SYNTHESIS OF NOVEL NITRONE DERIVATIVES OF EDARAVONE

A Dissertation Submitted

By

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Registration No. 11400528

To

Department of Chemistry

In partial fulfillment of the requirement for the

Award of the Degree Of

M.Sc. Chemistry (Hons.)

Under The guidance of

Dr. Viraj H. Mankar

2017

CERTIFICATE

This is to certify that **Samala Sai** has completed the M.Sc. (Hons.) Dissertation-II titled **"Synthesis of Novel Nitrone derivatives of Edaravone"** under my supervision. To the best of my knowledge, the present work is the result of her original investigation and study. No part of this dissertation has ever been submitted for any other degree or diploma.

The dissertation is fit for the submission for the partial fulfillment of the condition for the award of degree of M. Sc (Hons.) in Chemistry.

Date: **Signature of Supervisor**

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DECLARATION

I hereby declare that the dissertation entitled, "**Synthesis of Novel Nitrone derivatives of Edaravone",** submitted for M. Sc (Hons.) Degree to Department of Chemistry, Lovely Professional University is entirely original work and all ideas and references have been duly acknowledged. The dissertation has not been formed the basis for the award of any other degree.

Date: **Samala Sai**

Reg.no. 11400528

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I would like to thank God for giving me the strength in making this research journey a successful.

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I would also like to thank all the faculty members of the Chemistry Department for their moral support.

Samala Sai

CONTENTS

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of death around the world. It contributes about 50% of global morality [1]. The death rate of the cardiovascular disease had been increased proportionally in India according to the reports of the World Health Organization as well as along with the World Bank. Cardiovascular disease (CVD) also includes the wide range of diseases such as the cerebrovascular disease, ischemic heart disease (IHD) and the myocardial infarction disease (MI). The various cardiovascular system components such as arteries and the myocardium are being affected by the cardiovascular diseases. Diseases including cancers, chronic obstructive pulmonary disease, CVD, and diabetes are generated due to change in the habits such as diet, physical activity and tobacco consumption [2].

Cardiovascular diseases arise due to the impaired flow of blood through the blood vessels and the arteries. The most common cause of the cardiovascular disease is the atherosclerosis. Atherosclerosis is a pathological process where structural changes take place in the intima and media of arterial vessels [3]. It was found that it happens mainly because of the inflammatory cell infiltration, cholesterol accumulation and along with the vascular smooth muscle cell migration. atherosclerosis involves the fatty acid deposits in the blood vessels.

Reactive oxygen species (ROS) damages the endothelium and thus causing the formation of the atheroma. Thus, now various degenerative diseases are caused or exacerbated by the reactive oxygen species [4]. Many animal and invitro studies have found that oxidative modification of the low-density lipoproteins in our body is the initial event in atherosclerosis. Oxidation undergoes in multiple steps and mediated by the free radicals [5].

Free radical is an atom or molecule with one or more unpaired electrons. In cells, most of the free radicals are damaged due to the reactive oxygen species (ROS).It includes hydroxide radical (-OH), singlet oxygen (O), molecular oxygen (O_2), hydrogen peroxide (H_2O_2) etc.

Free radicals are produced by the mitochondria, peroxisomes, arachidonate pathways, xanthine oxidase, phagocytosis, and ischemia/reperfusion injury in the biological system. Free radicals are also produced from the environmental pollutants, cigarette smoke, pesticides, and ozone [6].

Ischemia is a feature of both stroke and myocardial infarction and results in an inadequate Supply of blood and oxygen to the brain or heart [7] Acute Ischemic Stroke (AIS) affects

Approximately 80% of population than all other strokes, which seriously harming to human health. Ischemic stroke is an acute heterogeneous syndrome caused by several major and some uncommon disorders leading to an occlusion of blood vessels, which supplying blood oxygen to brain tissues [8].

After deprivation of oxygen, some neurons will die within minutes along with further immediate irreversible brain injury. This will lead to stop brain function, partially or completely. Free radicals are a valid target for therapeutic intervention for the treatment of AIS, because oxidative stress is a major component of the ischemic stroke cascade, which is activated after vascular occlusion [9].

