# UTILITY OF ORGANOMETALLIC REAGENTS AND ARYLHYDRAZONONITRILES IN SYNTHESIS OF AROMATIC AND HETEROAROMATIC COMPOUNDS

### A Thesis

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By

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Title: Utility of Organometallic Reagents and Arylhydrazononitriles in Synthesis of Aromatic and Heteroaromatic Compounds

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# **SUMMARY**

Efforts have been directed towards developing a new synthetic routes for 2-arylhdrazononitriles as well as aminopyrazoles and amino-1,2,3-triazoles as precursors to condensed azoles of potential biological activities. Reported here the results of trials to utilize 2-arylhdrazononitriles and its derivatives as precursors to 4-aminopyrazole-5-carboxylic acid derivatives and 4-aroyl-2-substituted-1,2,3-triazoles. Interesting novel synthesis of eneazo derivatives and their electrocyclization into cinnoline is also included.

• The work will be divided into four parts:

## PART I

# <u>Studies With 2-Arylhydrazononitriles: New Synthetic Routes to 3-Sub-</u> <u>stituted-2-Arylhydrazononitriles</u>

In this part have been developed two new synthetic routes for the 2-arylhydrazononitriles:

1- We applied the new reported route to 3-indoloylacetonitriles 1 and described a way to convert it into the hydrazononitrile 2. Utilizing a similar methodology enabled synthesis of 3 which can be converted easily to the corresponding arylhydrazones 4.



2- Uility of Grignard reagent to synthesis the not readily obtainable arylhydrazononitrile:

Thus reacting the readily obtainable 2-phenylhydrazonomalononitrile (5) with excess phenylmagnesium bromide in diethyl ether solution at room temperature, afforded 6 which was further converted into 7 on boiling in acetic acid. Furthermore 7 reacted with phenylmagnesium bromide to afford 8 which could be also obtained from the reaction of ethyl 2-phenyl-hydrazono-2-cyanoethanoate (9) with phenylmagnesium bromide.



### PART II

<u>Studies With 2-Arylhydrazononitriles: New Simple Approach for</u> <u>Synthesis of Polysubstituted 1-Arylpyrazole-4-amine and 2-Aryl-1,2,3-</u> <u>triazole-5-amines</u>

This part involve

1) Synthesis of polysubstituted 1-arylpyrazole-4-amine

a) The arylhydrazones **2a,b**, **4a-c**, **7** and **8** reacted easily with chloroacetonitrile in presence of triethylamine to afford the corresponding 4-aminopyrazole-5-carbonitriles **10a-g**.



b) It has been found that the arylhydrazones 2a,b reacts with chloroacetone
(11a) and with ethyl chloroacetate (11b) to afford the corresponding
4-aminopyrazole derivatives 12a-d.



c) The arylhydrazones **4a,b** afford the corresponding pyrrolo[3,2-*c*]pyrazole-3-carboxamide derivatives **13** when reacted with excess chloroacetonitrile.



d) The formed 4-aminopyrazole-5-carbonitriles **10a**, **f** could be used as precursors for pyrazolo[4,3-*d*]pyrimidine derivatives by reaction with acetic anhydride, benzoyl chloride and or phenyl isothiocyanate.



#### 2) Synthesis 2,4-disubstituted-1,2,3-triazol-5-amines

The arylhydrazones **2**, **4a**,**b** and **7** reacted with hydroxylamine hydrochloride in anhydrous DMF and in presence of anhydrous sodium acetate to afford the corresponding 2-aryl-1,2,3-triazol-5-amine derivatives **17a-e**.



The aminotriazole 17c condensed with DMFDMA to afford the triazolo[4,5-*d*]pyrimidin-4-one derivatives **18**.



## PART III

#### Synthesis and Reactivity of 2-Arylazo-3-phenylcinnamonitriles

This part involves

a) The utility of the arylhydrazone 8 in synthesis of the azadiene derivative
19 by refluxing 8 in acetic acid. The formed azadiene can be easily reduced by hydrazine hydrate to afford 20.



b) The utility of the phenylhydrazone 21, obtained by the reaction of the phenylhydrazone 9 with phenylmagnesium bromide in the synthesis of the azadiene derivative 22 and the cinnoline 23 *via* reflux in acetic acid. Also the photolysis of 22 by sunlight in toluene solution afforded the cinnoline 23 *via* a  $6\pi$  photochemical electrocyclization.



### PART IV

# Routes to Functionally 3-Substituted Indoles and pyrazolo[1,5-a]pyrimidine-3-carboxamides

a) Indole reacts with phenylacetic acid and p-nitrophenylacetic acid 24a, b in presence of acetic anhydride to yield the 3-acylindole derivatives 25a,b. compound 25b coupled readily with benzenediazonium chloride to furnish the corresponding hydrazones 26. While the phenylhydrazone 28 could be formed from 25a *via* intial conversion of the latter compound into the enamine 27 and subsequent coupling with the benzenediazonium chloride.





b) The cyanoacetylindole 1 condensed with DMFDMA to yield the enaminonitrile **29** which reacted with ethyl thioglycolate and with ethyl glycinate in ethanol / potassium carbonate solution to yield **30**. Moreover the cyanoacetylindole 1 undergoes condensation with the aromatic aldehydes to afford the corresponding arylidene **31**.



c) The cyanoacetamides **3a-c** condensed with DMFDMA to furnish the enaminonitriles **32a-c** which reacted with hydrazine hydrate to yield pyrazoles **33a-c**.



d) The pyrazole derivative 33b reacted with DMFDMA to give the pyrazolo[4,3-*d*]pyrimidine 34 whereas 33a provided the intermediate 35 rather than the corresponding pyrazolopyrmidine. The Reaction of 33a,b with the enamine 36 afforded 7-aminopyrazolo[1,5-*a*]pyrimidines 37. Compounds 33 also reacted with the enaminone 38 and with the enaminal 39 to yield the pyrazolo[1,5-*a*]pyrimidinecarboxamide 40 and 41, respectively.



- The structures of the prepared compounds were assigned on the basis of IR, proton, carbon-13 and mass spectra as well as their elemental analysis data. Mechanistic pathways were proposed whenever feasible to explain how the products were formed.
- Chapter 2 includes the discussion and the experimental details of the Candidate's work as well as the physical constants and spectral properties of the prepared compounds. The relevant references are compiled at the end of the thesis in chapter 3.