STUDIES ON THE SYNTHESIS AND REACTIONS OF SOME HETEROCYCLIC COMPOUNDS

By

MOHAMED GOMAA ALI BADRY

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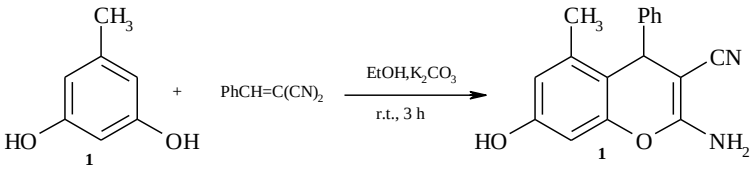
Part I

An approach to heterocyclic synthesis based on *2-Amino-5-hydroxy-4-phenyl-7-methyl-4H[1]benzopyran-3-carbonitrile*

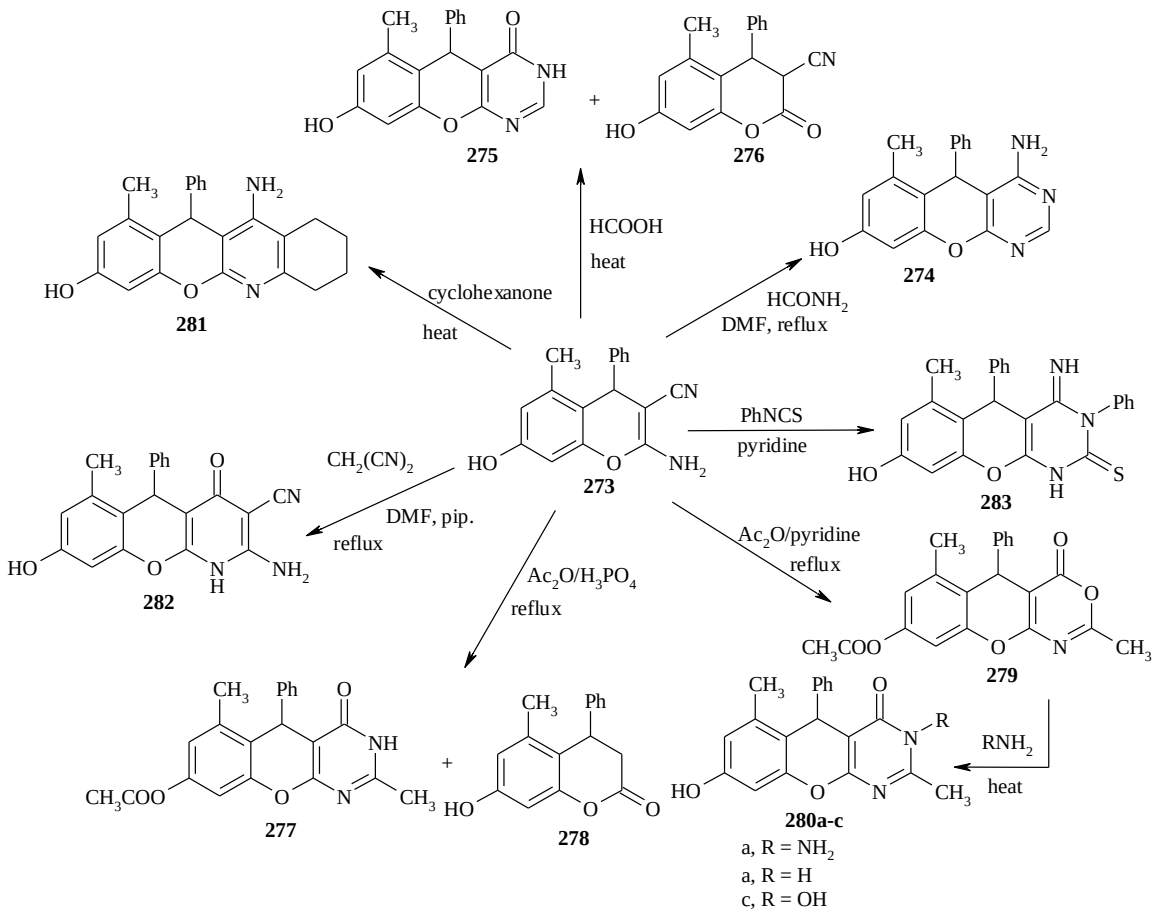
The synthesis of the chromene **273** was achieved through the combination between orcinol monohydrate and benzylidenemalononitrile in absolute ethanol containing anhydrous potassium carbonate at room temperature (Scheme 1). The structure of compound **273** was confirmed based on spectroscopic and analytical data.



