



## SYNTHETIC APPROACHES FOR QUINOLINE AND ISOQUINOLINE

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Received: 10 March 2011, Revised and Accepted: 11 April 2011

**ABSTRACT**

The Quinoline and Isoquinoline nucleus is found to be very important in pharmacy field. In recent years, a lot of synthetic drugs have been synthesized in different yield.

In the present review, several other synthetic approaches are discussed involving easily available chemicals and producing high yields.

**Keywords:** Quinoline, Isoquinoline

**INTRODUCTION****Quinoline**

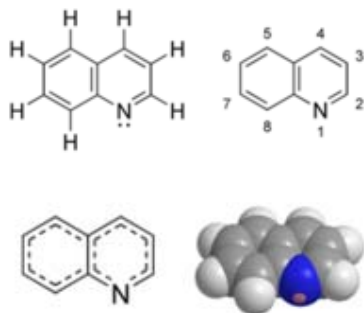
**Quinoline** is a heterocyclic aromatic organic compound. It has the formula  $C_9H_7N$  and is a colourless hygroscopic liquid with a strong odour. Aged samples, if exposed to light, become yellow and later brown. Quinoline is only slightly soluble in cold water but dissolves readily in hot water and most organic solvents<sup>1</sup>

Quinoline is mainly used as a building block to other specialty chemicals. Approximately 4 tonnes are produced annually according to a report published in 2005. Its principal use is as a precursor to 8-hydroxyquinoline, which is a versatile chelating agent and precursor to pesticides. Its 2-and4-methyl derivatives are precursors to cyanine dyes. Oxidation of quinoline affords

quinolinic acid (pyridine-2,3-dicarboxylic acid), a precursor to the herbicide sold under the name "Assert"<sup>2</sup> Like other nitrogen heterocyclic compounds, such as pyridine derivatives, quinoline is often reported as an environmental contaminant associated with facilities processing oil shale or coal, and has also been found at legacy wood treatment sites. Owing to high water quinoline has significant potential for mobility in the environment, which may promote water contamination<sup>3</sup>

**Isolation and synthesis**

Quinoline was first extracted from coal tar in 1834 by Friedlieb Ferdinand Runge.<sup>4</sup> Coal tar remains the principal source of commercial quinoline.

**Quinoline****IUPAC name**

Quinoline

Other names

1-benzazine, 1-azanaphthalene, benzo[b]pyridine

**Properties****Molecular formula** $C_9H_7N$ **Molar mass**

129.16 g/mol

**Density**

1.093 g/ml

**Melting point**

-15 °C

**Boiling point**

238 °C

**Solubility in water**

Soluble

**Isoquinoline**

Isoquinoline and quinoline are benzopyridines, which are composed of a benzene ring fused to a pyridine ring<sup>5</sup>. In a broader sense, the term isoquinoline is used to make reference to isoquinoline derivatives. 1-Benzylisoquinoline is the structural backbone in naturally occurring alkaloids including papaverine and morphine. The isoquinoline ring in these natural compound derives from the aromatic amino acid tyrosine.<sup>6,7,8,9,10,11</sup>

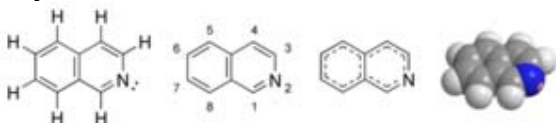
**Properties**

Isoquinoline is a colorless hygroscopic liquid at room temperature with a penetrating, unpleasant odor. Impure samples can appear brownish, as is typical for nitrogen heterocycles. It crystallizes platelets that have a low solubility in water but dissolve well in ethanol, acetone, diethyl ether, carbon disulfide, and other common organic solvents. It is also soluble in dilute acids as the protonated derivative.

Being an analog of pyridine, isoquinoline is a weak base<sup>12</sup>, with an  $pK_b$  of 8.6. It protonates to form salts upon treatment with

strong acids, such as HCl. It forms adducts with Lewis acids, such as  $BF_3$ .

