



Synthesis involving metals by Metallation at Specific Position

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Abstract:

Biogenetic definitions of the aromatic polyketides are due to the work of Birch (1951), by whom a detailed theoretical analysis of carbon skeletons and oxygenation patterns of known compounds was first combined with an extensive series of tracer incorporation experiments. The elaboration of the β -ketide chain in metabolites derived from poly- β -ketide precursors, normally proceeds by condensation of terminal unit of acetyl Co-enzyme A with chain building units of malonyl Co-enzyme A. More than thirty years elapsed, still increasing number of new isocoumarins has been found in nature exhibiting a wide structural diversity in their natural source and biosynthetic pathways. These findings are a constant stimulant for synthetic work, which have been undertaken either to confirm novel structures or to provide substantial amounts of material for biological and pharmaceutical studies in those cases in which an isocoumarin exhibiting interesting properties or was suspected of being responsible for the significant properties associated with its natural source. In view of biological activity of isocoumarin and 3,4-dihydroisocoumarin, it was planned to synthesize some of outlined compounds. The work is divided in two groups, Naturally occurring isocoumarin and Non naturally occurring isocoumarins and 3,4-dihydroisocoumarins. Experimental design will be carried out for Synthesis, characterization and therapeutic evaluation of sulphur, nitrogen and oxygen containing novel hetro cycles and their antimicrobial activities will be carried out with reference to (i) Synthesis of sulphur, nitrogen and oxygen containing novel Hetrocycles (ii) Characterization of sulphur, nitrogen and oxygen containing novel Hetrocycles and (iii) Therapeutic evaluation of sulphur, nitrogen and oxygen containing novel Hetrocycles. Data Analysis and Interpretation of sulphur, nitrogen and oxygen containing novel hetrocycles will be carried out in two following part (1) Spectroscopy (2) Antiviral and Antibacterial activities. Spectoscopy will be carried out by the Ultraviolet spectroscopy, Infrared spectroscopy and NMR and mass spectrometry as well as antimicrobial activities.

Keywords: Antimicrobial activities, Hetrocycles, Isocoumarin, Nitrogen and oxygen, Therapeutic evaluation of sulphur

1. Introduction

A wide spectrum of synthetic methods have been used towards the synthesis of isocoumarins and 3,4-dihydroisocoumarins. A number of new methods 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.

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

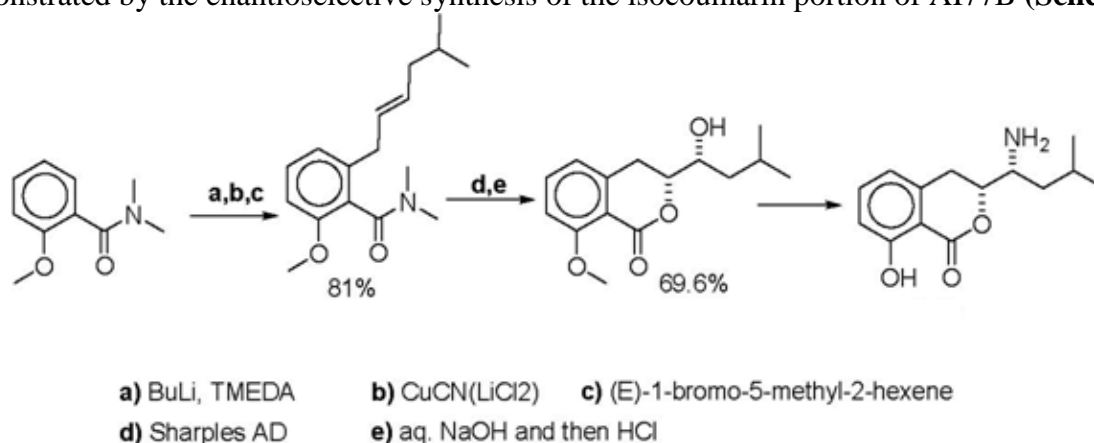
2. Methods involving metallation at specific position

- 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

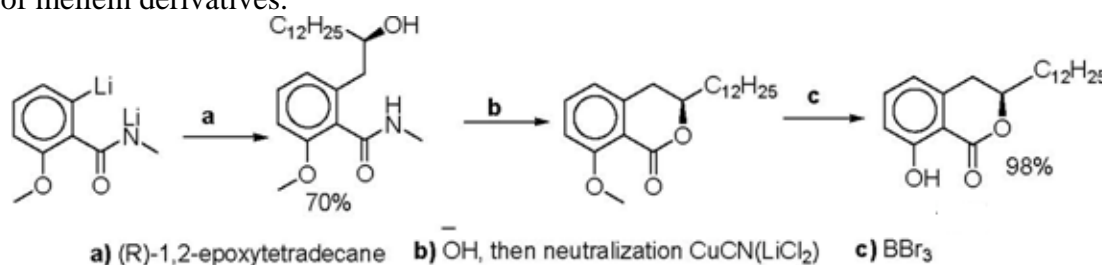
2.1 Lithiation Reaction

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 reviewed. Summarizing the general concepts, carboxylic acid derivatives suitable for promoting *ortholithiation* 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 trans-metallation 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**)