The degenerative diseases are a result of uncontrolled free radical reactions. The Oxygen Free Radical (OFR) related mutagenesis causes cancer initiation and progression [10]. Almost all Cardiovascular diseases begin due to the cell damage caused by free radicals in biological Systems. Free-radical mechanisms have been implicated in the pathophysiology of several human diseases, including cancer, atherosclerosis, malaria, and rheumatoid arthritis along with neurodegenerative diseases [11].

LITERATURE REVIEW

Edaravone is initially created as a powerful free radical scavenger, and has been generally used to treat the ischemic stroke in Japan since 2001 [12]. Edaravone contains a potential cancer prevention agent action which incorporates upgrade of the prostacylin generation, inhibits the lipoxygenase digestion of arachidonic corrosive by trapping hydroxyl radicals, hindrance of the alloxan incited lipid peroxidation and extinguishing of the dynamic oxygen, which prompts the assurance of the different cells, for example, the endothelial cells against harm by ROS [13].

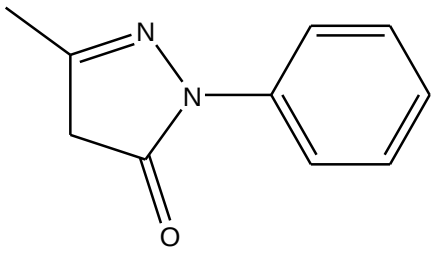


Fig. 1: Structure of Edaravone

As of late it has been demonstrated that edaravone enhances the endothelial capacity through abatement in ROS smokers. In this manner from a clinical viewpoint it is essential to choose a proper medication that is endothelial work over patients with cardiovascular infirmities.

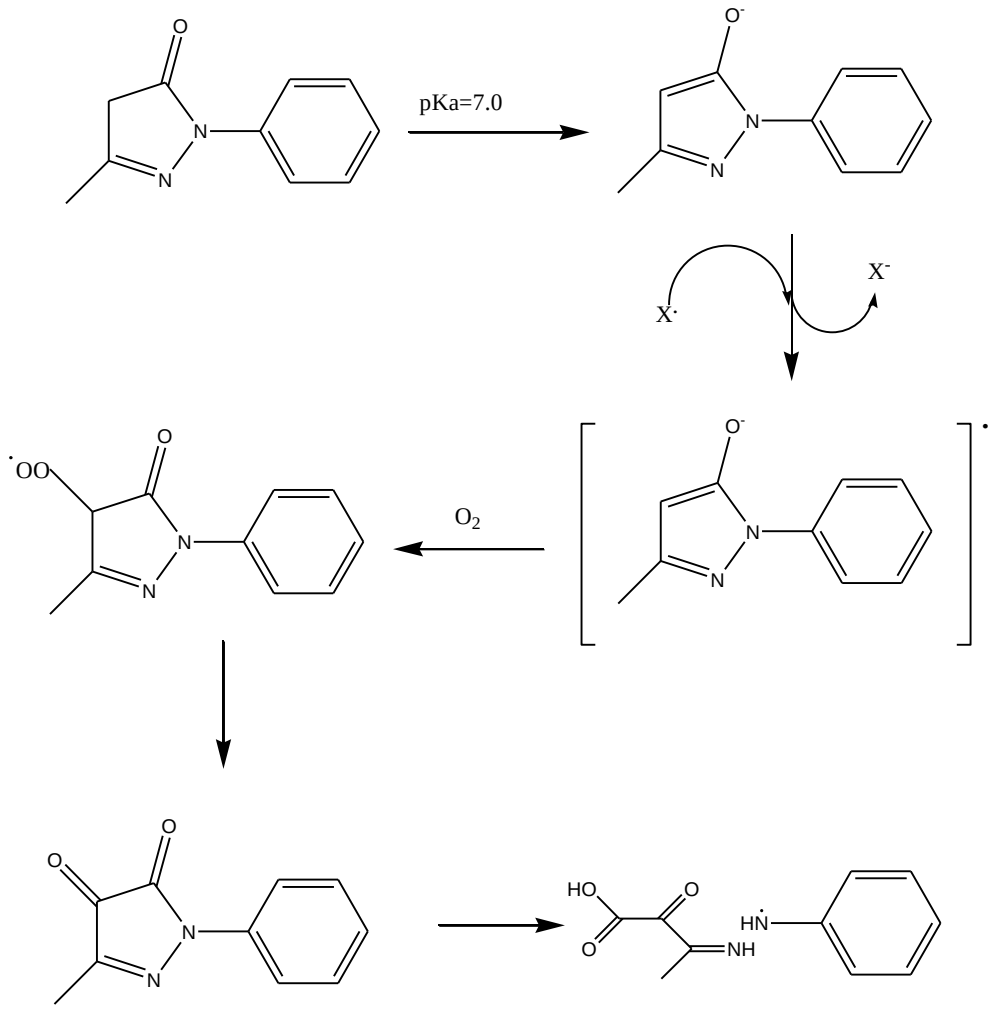
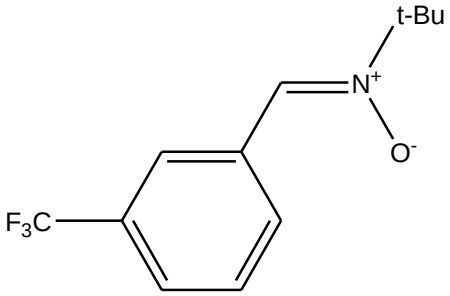
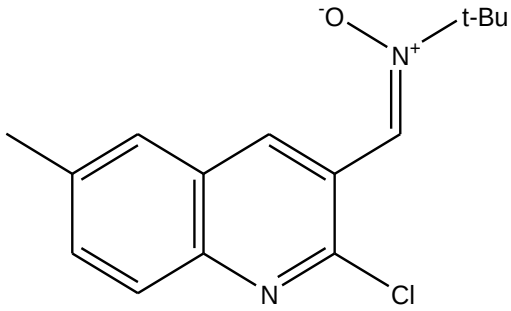