### Isoquinoline



#### IUPAC name

Isoquinoline

Other names

benzo[c]pyridine, 2-benzanine

#### Properties

##### Molecular formula

$C_9H_7N$

##### Molar mass

129.16 g/mol

##### Appearance

yellowish oily liquid, hygroscopic  
platelets when solid

##### Density

1.099 g/cm<sup>3</sup>

##### Melting point

26 - 28 °C

##### Boiling point

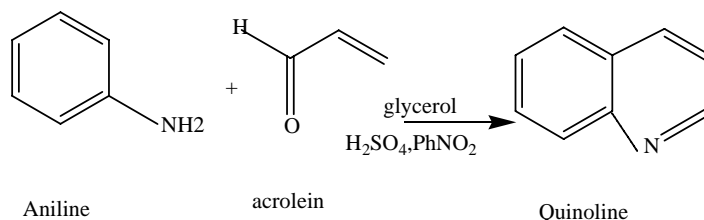
242 °C, 515 K, 468 °F

### QUINOLINE SYNTHESIS

#### Name Reactions

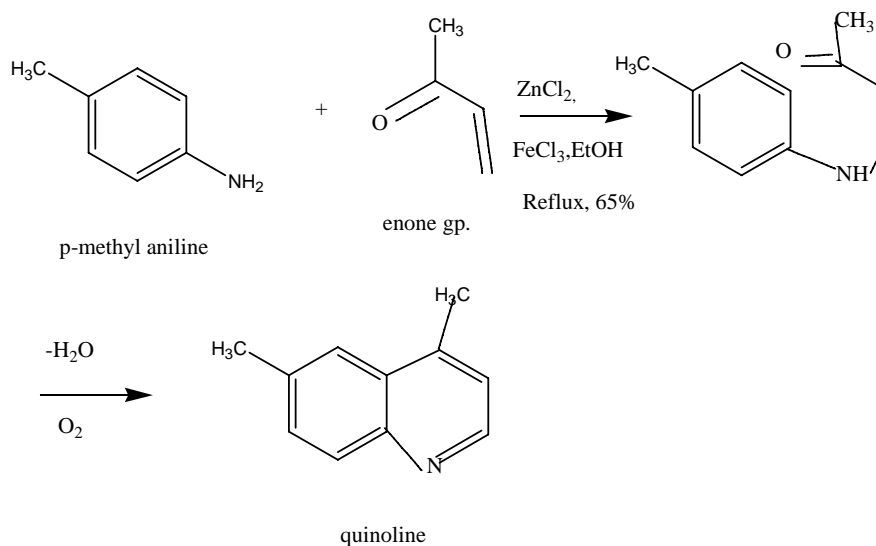
##### SKRAUP SYNTHESIS:<sup>13,14,15</sup>

Quinoline is produced when aniline, conc. Sulfuric acid, glycerol and mild oxidising agent are heated together<sup>16</sup>. The reaction proceeds via dehydration of glycerol to acrolein. It is the best reaction for synthesis of quinoline<sup>17</sup>



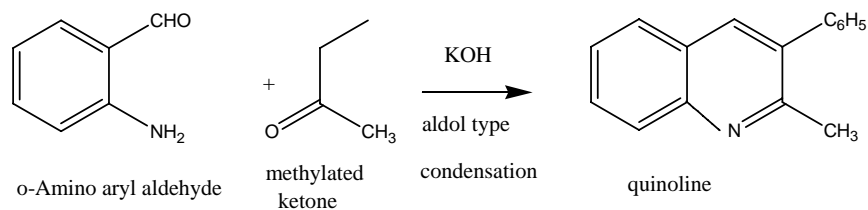
##### DOEBNER-MILLER RING SYNTHESIS:<sup>13</sup>

The interaction of enone gp. (carbonyl gp.) to aniline takes place producing quinoline derivative. Improvement to this reaction includes the use of 2 phase organic or aqueous acid system.<sup>18</sup>

