APPLICATION OF 1,3-DIPOLAR CYCLOADDITION REACTIONS IN THE SYNTHESIS OF ATORVASTATIN AND BILE ACID-BASED CYCLOADDITIONS OF C,N-DIARYLNITRONES

by

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Submitted
in fulfilment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

to the

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AUGUST, 2004

DEDICATED

TO

MY PARENTS

CERTIFICATE

This is to certify that the thesis entitled, "**Application of 1,3-dipolar cycloaddition reactions in the synthesis of atorvastatin and bile acid-based cycloadditions of C,N-diarylnitrones**", being submitted by Mr. T. Srinivasa Rao to the Indian Institute of Technology, Delhi, for the award of the degree of Doctor of Philosophy in Chemistry, is a record of bonafide research work carried out by him. Mr. T. Srinivasa Rao has worked under my supervision and guidance and has fulfilled all the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

The results embodied in this thesis have not been submitted, in part or in full to any other University or Institute for the award of any degree or diploma.

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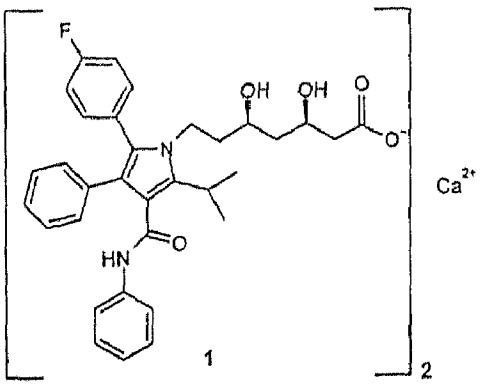
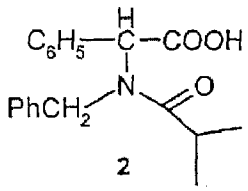
ABSTRACT

The 1,3-dipolar cycloaddition reaction is one of the most useful reactions for the synthesis of five-membered heterocyclic compounds. The versatile scope of these reactions comes from the wide array of dipoles, dipolarophiles and the stereo-conservative mechanism of the cycloaddition. The ease of generation of 1,3-dipoles, coupled with the often observed highly regio- and stereoselective nature of their cycloaddition reactions, has led to a number of syntheses which utilize such a reaction as the key step. High stereocontrol has in many cases also been obtained using chiral auxiliaries, where the chiral moiety could be recovered. The present thesis deals with studies on the regioselectivity of 1,3-dipolar cycloaddition reactions of mesoionic münchnones (1,3-oxazolium-5-olates) with different ester and amide functionalized acetylenic dipolarophiles in view of developing an efficient and economical route for the synthesis of atorvastatin 1. Atorvastatin (1, Lipitor®, Sortis®) is an HMG-CoA reductase inhibitor, which inhibits the action of HMG-CoA reductase and thereby decreases endogenous cholesterol synthesis, leading to a decrease in circulating low-density lipoprotein cholesterol, of great medicinal and commercial importance. Hence, there has been considerable interest in the recent past in the synthesis of atorvastatin 1.



The thesis has been divided into five chapters. **Chapter 1** describes a brief survey of the different types of 1,3-dipoles and the reactions of the selected 1,3-dipolar systems, nitrones, azomethine ylides and nitrile oxides, which have been widely used in organic synthesis in the recent past. It also deals with HMG-CoA reductase inhibitor atorvastatin **1** and its past synthesis. **Chapter 2** describes synthesis and utilization of secondary N-acylamino acids and N-aryl-2-phenyl-2-propynamides. Secondary N-acylamino acids have received considerable attention as they are frequently used as versatile synthetic intermediates in organic synthesis. To study the regioselectivity of 1,3-dipolar cycloaddition reactions of mesoionic münchnones (1,3-oxazolium-5-olates) in view of the efficient synthesis of pyrrole molecule, the key intermediate of atorvastatin **1**, we have synthesized secondary N-acylamino acids 2-[benzyl(isobutyryl)amino]-2-phenylacetic acid **2** and 2-[benzyl(4-fluorobenzoyl)amino]-3-methylbutanoic acid **3**.