Scheme: 1

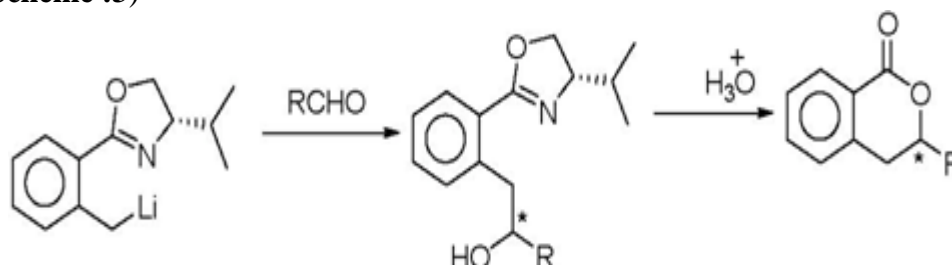
Enantiomerically pure natural 3,4-dihydroisocoumarins have been obtained from lithiated secondary benzamides and homochiral epoxides. Coupling between lithiated secondary benzamides and epoxides belongs to the beginning of the anionic chemistry of aromatic compounds; unfortunately, yields are generally modest and N-alkylation can complicate the reaction. Good yields have occasionally been reported though, as in the synthesis of the allergenic principle of *gingko biloba* (**Scheme :2**) and of a variety of mellein derivatives.



Scheme :2

Lateral lithiation of (S)-4-isopropyl-2-(*o*-tolyl)oxazoline in diethyl ether followed by the reaction with

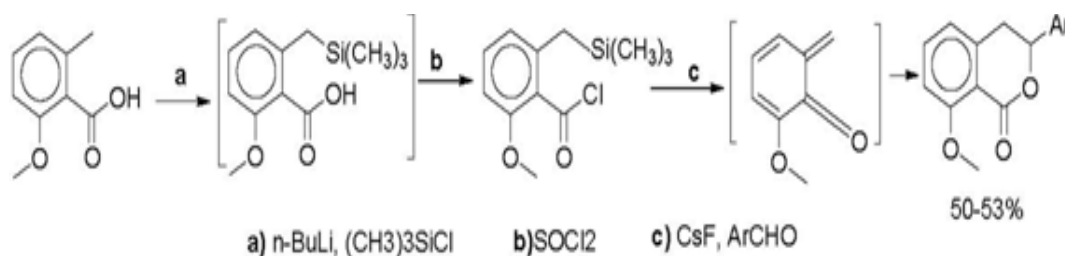
aldehydes in the presence of TMEDA produced the addition products with stereoselectivities up to 84% de. Utilization of TMEDA as a ligand is essential for the good selectivity. Rationale for the stereoselectivity is proposed based on *ab-initio* calculation of the lateral lithio species. The major (S,S)-products 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 :3**)



Scheme: 3

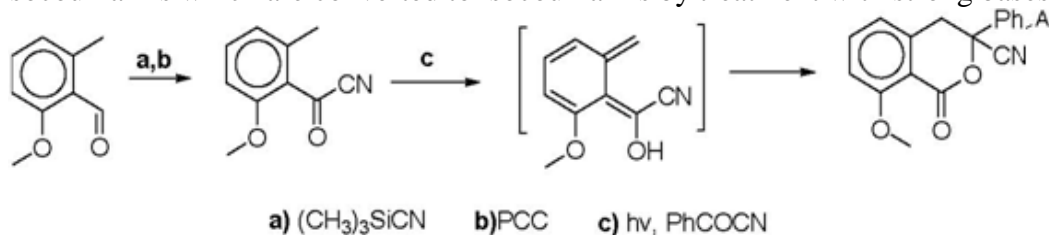
2.2 Silylation Method

Closely related to lithiation is the desilylation of 2-(trimethylsilylmethyl)-benzamides, which generates carbanions suitable for additions to aldehydes. 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 :4**).



Scheme :4

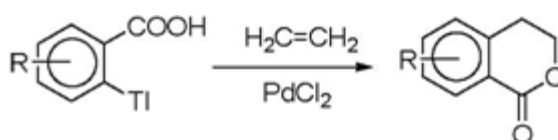
To this class of reactive intermediates belong the products of UV irradiation of *ortho*-toluyl cyanides which add to aliphatic and aromatic acyl cyanides to give 3-cyano-3-phenyl-8-methoxy-3,4-dihydroisocoumarins which are converted to isocoumarins by treatment with strong bases (**Scheme:5**).