The cyano and amino substituents, in combination with chromene double bond, provide a rich opportunity for heterocyclic construction. In a first experiment, reaction between chromene **273** and formamide in refluxing dimethylformamide (DMF) furnished the aminopyrimidine **274** in 80% yield (Scheme 2). In contrast, a cyclocondensation of compound **273** with hot formic acid resulted in the formation of a separable mixture of the pyrimidinone **275** and the dihydrocoumarin **276**, in 52 and 38% yields respectively (Scheme 2). The reaction between the chromene **273** and acetic

anhydride was conducted under both acidic and basic conditions. Thus, refluxing compound **273** in a mixture of acetic anhydride and phosphoric acid for several hours resulted in formation of the pyrimidine **277**, together with, once again, an enamine hydrolysis product, the dihydrocoumarin **278** (Scheme 2). In contrast, heating chromene **273** in a mixture of acetic anhydride and pyridine gave the oxazinone 2**79** (Scheme 2); the identities of all these compounds were deduced from spectroscopic data. A facile synthetic method for converting an oxazinone into the corresponding pyrimidinone is by reactions with amines. Thus, heating oxazinone 2**79** with hydrazine hydrate, formamide or hydroxylamine delivered around 60% isolated yields of the corresponding pyrimidinones 2**80a-c** (Scheme 2).

A number of other heterocyclic residues can be built onto the initial chromene **273**, by reason of the presence of the cyano enamine functional group combination. For example, condensation of the chromene **273** and cyclohexanone in the presence of the Lewis acid zinc chloride proceeded smoothly to give a 61% isolated yield of the pyridine derivative **281** (Scheme 2). Heating chromene **273** with malononitrile in refluxing DMF containing piperidine causes a reaction in a reverse sense, but one which produces a similar product, the 4-pyridinone **282**, in 75% isolated yield (Scheme 2).