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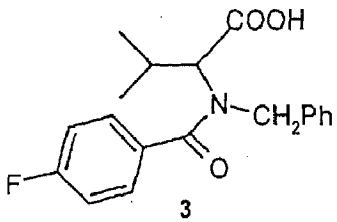

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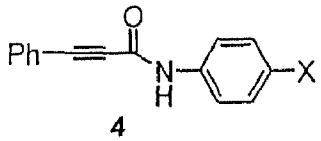

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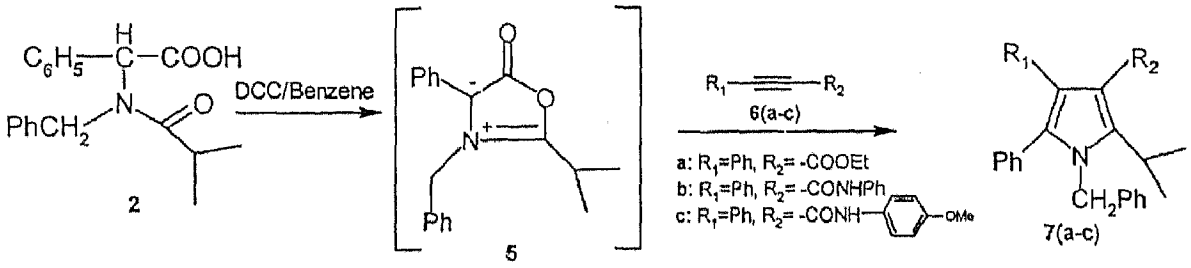
2-[Benzyl(isobutyryl)amino]-2-phenylacetic acid **2** was synthesized from mandelic acid, which is used in the regioselective studies of 1,3-dipolar cycloaddition reactions of mesoionic münchnone with acetylenic compounds. A highly efficient method has been developed for the synthesis of 2-[benzyl(4-fluorobenzoyl)amino]-3-methylbutanoic acid **3** from L-valine. N-Aryl-3-phenyl-2-propynamides **4** were synthesized from *trans*-cinnamic acid in good yields. These acetylenic amides are used in our studies, on regioselectivity of 1,3-dipolar cycloadditions of mesoionic münchnones.

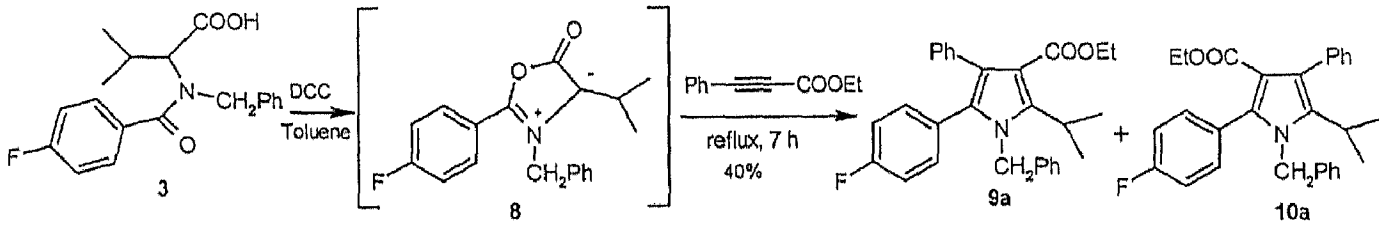
Chapter 3 describes regioselective studies of 1,3-dipolar cycloaddition reactions of mesoionic münchnones with acetylenic dipolarophiles leading to efficient synthesis of atorvastatin. 1,3-

Dipolar cycloaddition reactions of mesoionic münchnones (1,3-oxazolium-5-olates) derived from cyclodehydration of secondary N-acylamino acids with acetylenic dipolarophiles give rise to a mixture of pyrrole regioisomers. The product distribution of regioisomers is highly dependent on substituents of mesoionic münchnone and dipolarophile. Mesoionic münchnone 5 derived from 2-[benzyl(isobutyryl)amino]-2-phenylacetic acid **2** by using DCC in benzene on reaction with acetylenic dipolarophiles **6(a-c)** gave only one regioisomer of the pyrrole molecules **7(a-c)** (**Scheme 1**).