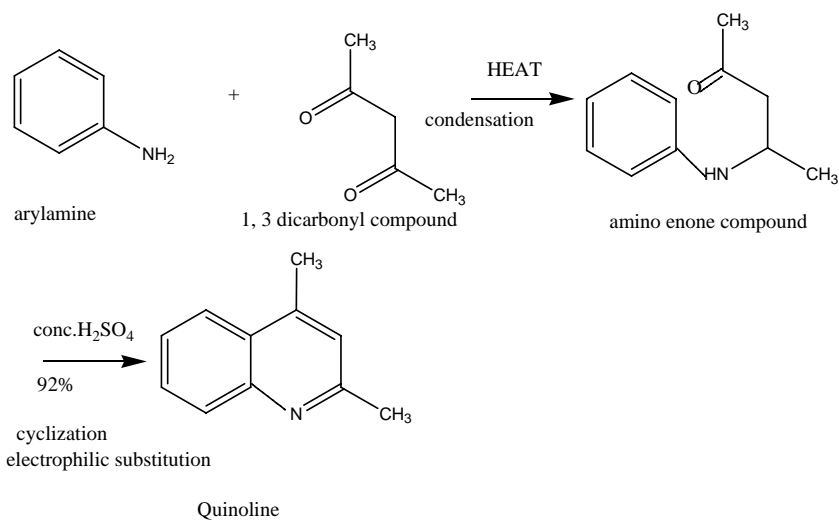


**FRIEDLANDER SYNTHESIS:** <sup>14</sup>

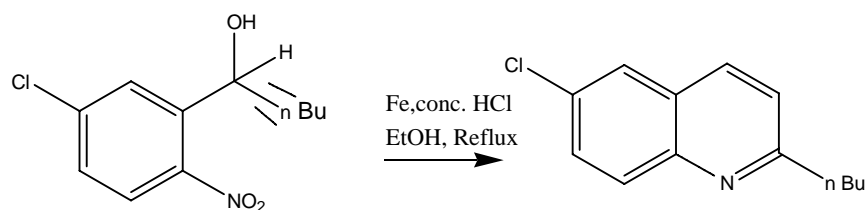
The reaction proceeds through aldol type condensation. *o*-amino aryl aldehyde is reacted with a ketone carrying an alpha methylene group.

**COMBES SYNTHESIS:** <sup>12,13</sup>

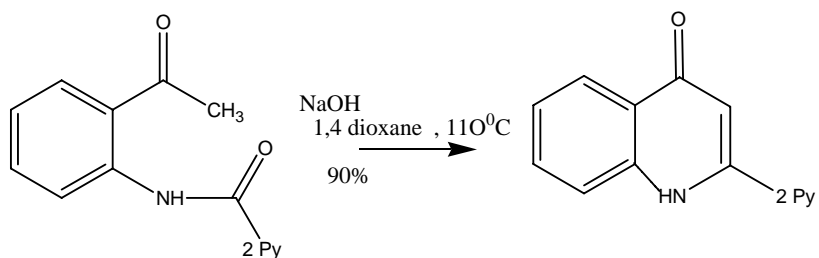
Condensation of 1,3 dicarbonyl compound with the arylamine gives the high yield of amino enone, which can be cyclized with conc. acid<sup>19</sup>. In order to access 4-unsubstituted quinoline, a 1,3 keto aldehyde, guarantees the regioselectivity <sup>20,21</sup>

**OTHER METHODS** <sup>13</sup>

A. Ring closure of *o*-amino aryl-alkynyl-carbinols, readily available by acetylide addition to an aryl ketone or aldehyde can be achieved with Cu and Pd catalysis. <sup>22</sup> *o*-nitroaryl-carbinols undergo nitro group reduction and ring closure simply by treatment with a metal/acid combination. <sup>23</sup>



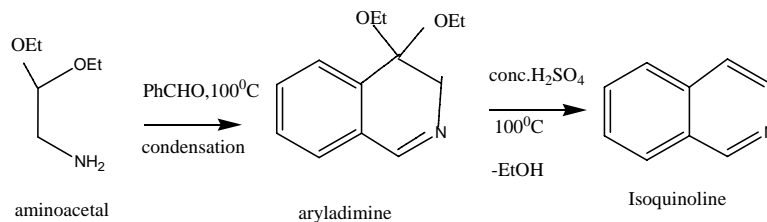
B. Pd catalysed amidation of halo-arens allows simple assembly of precursors to 4-quinolones. <sup>24</sup>