Fig. 2: Mechanism of antioxidant action of Edaravone

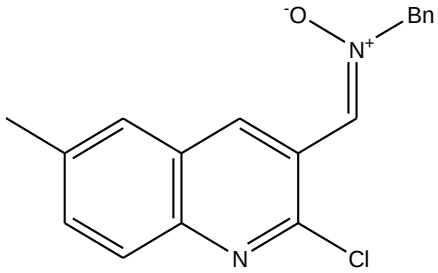
1. **(Z)-2-Methyl-N-(3-(trifluoromethyl)benzylidene)propan-2-amine oxide**



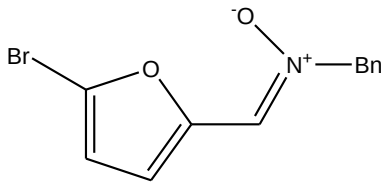
2. **(Z)-N-[(2-chloro-6-methylquinolin-3-yl)methylene]-2-methylpropan-2-amine oxide**



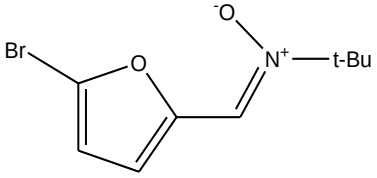
3. **(Z)-N-[(2-chloro-6-methylquinolin-3-yl)methylene]-1-phenylmethanamine oxide**



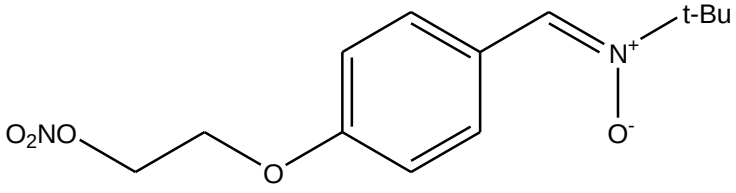
4. **(Z)-N-[(5-Bromofuran-2-yl)methylene]-1-phenylmethan-amine oxide**