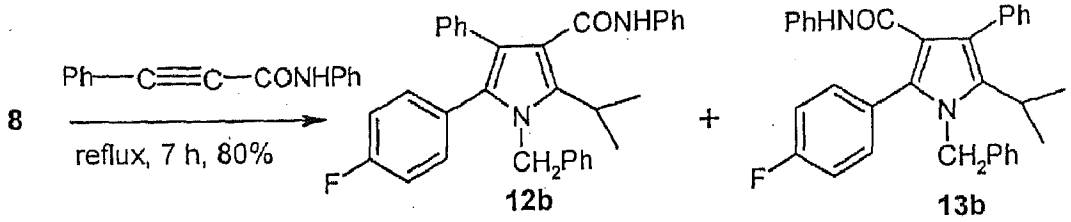
Scheme 1

Mesoionic münchnone **8** derived from 2-[benzyl(4-fluorobenzoyl)amino]-3-methylbutanoic acid **3** by using DCC in toluene, reacts with ethyl phenylpropiolate to give a mixture of two regioisomers **9a** and **10a** in 1:9 ratio (**Scheme 2**).



Scheme 2

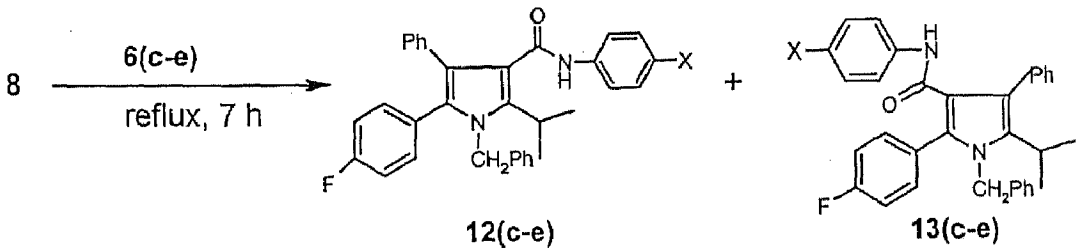
However, the reaction of **8** with N1,3-diphenyl-2-propynamide gave a mixture of pyrrole regioisomers **12b** and **13b** almost in 1:1 ratio (**Scheme 3**).



Scheme 3

Interestingly, the regioisomer **12b** which is the desired regioisomer in the synthesis of atorvastatin, is easily separated from **13b** on crystallization by using 1:1 mixture of benzene:hexane solvent system. The regiochemistry of this pyrrole molecule **12b** was further confirmed by single crystal X-ray crystallography.

1,3-Dipolar cycloaddition reactions of mesoionic münchnone 8 with other acetylenic amides 6(c-e) in toluene have also been carried out (**Scheme 4**). These reactions also gave two regioisomers **12** and **13** in 73-78% mixture yield.

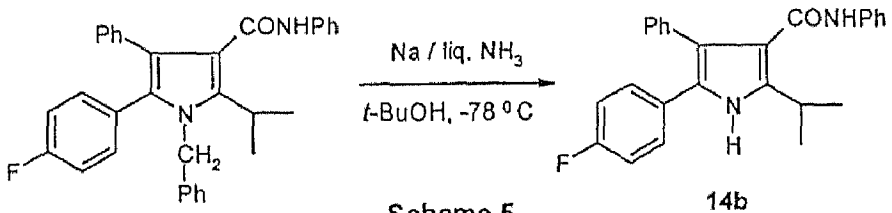


Scheme 4

In the above reactions also, the regioisomeric ratio was found from ^{1}H NMR spectroscopy. It is observed that the electron-donating nature of substituents at para position of phenyl ring on the amide nitrogen increases the formation of regioisomer **12**.