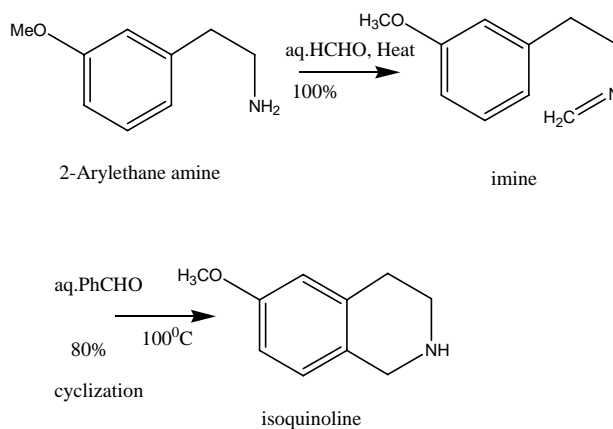
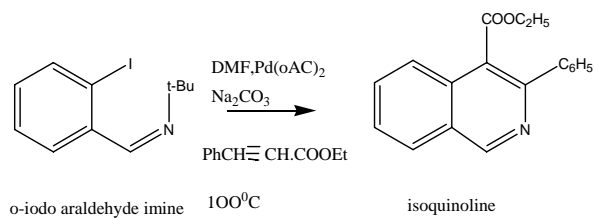
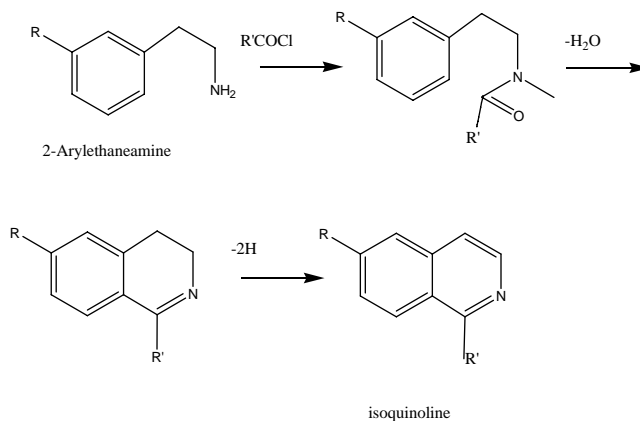
**ISOQUINOLINE SYNTHESIS****POMERANZ-FRITSCH SYNTHESIS:** <sup>13</sup>

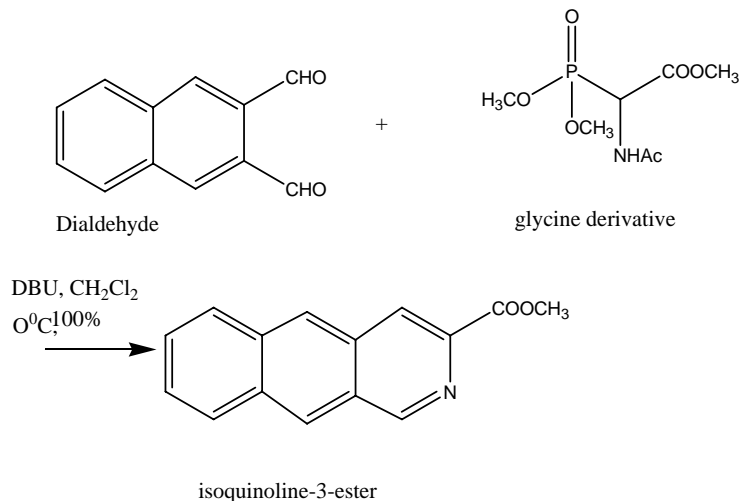
This reaction is carried out in 2 steps:

- 1) aryl aldehyde is condensed with amino acetal to form an aryl-aldimine.
- 2) aldimine is cyclized by treatment with strong acids.<sup>25,26</sup>

**PICTET-SPENGLER SYNTHESIS:** <sup>13</sup>

2-aryl ethanamines react with aldehyde easily to give imines. 1,2,3,4 tetrahydro isoquinoline results from the cyclization with acid catalysis.

**ISOQUINOLINE FROM O-ALKYNYL-ARALDEHYDE IMINES:** <sup>13</sup>**ISOQUINOLINE ETHANEAMIDES:** <sup>13</sup>

FROM DIALDEHYDES:(Wittig-Horner reaction) <sup>13</sup>SYNTHESIS OF METHYL 2-(3-PYRIDYLCARBONYL)BENZOATE AND THE 2-(PYRIDYLCARBONYL)BENZOIC ACIDS: SYNTHESIS OF BENZO ISOQUINOLINE-5, 10-DIONE (2-AZAANTHRAQUINONE). <sup>27</sup>

Methyl 2-(3-pyridylcarbonyl) benzoate (**1**) and 2-(3-pyridylcarbonyl)

