

ADVANCED SYNTHETIC APPLICATIONS OF SEMMLER-WOLFF REARRANGEMENT

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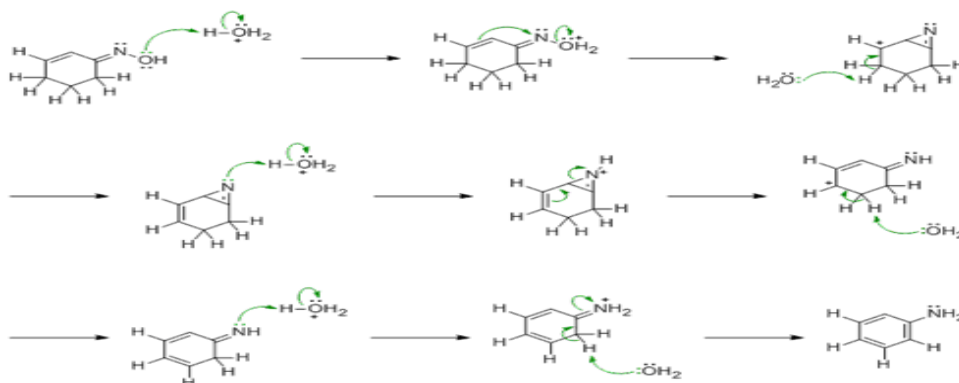
Abstract- The main objective of this research paper is to develop substituted anilines, o-phenylenediamine, amine substituted naphthalene, phenanthren, pyridine, indole, indazoles and quinalones and conversion of cyclohexenone oximes or α , β -unsaturated cyclohexenyl ketoxime to an aromatic amine in the presence of an acid by using semmler-wolff rearrangement. The substituted anisidines derivatives have been found to be useful as intermediates in the preparation of agents of hepatitis C viral (HCV) infections and advanced medicinal compound namely synthesis of AZD1981.

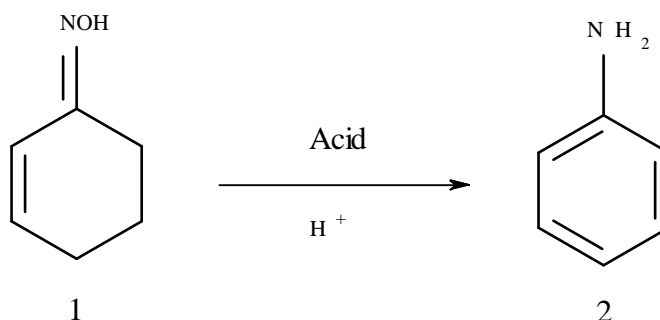
Index Terms- o-phenylenediamine, cyclohexenone oximes, aromatic amine, agents of hepatitis C viral

INTRODUCTION

Aniline derivatives are very significant synthetic intermediates for pharmaceutical and agrochemicals, and development of new methods for aniline synthesis is still important in organic synthesis, particularly in industrial disciplines because of their broad applicability. In general, substituted anilines have been synthesised by reduction of nitro arenes given through the nitration of aromatic rings. Although this method has been used most commonly, there emerge some problems when applied to selective organic synthesis: the regioselectivity of nitration substituted benzene is not so high, and the desired introduction of nitro group is sometimes deteriorated owing to the unwanted orientation dictated by the nature of ring substituent's. The Friedel-Craft acylation or alkylation of simple anilines, which, however, often suffers from disadvantage that Lewis acid catalysts are deactivated by their coordination to an amino group.

For the preparation of aromatic amines, in 1892 a Dtsch Scientist F.W. Semmler¹ investigated the conversion of cyclohexenone oximes or α , β -unsaturated cyclohexenyl ketoxime to an aromatic amine in the presence of an acid (Scheme 1). This transformation involved elimination of water followed by dehydrogenation of ring in the presence of acid to form the aromatized aniline (Fig-1).



