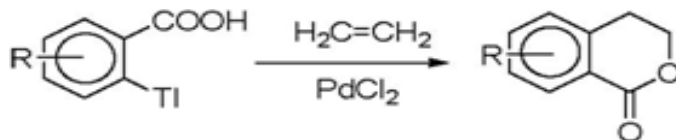
To this class of reactive intermediates belong the products of UV irradiation of *ortho*-toluyl cyanides which add to aliphatic and aromatic acyl cyanides to give 3-cyano-3-phenyl-8-methoxy-3,4-dihydroisocoumarins which are converted to isocoumarins by treatment with strong bases (**Scheme 1.5**)¹⁶.



(Scheme 1.5)

2.3 Thallation-olefination of Arenes

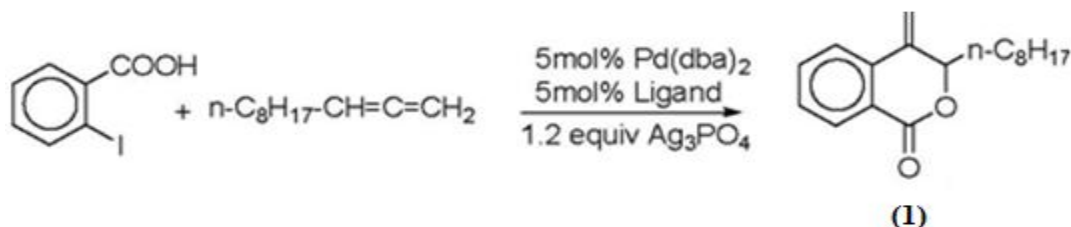
Isocoumarins and 3,4-dihydroisocoumarins were prepared in a single pot reaction¹⁷, by reacting a benzoic acid with an electrophilic thallium salt in the presence of an organic solvent to give O-thalliated benzoic acid followed by reaction with an organic compound e. g. an alkene in the presence of PdCl₂ (Scheme 1.6).



(Scheme 1.6)

2.4 Palladium catalyzed method

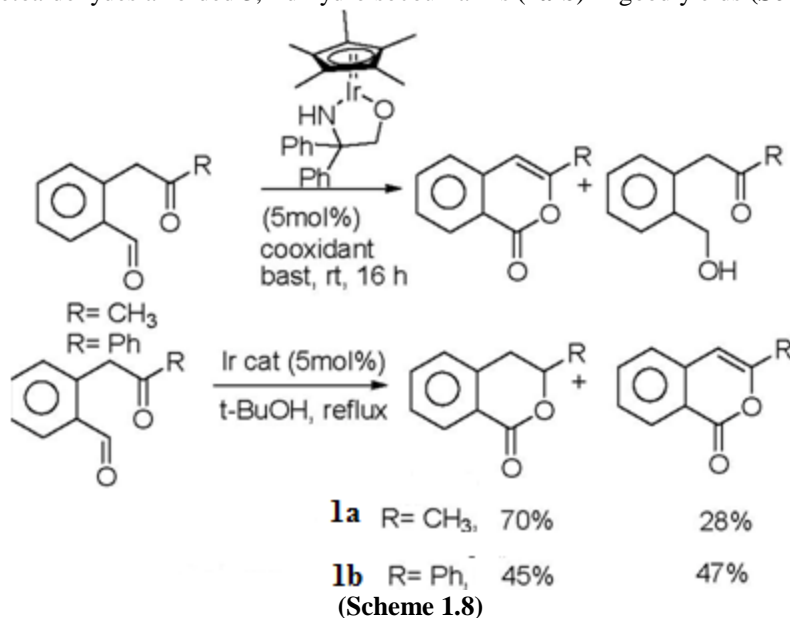
Aryl iodides with a nucleophilic substituent at the ortho position react with 1,2-dienes in the presence of a palladium catalyst¹⁸ and a chiral bisoxazolineligand to afford isocoumarin (1) in good yield and with 46-86% enantiomeric excess (Scheme 1.7).



(Scheme 1.7)

2.5 Iridium Catalyzed Method

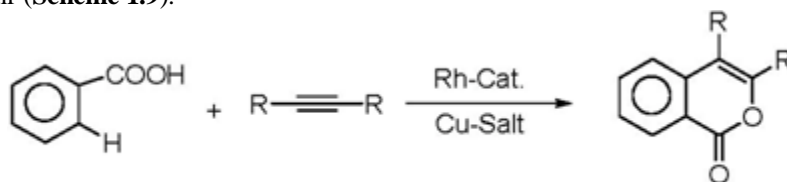
Two new cyclizations of ketoaldehydes¹⁹ have been developed using an Ir-ligand bifunctional catalyst. Oxidative lactonization of δ -ketoaldehydes proceeded smoothly at room temperature to give coumarin derivatives in excellent yields. Intramolecular Tishchenko reaction of δ -ketoaldehydes afforded 3,4-dihydroisocoumarins (1a-b) in good yields (Scheme 1.8).



(Scheme 1.8)

2.6 Rhodium-Catalyzed Oxidative Coupling of Benzoic Acids with Alkynes via Regioselective C-H Bond Cleavage

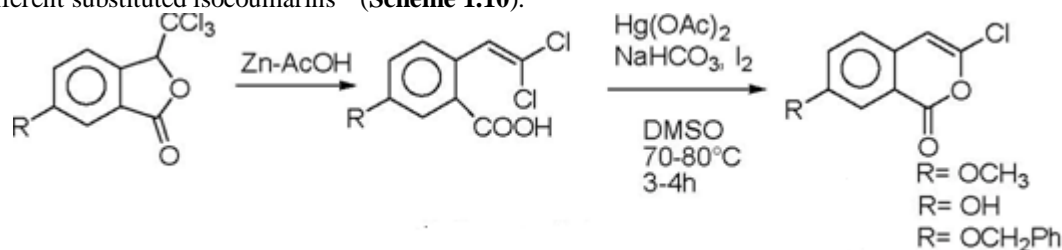
The oxidative coupling of benzoic acids with internal alkynes effectively proceeds in the presence of [Cp*⁺RhCl₂]₂ and Cu(OAc)₂·H₂O as catalyst²⁰ and oxidant respectively to produce the corresponding isocoumarin derivatives. The copper salt can be reduced to a catalytic quantity under air (Scheme 1.9).



(Scheme 1.9)

2.7 Mercury Catalyzed Method

Sulphuric acid-catalyzed chloralhydrate condensation with different substituted benzoic acids formed trichlorophthalides, from which Zn+AcOH reduction afforded various dichloro derivatives. These derivatives on treatment with alkaline $\text{Hg}(\text{OAc})_2 + \text{I}_2$ furnished different substituted isocoumarins²¹ (Scheme 1.10).



(Scheme 1.10)

CONCLUSION

From the above discussion it is concluded that isocoumarins and 3,4-dihydroisocoumarins have been extensively prepared by such methods, involving metallation at specific position like Lithiation Reaction, Silylation Method, 2,3-Thallation-olefination of Arenes, Palladium catalyzed method, Iridium catalyzed method, Rhodium-Catalyzed Oxidative Coupling of Benzoic Acids with Alkynes via Regioselective C-H Bond Cleavage and Mercury catalyzed method are used.

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