Scheme: 5

2.3 Thallation-olefination of Arenes

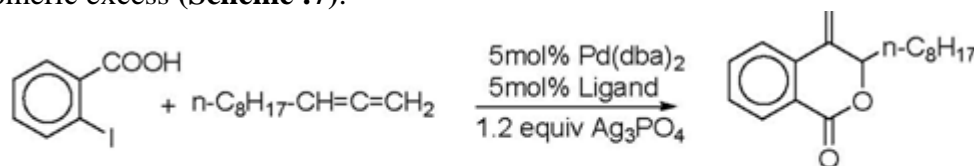
Isocoumarins and 3,4-dihydroisocoumarins were prepared in a single pot reaction, by reacting a benzoic acid with an electrophilic thallium salt in the presence of an organic solvent to give O-thalliated benzoic acid followed by reaction with an organic compound e. g. an alkene in the presence of PdCl₂ (**Scheme :6**).



Scheme :6

2.4 Palladium catalyzed method

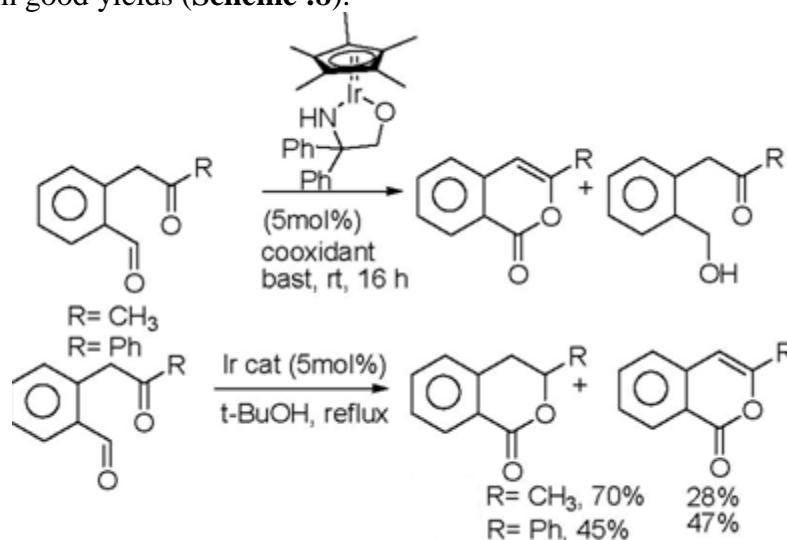
Aryl iodides with a nucleophilic substituent at the ortho position react with 1,2-dienes in the presence of a palladium catalyst and a chiral bisoxazoline ligand to afford isocoumarin in good yield and with 46-86% enantiomeric excess (**Scheme :7**).



Scheme :7

2.5 Iridium catalyzed method

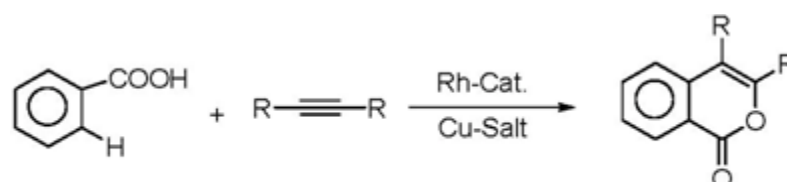
Two new cyclizations of ketoaldehydes have been developed using an Ir-ligand bifunctional catalyst. Oxidative lactonization of δ -ketoaldehydes proceeded smoothly at room temperature to give coumarin derivatives in excellent yields. Intramolecular Tishchenko reaction of δ -ketoaldehydes afforded 3,4-dihydroisocoumarins in good yields (**Scheme :8**).



Scheme: 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 $[\text{Cp}^*\text{RhCl}_2]_2$ and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as catalyst and oxidant respectively to produce the corresponding isocoumarin derivatives. The copper salt can be reduced to a catalytic quantity under air (**Scheme 1.9**).

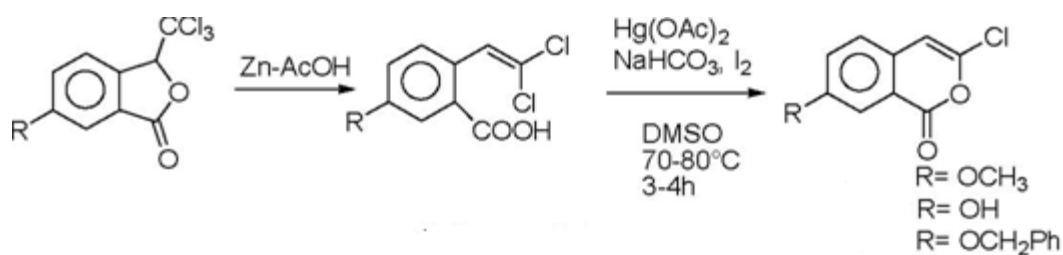


Scheme: 9

2.7 Mercury catalyzed method

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

isocoumarins (**Scheme :10**).



Scheme :10

3. 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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