5. **(Z)-N-[(5-Bromofuran-2-yl)methylene]-2-methylpropan-2-amine oxide**

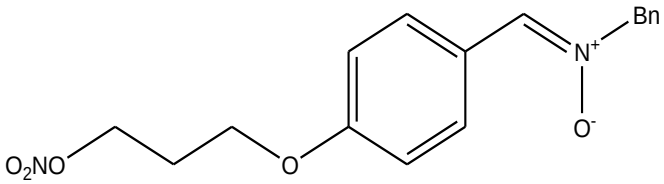


6. **(Z)-2-Methyl-N-(4-(2-(Nitrooxy)ethoxy)benzylidene)propan-2-amine oxide**

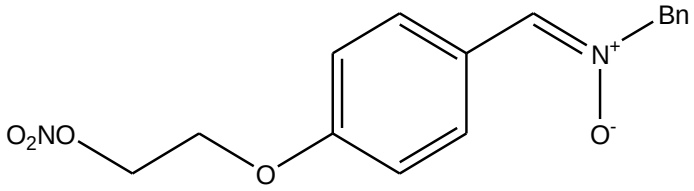


(Z)-α- aryl and heteroaryl – N – alkyl nitrones (1,2,3,4,5,6) have found to be potential agents for the treatment of the ischemia stroke. Cell viability related research have shown that these nitrones shown the good neuro protection. The nitrone (2) have shown that they can cross the blood brain barrier (BBB) using the parallel artificial membrane permeability assay (PAMPA).The quinoline nitrones (2,3) have shown the both neuroprotective and antioxidant properties for the treatment of the stroke [14] .

7. **(Z)-N-(4-(3-(Nitrooxy)propoxy)benzylidene)-1-phenylmethanamine oxide**



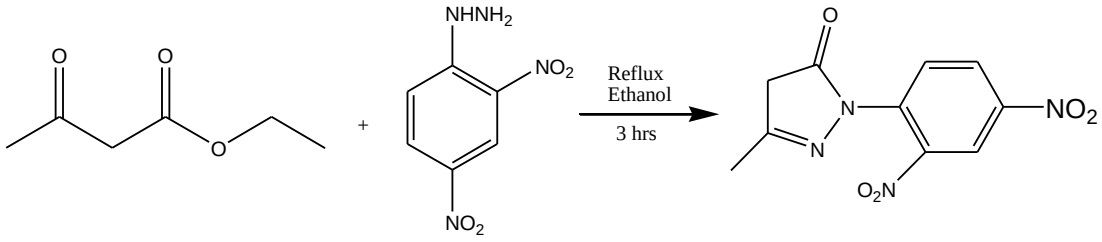
8. **(Z)-N-(4-(2-(Nitrooxy)ethoxy)benzylidene)-1-phenylmethanamine oxide**