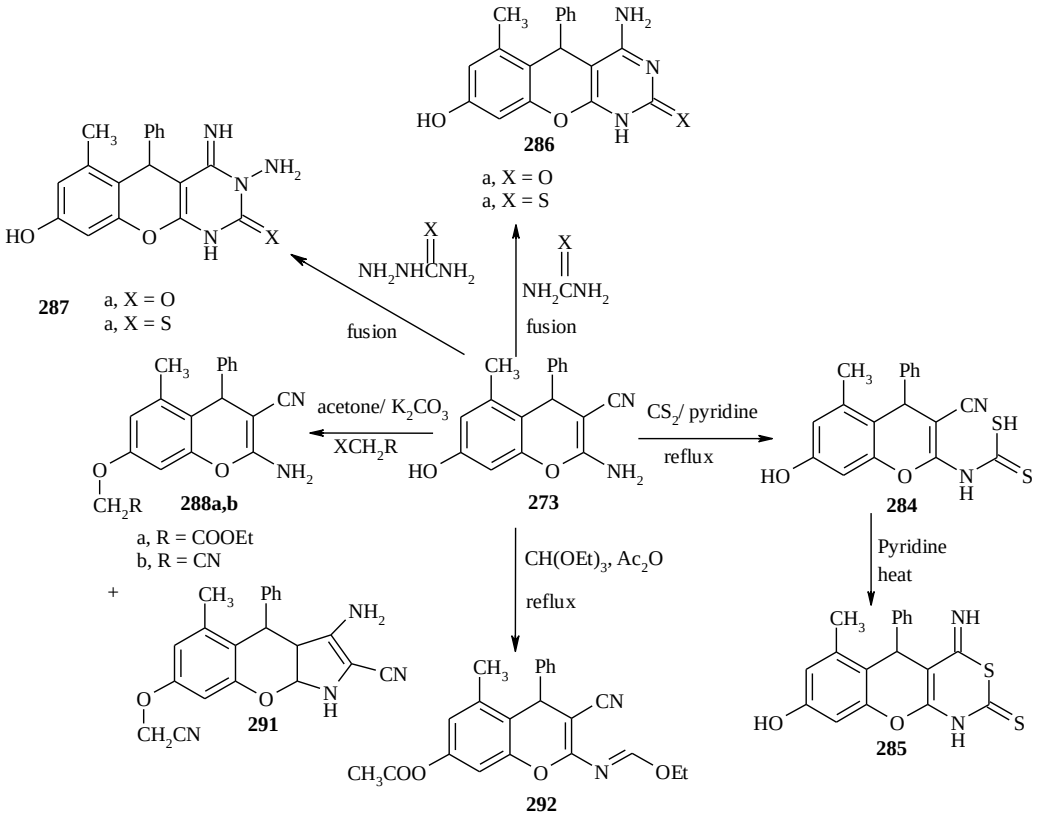
Scheme 2

Moreover, the chromene **273** was reacted with sulfur containing reagents such as phenyl isothiocyanate and carbon disulfide in refluxing pyridine and gave compounds **283** and **284** respectively. Compound **284** was further refluxed in pyridine to afford the thiazine **285**.

Another route for contracting pyrimidine nucleus was the cyclocondensation between the chromene **273** and urea, thiourea, semicarbazide and thiosemicarbazide under fusion conditions furnishing compounds **286a,b** and **287a,b** respectively.

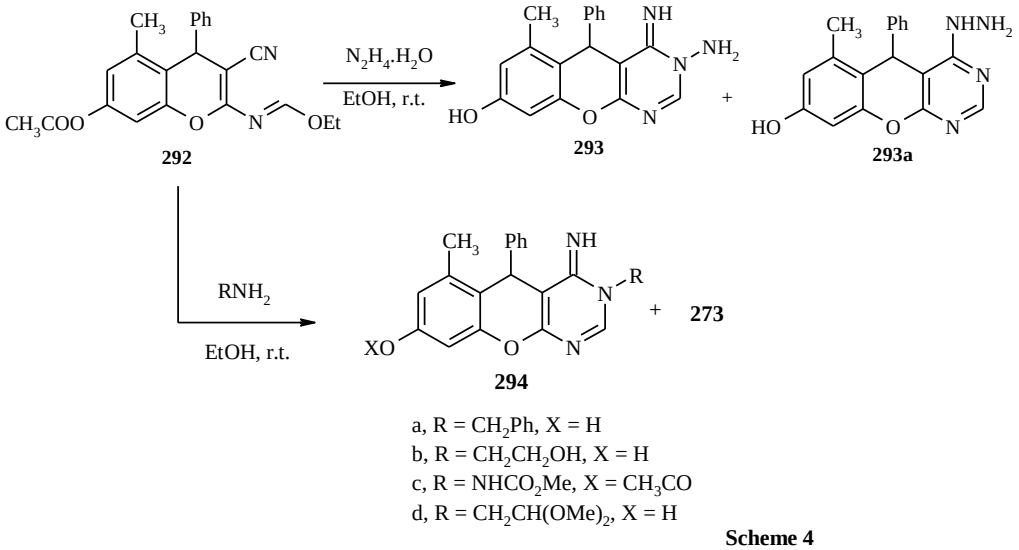
alkylation of the initial chromene **273** was investigated, with the aim of setting up precursors suitable for pyrrole formation, for example. Unfortunately, such reactions occurred predominantly at the phenol hydroxy

group: the *O*-alkylation products **288a,b** were formed when chromene **273** was exposed to either ethyl bromoacetate or chloroacetonitrile in acetone containing anhydrous potassium carbonate. As the 2-amino group in chromene **273** is, in effect, a vinylogous cyanamide, these outcomes are perhaps not so surprising. In the case of bromoacetate, the *O*-alkylation product **288a** was the sole product. However, in the case of chloroacetonitrile, both the *O*-alkylation product **288b** and the pyrrole **291** were isolated, in 48% and 47% yields respectively. All spectroscopic and analytical data were consistent with the structure **291** proposed. Condensation between the chromene **273** and triethyl orthoformate in acetic anhydride under reflux furnished the imine **292**.