Chapter 4 describes the N-debenzylation of substituted pyrrole and indole molecules having ester, amide, halo and nitrile groups and synthesis of a key intermediate of atorvastatin. The protection of heterocycles such as pyrroles, imidazoles and indoles is an important topic due to the importance of nitrogen heterocycles in biological systems. Benzyl group is an important

protective group for the nitrogen containing compounds. We have carried out experiments to N-debenzylate the pyrrole molecule **12b** by many literature methods. But we did not succeed in those experiments except using of Na in liquid ammonia in the presence of *t*-BuOH at –78 ^{0}C. N-Benzyl pyrrole **12b** was debenzylated by using four equivalents of Na in liquid NH_3 in the presence of two equivalents of *t*-BuOH at –78 $^{\circ}$C for 10 minutes, to afford N-debenzylated pyrrole **14b** in 83% yield (**Scheme 5**).

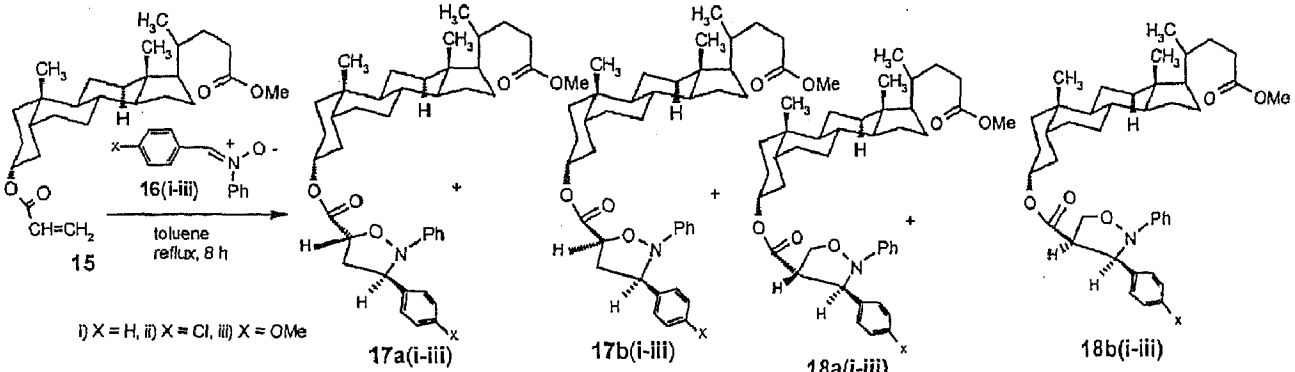


Scheme 5

N-Debenzylation of various substituted pyrroles and indoles having ester, amide and nitrile functional groups using Na in liq. NH_3 in the presence of *t*-BuOH at –78 $^{\circ}$C in 10 min afforded corresponding N-debenzylated molecules in good yields. Thus, the pyrrole molecule **14b**, which is an intermediate for atorvastatin synthesis was synthesized in an efficient and economical route by using 1,3-dipolar cycloaddition reaction of mesoionic münchnone (1,3-oxazolium-5-olate) with N1,3-diphenyl-2-propynamide and N-debenzylation using sodium in liquid ammonia in the presence of *t*-BuOH at –78 $^{\circ}$C as key steps.