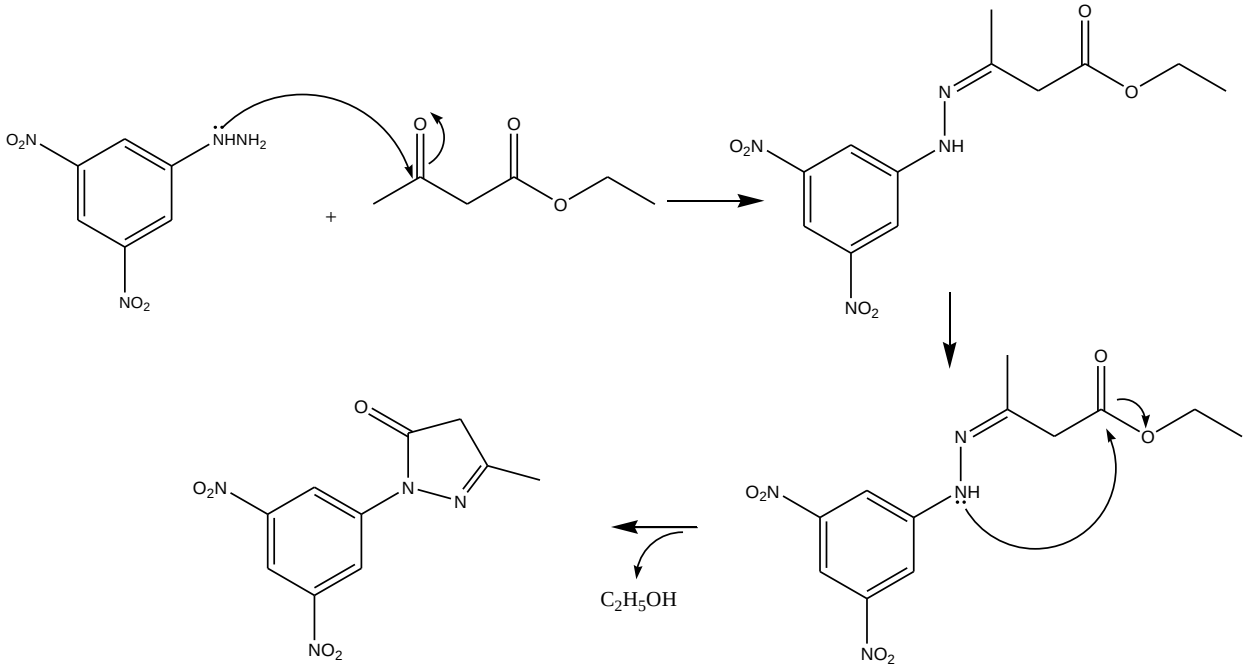
The nitrone (7,8) have shown that they can cross the blood brain barrier (BBB) using the parallel artificial membrane permeability assay (PAMPA) [14].

Experimental Work

SYNTHESIS OF 1-(2,4-DINITROPHENYL)-3-METHYL-1HPYRAZOL- 5-ONE



MECHANISM



EXPERIMENTAL PROCEDURE

Ethylacetoacetate (1.58ml) and 2,4-Dinitrophenylhydrazine (2.47g) was taken in a round bottom flask.Add 5ml of ethanol to the mixture. The reaction mixture was refluxed at 80^0C -90^0C for 3 hours.After the reaction is completed, the reaction was allowed to cool at the room temperature and transferred in to a beaker. Now the solid product was formed. The solid product was dissolved in minimum quantity of ethanol and heated over the water bath. The crystals formed are filtered. Now dry it we get the orange colored product.

Compound	**Molecular weight**	**Moles**	**Density**	**Gram quantity**	**Eqivalent**
Ethylacetoacetate	130.14	0.0125	1.02	1.62g=1.58ml	1
2,4-Dinitrophenylhydrazine	198.138	0.0125		2.47g	1
Ethanol				5ml	