Scheme 3

For further heterocyclic synthesis, the condensation between imine **292** and amines including hydrazine hydrate, benzylamine, ethanolamine, methyl carbazate and aminoascetaldehyde dimethylacetal in ethanol at room temperature and gave the pyrimidines **293** and **294a-d** accompanied in some cases with by-products (Scheme 4).



292 **293** **293a** **294**

a, R = CH_2Ph, X = H
b, R = CH_2CH_2OH, X = H
c, R = $NHCO_2Me$, X = CH_3CO
d, R = $CH_2CH(OMe)_2$, X = H

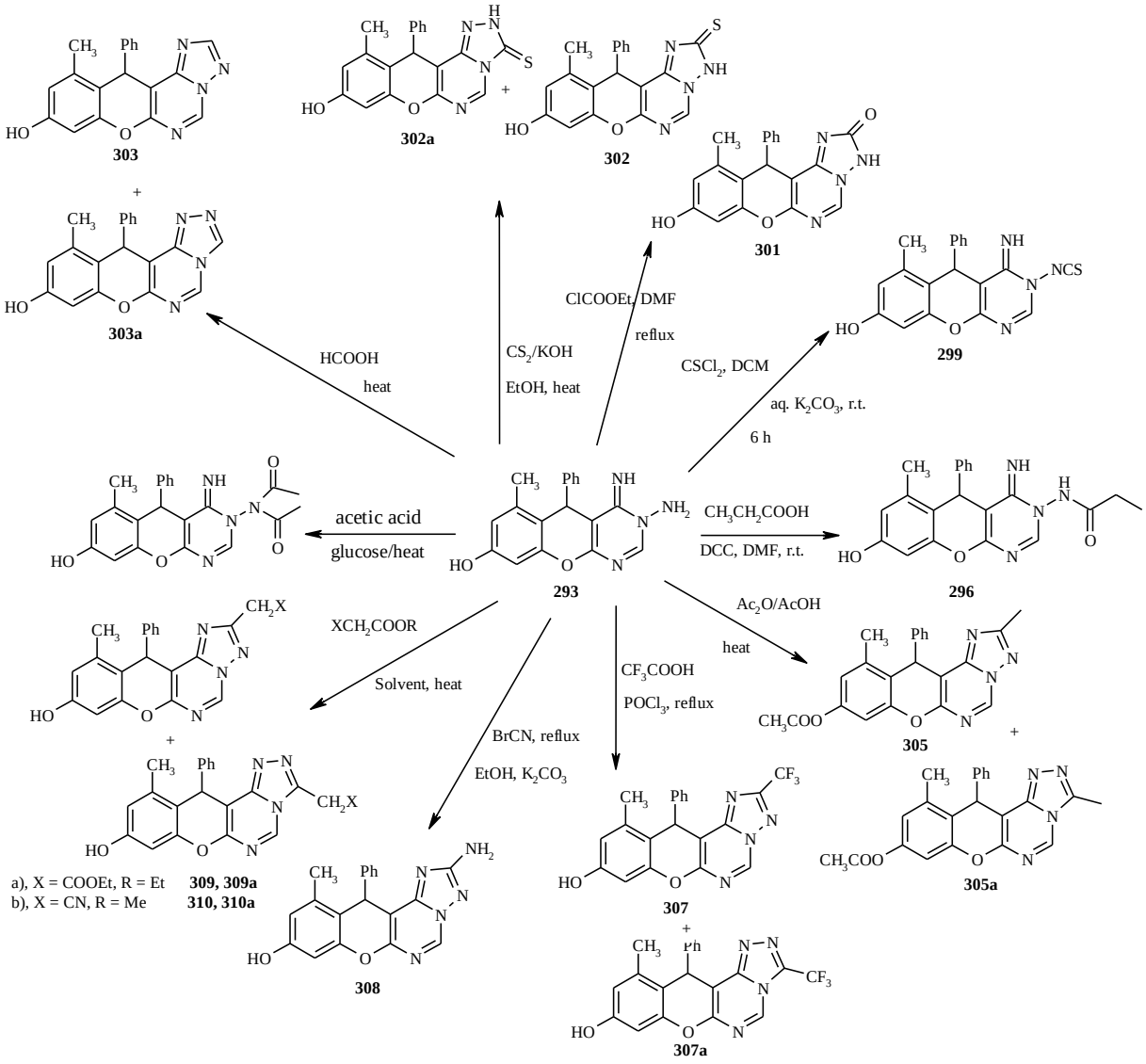
Scheme 4

Consequently, the *N*-aminopyrimidine **293** which was obtained as a pair of isomers, was further subjected to reaction with several reagents such as propionic acid, acetic acid and thiophosogene furnishing compounds **296**, **298** and **299** respectively.

Many differently substituted triazolopyrimidines were synthesised starting from the isomeric mixture **293** and **293a**, the majority of which were obtained as a pair of isomers as a result of Dimroth-type