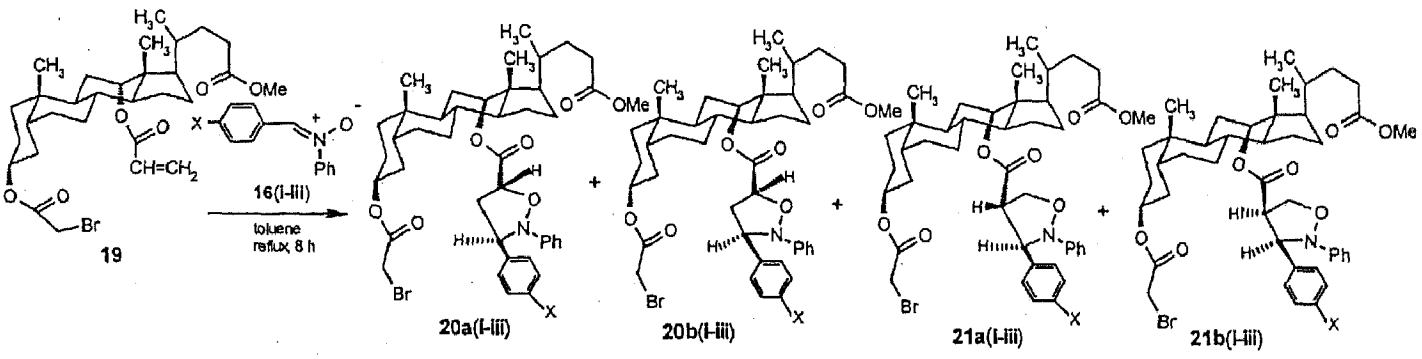
Chapter 5 describes the 1,3-dipolar cycloaddition reactions of C,N-diarylnitrones with bile acid-based chiral dipolarophiles. Bile acids are inexpensive and readily accessible chiral rigid backbones with hydrophilic and hydrophobic faces, having ease of selective functionalization of the hydroxyl groups. The bile acid-based chiral dipolarophiles **15** and **19** were synthesized from lithocholic acid and deoxycholic acid respectively. The 1,3-dipolar cycloaddition reactions of methyl 3α-acryloyl-lithocholate **15** with C,N-diarylnitrones **16(i-iii)** were carried out at reflux temperature of toluene for 8 h (**Scheme 6**). These reactions gave a diastereomeric mixture of 5-

substituted isoxazolidines **17a(i-iii)** and **17b(i-iii)** in 70-72% ratio. In these reactions, there is a reversal of diastereoselectivity giving 5-*trans*-diastereomers as the major products as compared to the reaction of C,N-diphenylnitrone with methyl acrylate where the 5-*cis*-isomer is the major product.



Scheme 6

1,3-Dipolar cycloaddition reactions at 12α-position of the bile acid by using methyl 3α-(2-bromoacetyl)-12α-acryloyl-deoxycholate **19** with C,N-diarylnitrones **16(i-iii)** in toluene at reflux temperature for 8 h showed a high degree of regioselectivity and gave a diastereomeric mixture of 5-substituted isoxazolidines **20a(i-iii)** and **20b(i-iii)** in 85-88% ratio (**Scheme 7**). These reactions also showed a reversal of diastereoselectivity giving 5-*trans*-diastereomers as the major products.



Scheme 7

In the preliminary study carried out on the diastereofacial selectivity of the cycloaddition between methyl 3α-acryloyl-lithocholate **15** with C,N-diphenylnitrone **16i**, the 5-*trans*-isomer **17ai** gave no diastereofacial selectivity, but in the 5-*cis*-isomer **17bi**, 86% *de* was obtained. However, in the case of cycloaddition between methyl 3α-(2-bromoacetyl)-12α-acryloyl-deoxycholate **19** with C,N-diphenylnitrone **16i**, the 5-*cis*-isomer **20bi** again gave a similar diastereofacial selectivity (83% *de*) but interestingly in 5-*trans*-isomer **20ai**, 100% *de* was obtained. Hence, bile acids can be considered as a potential chiral auxiliary for controlling the regio-, diastereo- and diastereofacial selectivity of 1,3-dipolar cycloadditions.

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