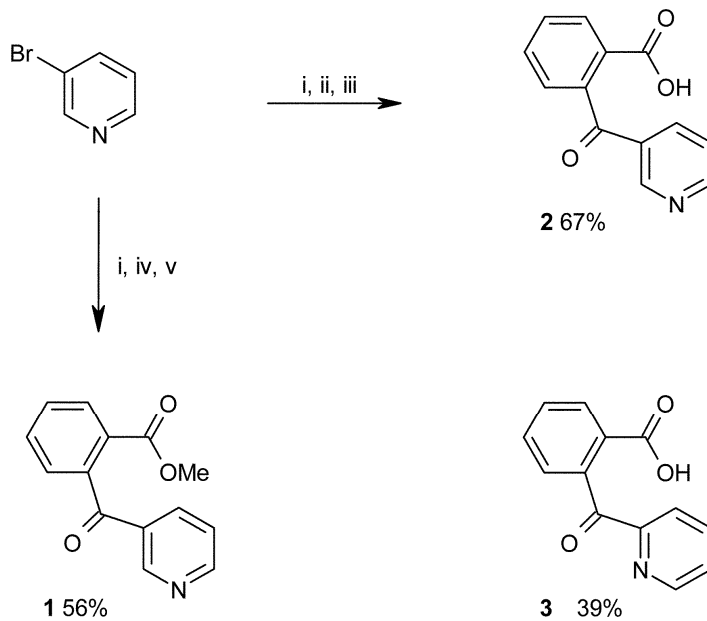
Benzoic acid (**2**) were easily prepared from 3-bromopyridine

Via a bromine–lithium exchange reaction <sup>28</sup>.To reach

The acid **2**. Esterification of the acid **2** was not necessary to get

The ester **1**; this latter was obtained in 56% yield quenching

3-lithiopyridine with dimethyl phthalate. <sup>29,30</sup>



(i) 1 equiv. BuLi, Et<sub>2</sub>O, 75 °C, 1 h;

(ii) 1 equiv. phthalic anhydride, 75 °C, 2 h;

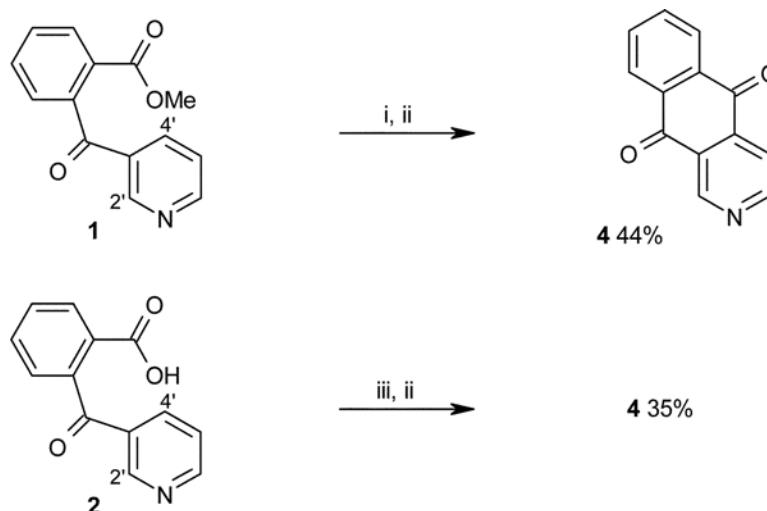
(iii) acidic hydrolysis;

(iv) 1 equiv. dimethyl phthalate, 75 °C, 2 h;

(v) hydrolysis

**SYNTHESIS OF BENZO ISOQUINOLINE-5, 10-DIONE(2-AZAANTHRAQUINONE).<sup>27</sup> INTERESTINGLY, WHEN EXPOSED TO THIS BASE IN TETRAHYDROFURAN**

(THF) at 0 °C, the ester **1** was deprotonated and the lithio derivative at C4 was converted in situ to biologically active 2-azaanthraquinone (**4**) in 44% yield. The product **4** was also formed from the related acid **2**, albeit in lower yield (35%)<sup>31,32</sup>.



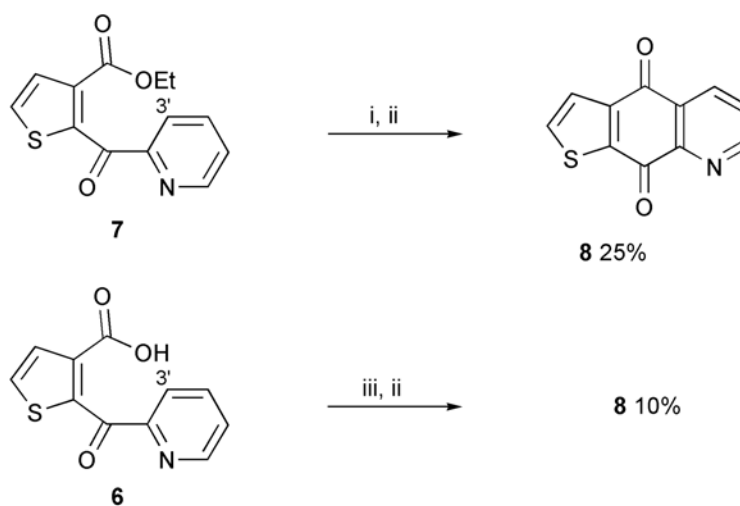
- i. 3 eq. LTMP, THF, 2 hr
- ii. hydrolysis
- iii. 3 eq LTMP, THF, 2 hr