rearrangement. Thus heating compound **293** with ethyl chloroformate in DMF for 1 h gave the trizolopyrimidine **301** while its reaction with carbon disulfide in an alcoholic potassium hydroxide afforded the isomers **302** and **302a**.

The condensation of compound **293** with hot formic acid gave the isomeric mixture **303** and **303a** which subsequently acetylated in a mixture of acetic

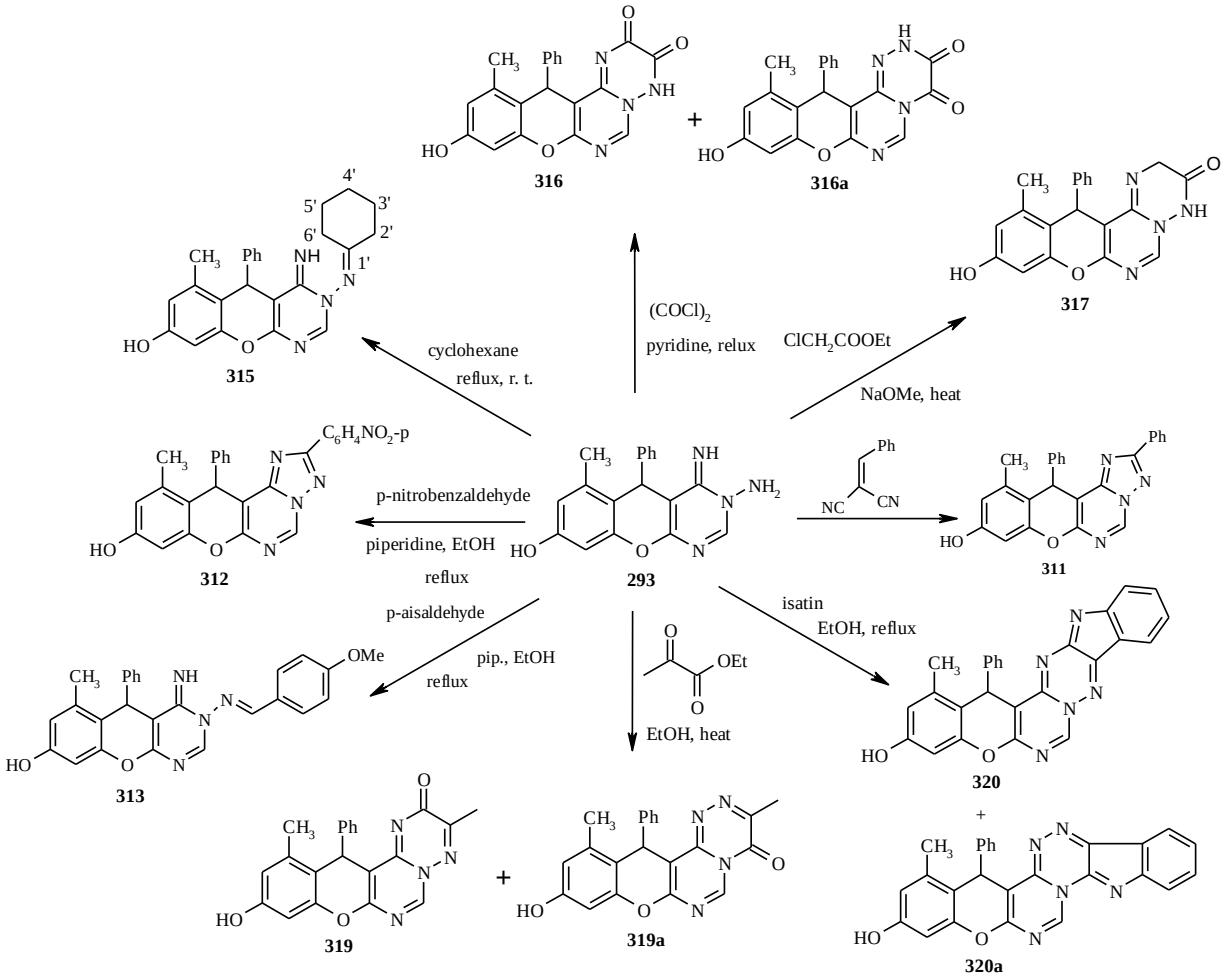
anhydride and acetic acid furnishing the acetates **304** and **304a**. Similarly, boiling the *N*-aminopyrimidine **293** in acetic anhydride afforded the trimethyltriazolopyrimidine as a pair of isomers **305** and **305a**. Condensation of compound **293** with trimethyl orthoacetate and trifluoroacetic acid under reflux conditions afforded compound **306** and the isomeric mixture **307** and **307a** respectively. Heating compound **293** with cyanogens bromide in absolute ethanol containing anhydrous potassium carbonate afforded the aminotriazolopyrimidine **308**.