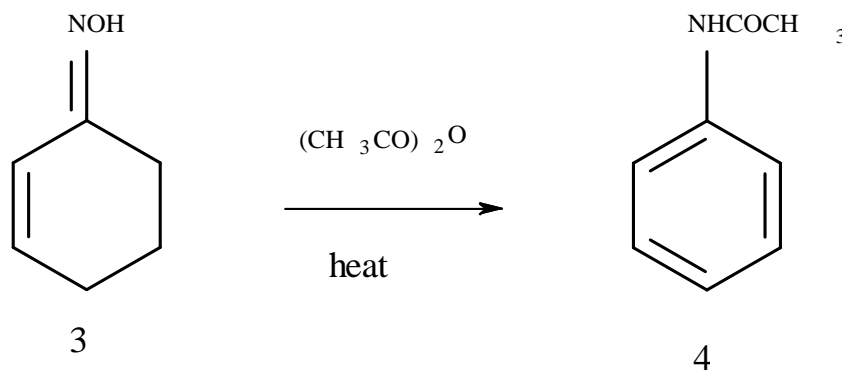


Scheme 1: Aromatization of cyclohexenone oxime

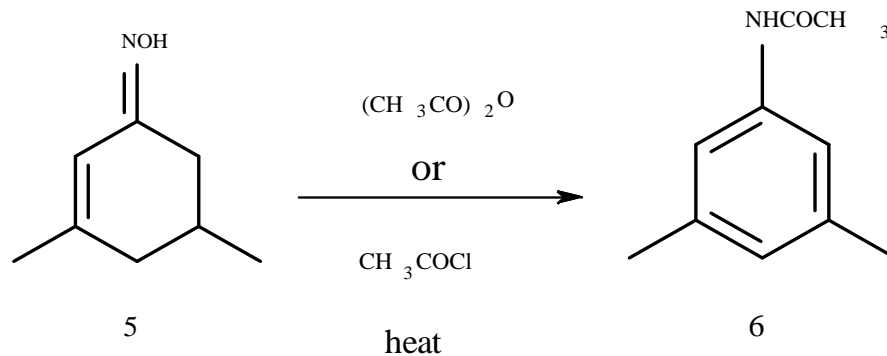
Fig-1: Mechanism of F.W Semmler rearrangement

Several years later, Wolff² conducted a more detailed investigation of Semmler reaction phenomenon. The oximes of certain cyclohexenones are converted to amines (in the form of the hydrochloride or aceto derivative) by heating with reagents as hydrochloride, acetic anhydride or acetyl chloride. The reaction conditions suggest dehydration, followed by rearrangement, but it is difficult to describe the intermediate. The normal dehydration of an oxime to a nitrile is denied by the preservation of the ring structure which includes the oxime carbon atom. The simplest such rearrangement is that of cyclohexenone oxime (3) (Scheme 2) and another is that of the oxime of 3, 5-dimethyl-cyclohexenone (5) converted to 6 (Scheme 3). This rearrangement is called as “Semmler-Wolff” aromatization or rearrangement. In literature, the synthetic utility of Semmler-Wolff aromatization is not explored in detail therefore some it’s applications in literature are presented below.

Scheme 2: Aromatization of cyclohexenone oxime



Scheme 3: Aromatization of 3, 5-dimethyl cyclohexenone oxime

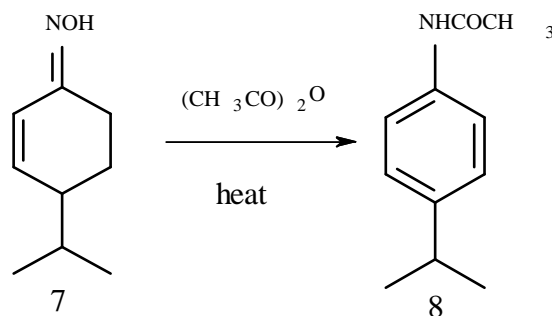


I. EXPERIMENTAL

This rearrangement or aromatization described by Semmler and later developed by Wolff is the aromatization of cyclohexenone oximes to equivalent anilines by a different type of acidic reagents. This application is used in synthesis of substituted anilines, o-phenylenediamine, amine substituted naphthalene, phenanthren, pyridine, indole, indazoles and quinalones explained in below sections.

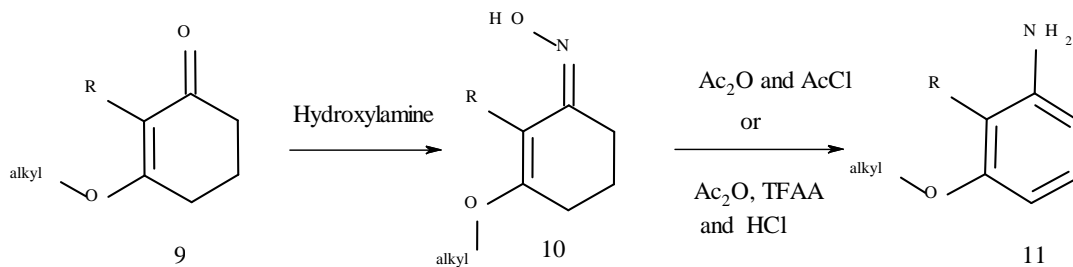
3.2.1 Aniline derivatives

In 1937, Macbeth converted the 4-isopropylcyclohex-2-en-1-one oxime to corresponding amine 8 (Scheme 4) by heating with acetic anhydride