**SYNTHESIS OF BENZO[G]QUINOLINE-5,10-DIONE (1-AZAANTHRAQUINONE):<sup>27</sup>**

The protocol was extended to the acid **3**, giving biologically Active<sup>33</sup> 1-azaanthraquinone (**5**) in a poor yield of 16%. Intramolecular complexation of the Lewis acidic lithium atom of the COOLi group by the pyridine nitrogen could favour intermolecular addition of the lithiopyridine formed to a ketone CO group present.

**SYNTHESIS OF THIENO(3,2-G)QUINOLINE 4, 9-DIONE.<sup>27</sup>**

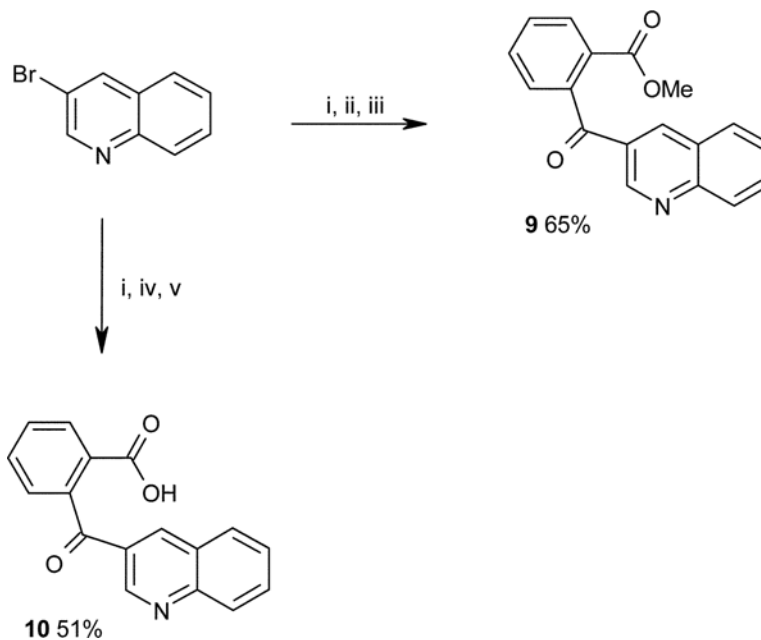
Active thieno[3,2-*g*]quinoline-4, 9-dione (**8**)<sup>34</sup>, was obtained in 10% and 25% yields, respectively, when the acid **6** and its ethyl Ester **7** were exposed to LTMP. The aforementioned less acidic **6** Hydrogen at C3 and, more importantly, the facile deprotonation of the thiophene ring under the conditions used could alter the course of the reaction<sup>35,36</sup>.



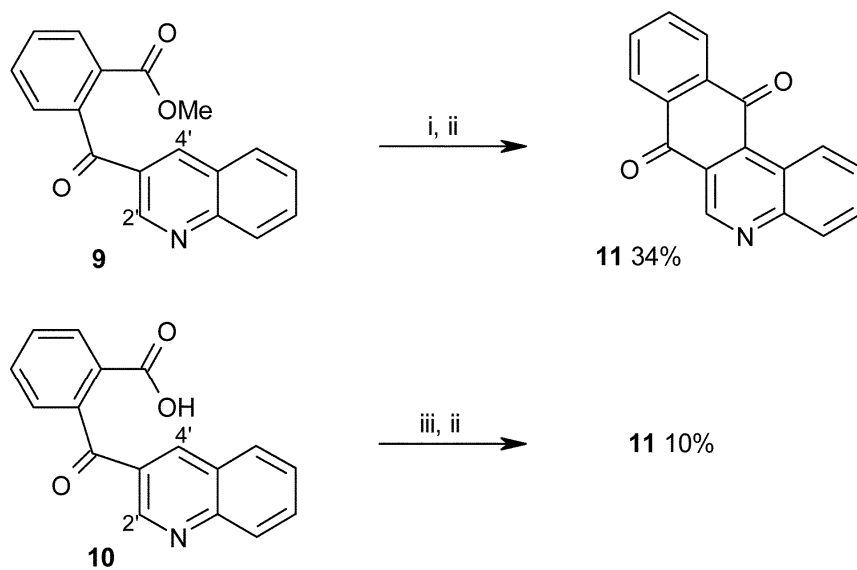
- i. 3 eq LTMP, THF, -75 °C, 2 hr
- ii. 3 eq LTMP, THF, 2 hr
- iii. 3 equiv. LTMP, THF, 0 °C,