Scheme 5

Active methylene compounds such as diethyl malonate and methyl cyanoacetate have been condensed with compound **293** and furnished the expected products as isomeric mixtures **309**, **309a** and **310**, **310a**. The combination between compound **293** and benzylidenemalononitrile at room temperature afforded unexpected triazolopyrimidine **312**. The base-catalyzed condensation between compound **293** and aromatic aldehydes gave the triazolopyrimidine **313** in case of *p*-nitrobenzaldehyde and the Schiff base

313 in case of *p*-anisaldehyde. Similarly, reaction with cyclohexanone afforded the condensation product **315**. Moreover, a number of fused triazines could be prepared through the combination between compound **293** and different reagents as oxaloyl chloride, ethyl chloroacetate, ethyl pyruvate and isatin under reflux furnishing the expected products as pairs of isomers (except in case of ethyl chloroacetate) **316**, **316a**, **317**, **319**, **319a** **320**, **320a** respectively. The structures of all these compounds were confirmed by spectroscopic data.

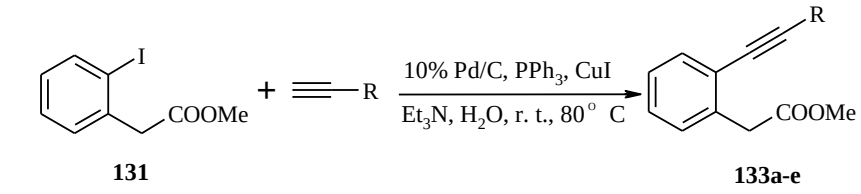


Scheme 6

Part II

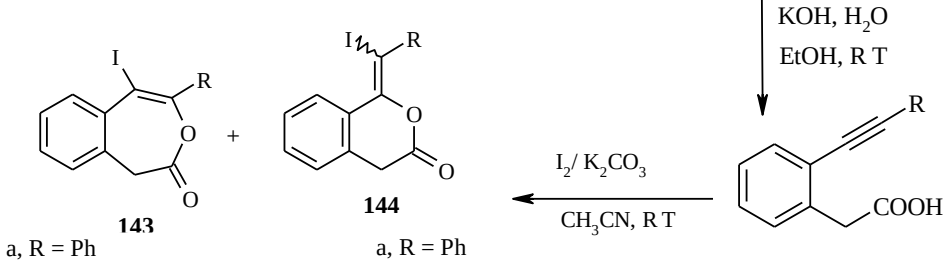
Starting with the readily available 2-iodophenylacetic acid which was converted to the methyl ester **131** through reaction with methyl alcohol in the presence of acetyl chloride. The obtained ester was coupled to a range of alkynes (some of which were prepared from aldehydes using Bestmann-Ohira reagent) through a Sonogashira reaction and gave the methyl alkynyl phenylacetate **133a-e** which then hydrolyzed to the corresponding acids **141a-i**. The behaviour of the acids towards iodocyclization (I_2/K_2CO_3 in MeCN) was investigated and found to be dependent on the structure of the substituent on the alkyne terminus. Thus, when the subsistent was an alkyl, the 6-exo-dig mode was favored to give the alkylidenelactones**144**, however, changing the substituent into the more electron rich aromatic ones, resulted

in the predominance of the 7-endo-dig mode affording the corresponding benzoxepines **143**.



131 **133a-e**

Scheme 53



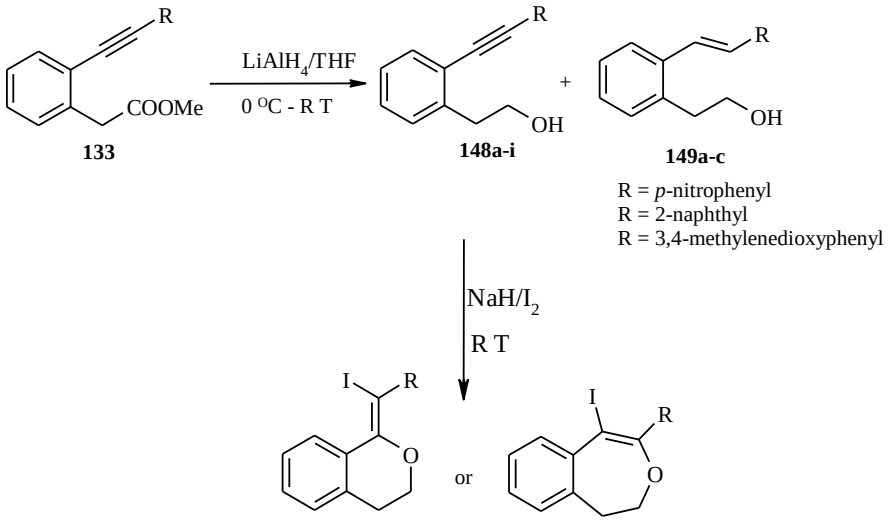
143 **144** **141a-i**

a, R = Ph
b, R = Bu
c, R = CH_2OH
d, R = *p*-C_6H_4-NO_2
e, R = *p*-$C_6H_4OCH_3$
f, R = 3,4-methylenedioxophenyl
g, R = 2,3,4-trimethoxyphenyl

a, R = Ph
b, R = n-Bu
c, R = CH_2OH

Scheme 1

The alkynyl esters were reduced to the corresponding alcohols **148** with $LiAlH_4$ in THF; these alcohols were subjected to cyclization with iodine and sodium hydride either in THF or neat. The products **151** obtained in case of using THF were found to contain iodine and formed as a result of 7-endo mode, on the other hand, the products **152** or **153** contained no iodine when no THF was used.