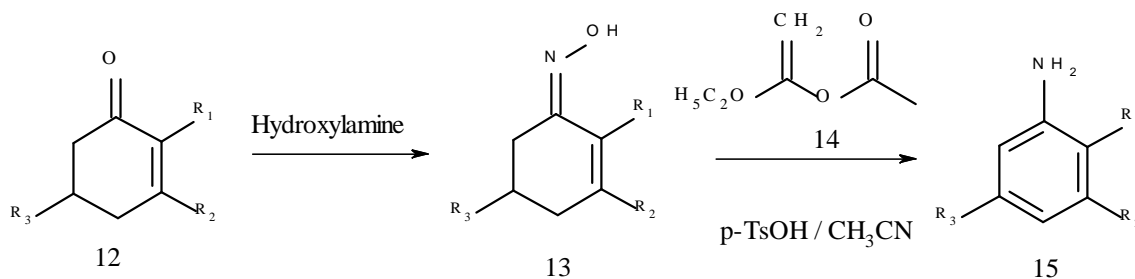
Scheme 4: Aromatization of 4-isopropylcyclohex-2-en-1-one oxime in the presence of Ac_2O , heat

In patent WO2007053755 in 2005, Inventor Fabrice Gallou³ disclosed a process for preparing substituted anisidines from cyclic alkyloxy-ketones 9 via aromatization using acetic anhydride followed by acetyl chloride or a mixture of acetic anhydride and trifluoroacetic anhydride followed by hydrogen bromide through a substituted oxime intermediate in which R is C1-C6 alkyl or halogen. The substituted anisidines derivatives have been found to be useful as intermediates in the preparation of agents of hepatitis C viral (HCV) infections.



Scheme-5: Preparation of substituted anisidine

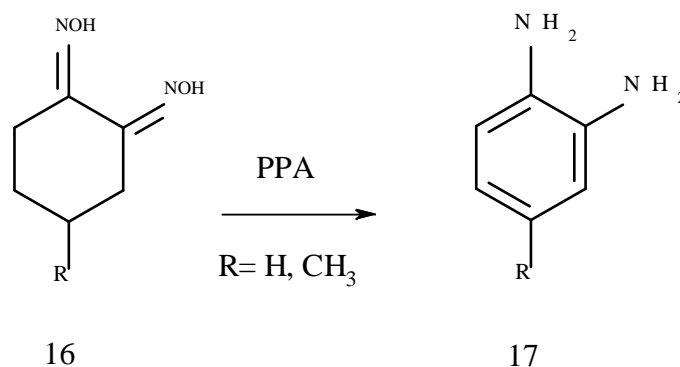
Yasumitsu Tamura⁴ in 1980 developed a mild and efficient method for Semmler-Wolff aromatization for synthesis of m-alkoxy, m-halogeno-, and m-thiocyanato-acetanilides from substituted cyclohexenone using catalytic amount of p-toluenesulfonic acid and an excess of ketene (Scheme-6).



Scheme-6: Preparing m-alkoxy, m-halogeno-, and m-thiocyanato-acetanilides

3.2.2 Phenylenederivaties

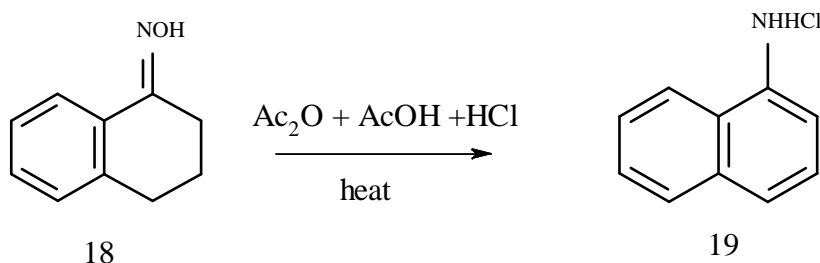
Y. Kobayashi and S. Wakamatsu⁵ reported the aromatization of cyclohexane-1,2-dione-dioxime and 4-methyl cyclohexane-1,2-dione-dioxime to corresponding o-phenylenediamine, 3,4-diamino toluene using PPA (Scheme-7) with 25-35%