**SYNTHESIS OF METHYL 2-(3-QUINOLYL CARBONYL BENZOATE AND 2-(3-QUINOLYL CARBONYL) BENZOIC ACID:** <sup>27</sup>

Methyl 2-(3-quinolylcarbonyl) benzoate (**9**) and 2-(3-quinolylcarbonyl) Benzoic acid (**10**) were prepared through a bromine-lithium exchange reaction of 3-bromoquinoline<sup>37</sup>

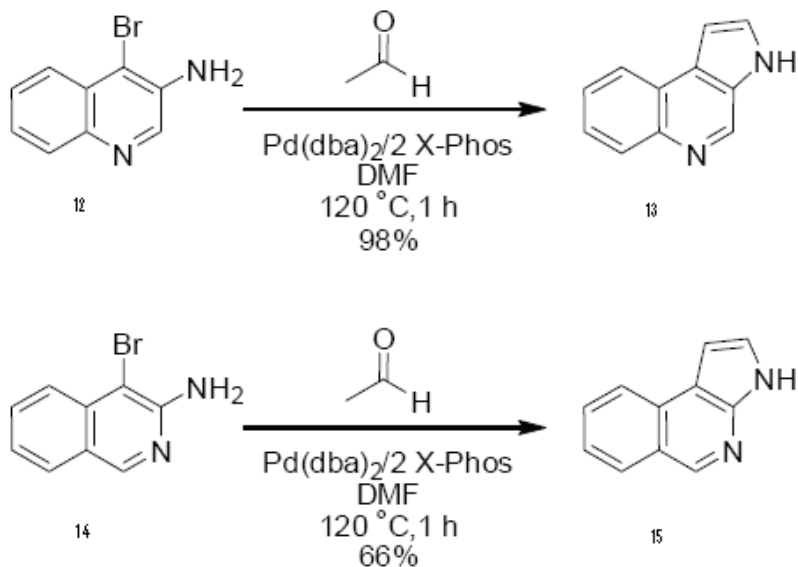


- i. eq tertiary BuLi, Et<sub>2</sub>O, 1 hr
- ii. 1 eq dimethyl, -75 °C 2 hr
- iii. hydrolysis
- iv. 1 eq phthalic anhydride -75 °C, 2 hr
- v. acidic hydrolysis

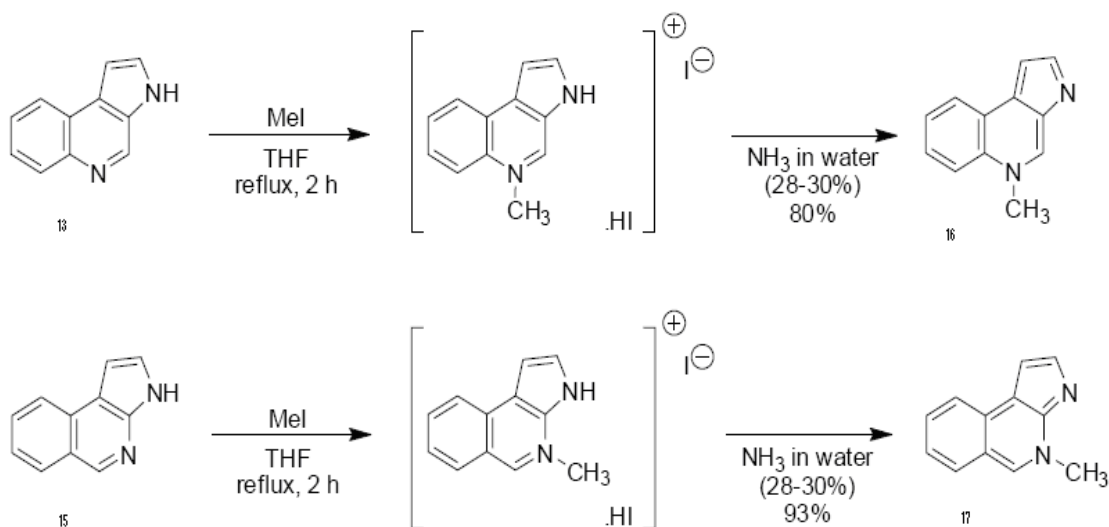
**SYNTHESIS OF BENZO(PHENANTHRIDINE-7,12 DIONE)**<sup>27</sup>