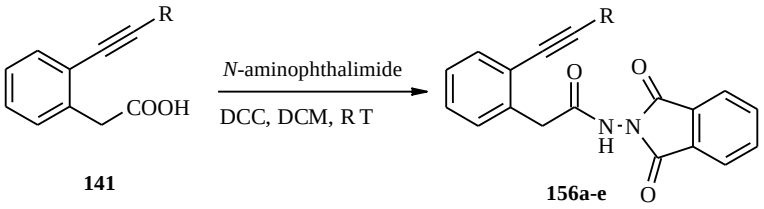


133 **148a-i** **149a-c**

R = *p*-nitrophenyl
R = 2-naphthyl
R = 3,4-methylenedioxyphenyl

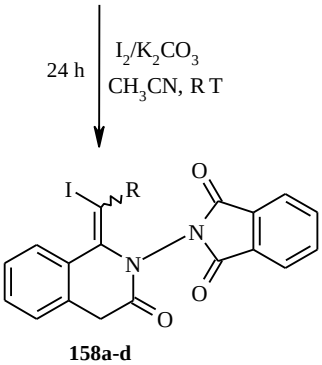
Scheme 2

For further studies to more cyclizations, the carboxylic acids were coupled to amines such as *N*-aminophthalimide and gave the corresponding phthalimide derivatives **156**. These phthalimides were investigated towards iodocyclization using three equiv. of both iodine and potassium carbonate in DCM and the products were the isoquinolines **158** as a result of 6-exo mode.



141 **156a-e**

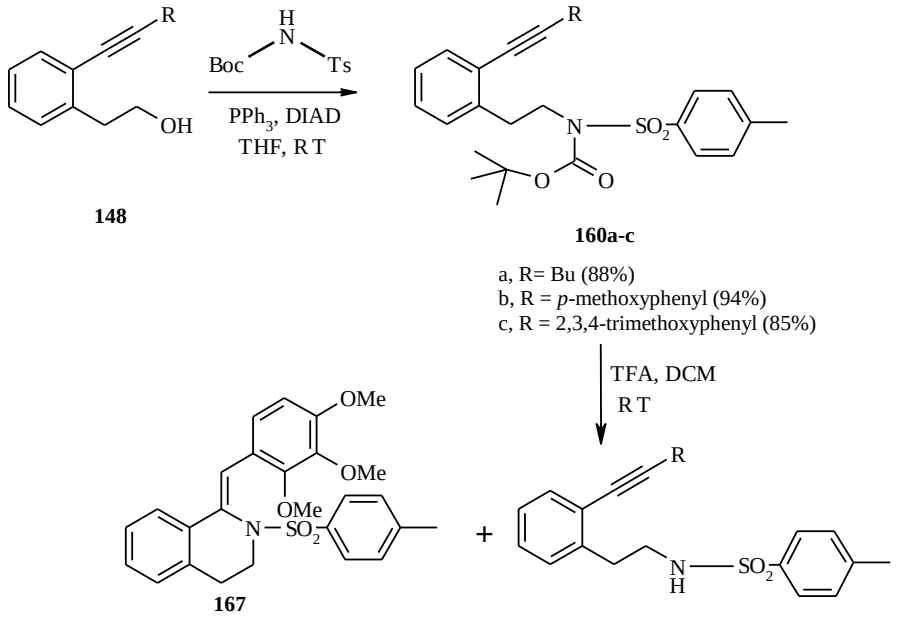
Scheme 67



158a-d

Scheme 3

Mitsunobu reaction another route for obtaining nitrogen nucleophiles which could be used in heterocyclic synthesis. The reaction was carried out between the alcohols and *N*-*t*-butyloxycarbonyl-*p*-toluenesulfonamide using the standard conditions affording the corresponding carbamates**160**. Consequently, the carbamates were subjected to Boc removal using TFA in DCM furnishing the corresponding sulfonamides **165** accompanied in some cases with other products such as ketone or the cyclizatrion products **167**.



Scheme 4

Acid-catalyzed cyclizations of the sulfonamides using triflic acid were studied and afforded the cylization products **175** in case of electron rich aromatic alkynes.

Attempts for iodocyclization of these sulfonamides were unsuccessful and afforded the diodide addition product in some cases.