YIELD

Theoretical yield= 3.41g

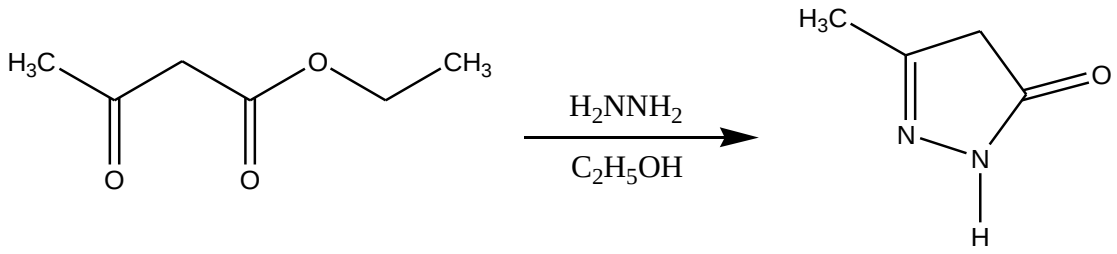
Practical yield=2.1g

Percentage yield=61.58%

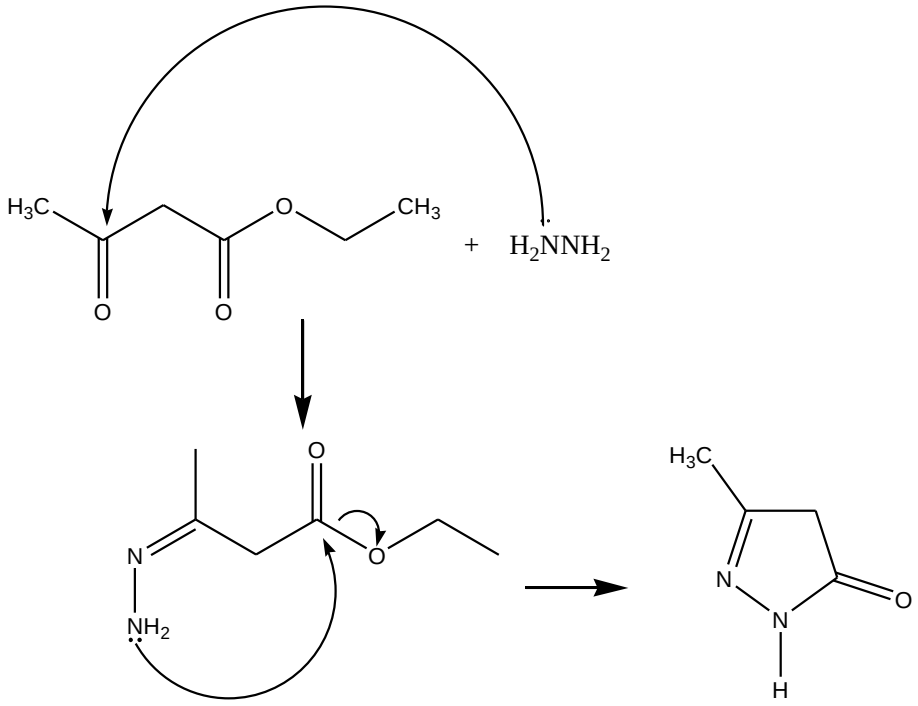
Melting point=81^0C

TLC Solventsystem: Ethyl Acetate: Hexane= 6:4

SYNTHESIS OF 3-METHYL-1H-PYRAZOL-5(4H)-ONE



MECHANISM



EXPERIMENTAL PROCEDURE

Firstly the apparatus was cleaned and dried. Take 3.9 ml Ethylacetoacetate and 1.82 ml of hydrazine hydrate in the round bottom flask. Now add 10 ml of ethanol in to the above mixture and also add 2 ml acetic acid to it. The reaction was refluxed around at 80^0C for 5 hours. After the reaction is completed, we get the solid product, wash it with ethyl acetate. Now we get the White coloured product.

Compound	Molecular Weight	Moles	Density (g/ml)	Gram Quantity	Equivalents
Ethylacetoacetate	130.14	0.0307	1.02	4g = 3.9ml	1
Hydrazine hydrate	50.6	0.03684	1.021	1.86g=1.821ml	1.2
Acetic acid				2ml	
Ethanol				10ml	

YIELD

Theoretical yield= 3.02g

Practical yield=1.34g

Percentage yield=44.37%

Compound	Molecular Weight	Moles	Density (g/ml)	Gram Quantity	Equivalents
Ethylacetoacetate	130.14	0.0614	1.02	8g = 7.8ml	1
Hydrazine hydrate	50.6	0.08596	1.021	4.34g=4.25ml	1.4
Acetic acid				3ml	
Ethanol				10ml	

YIELD

Theoretical yield= 6.024

Practical yield=3.43

Percentage yield=57%

CONCLUSION

Free radicals are an objective amid treatment of patients with cardiovascular sicknesses. Edaravone, the novel cancer prevention agent is utilized for its free radical rummaging activity in ischemic patients. Here we have orchestrated Edaravone subordinates utilizing diverse hydrazine's. Electron pulling back nitro gathering was joined into the Edaravone skeleton with an expect to upgrade its action. These subordinates may have potential cancer prevention agent and anticancer activity. The cell reinforcement movement can be checked by the Diphenyl Picryl Hydrazyl (DPPH) test. We couldn't dissect the natural action of these mixes because of time limitation and absence of required chemicals.

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