- i. 3 eq LTMP, THF, 2 hr
- ii. hydrolysis
- iii. 3 eq LTMP, THF, 2 hr

**SYNTHESIS OF 3H-PYRROLO [2,3-C] QUINOLINE AND 3H-PYRROLO [2,3- C] ISOQUINOLINE VIA A PD-CATALYZED ANNULATION REACTION<sup>38,39</sup>.**



**SELECTIVE N-5 METHYLATION OF 13 AND SELECTIVE N-4 METHYLATION OF 15<sup>40,41</sup>**



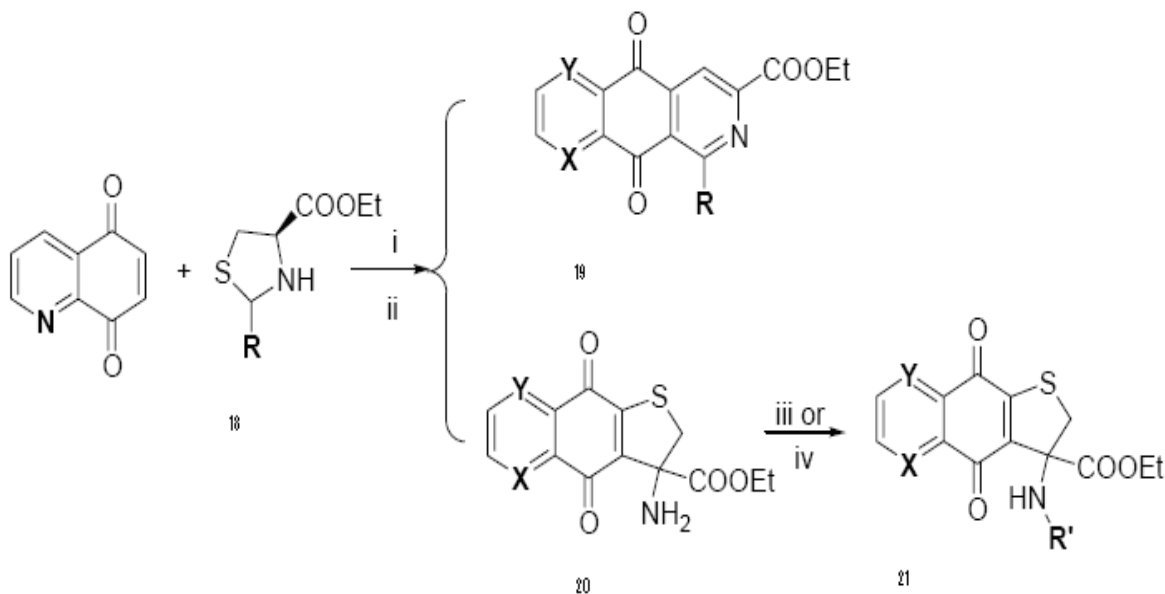
**SYNTHESIS OF NEW PYRIDO [4,3- G AND 3,4-G] QUINOLINE-5, 10-DIONE AND DIHYDROTHIENO [2,3-G AND 3,2-G]QUINOLINE-4,9-DIONE DERIVATIVES: <sup>42</sup>**

The compounds presented in this study were obtained by a cycloaddition reaction between the corresponding thiazolidine derivatives **18a-e** and quinoline-5,8-dione, using silver carbonate and DBU as base.<sup>43</sup>

**Scheme .** General synthetic method. Reagents:

- $\text{Ag}_2\text{CO}_3$ , DBU,  $\text{CH}_3\text{CN}$ ;
- $\text{HCl}/\text{H}_2\text{O}$ ;
- Aryl-COCl, TEA, THF;
- a: Boc-L-Phe, HBTU, HOBt, DIEA, DMF; b:  $\text{HCl}/\text{diethyl ethersolution}$ ; c: Phenylisocyanate,  $\text{CH}_2\text{Cl}_2$ ,  $\Delta$ .





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