yield. Scheme-7: Aromatization of cyclohexanedione dioximes

3.2.3 Naphthylamine derivatives

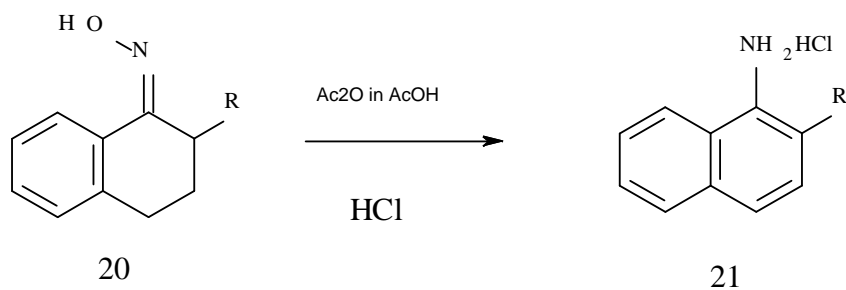
The Semmler-wolff reaction, applied this time to α -tetralone and substituted α -tetralone oximes, was investigated by Schroeter⁶ in 1930. A number of α -naphthylamines were obtained from this general reaction (Scheme 8).



Scheme 8: Aromatization of α -tetralone

This reaction was usually carried out in an acetic acid-acetic anhydride solution containing hydrogen chloride to get the product as naphthylamine hydrochloride (10). The explanation of the mechanism involved a "Lucken-molekul" as the intermediate. It was found that ortho-substitution led to a Beckmann rearrangement instead of to aromatization.

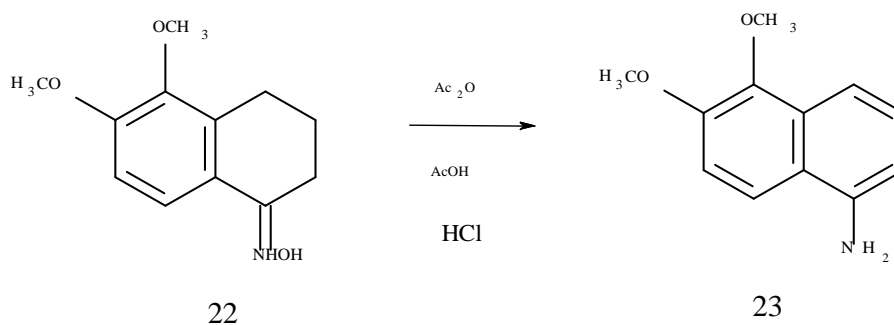
In 1962, Ludwig Auera and Richard Hewjts⁷ 2-(β -(2- and 4-Pyridyl)ethyl)-1-tetralone oximes converted to 2-[β -(2-pyridyl)ethyl]-1-naphthylamine dihydrochloride and to 2-[β -(4-pyridyl)ethyl]-1-naphthylamine using acetic acid and acetic anhydride passing dry hydrochloric gas into the reaction mass (Scheme 9).



R = 2-(β -(2-Pyridyl)ethyl) or 2-(β -(4-Pyridyl)ethyl)

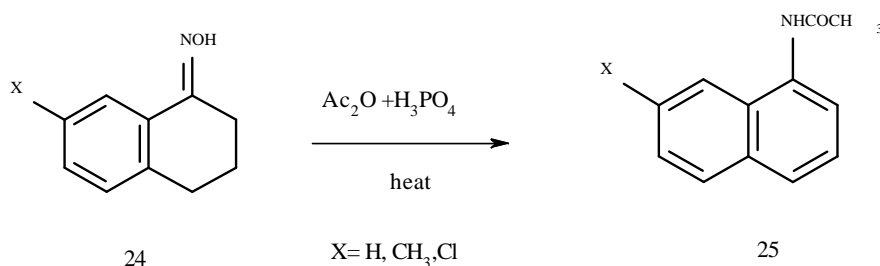
Scheme 9: Aromatization of β -substituted Pyridyl ethyl 1-tetralone

In 1966, William K. Sprenger⁸ et al reported the synthesis of 5,6-Dimethoxy-1-naphthylamine from 3,4-Dihydro-5,6-dimethoxy-1-(2H)-naphthalenone oxime using acetic anhydride and glacial acetic acid followed by passing dry HCl gas.



Scheme 10: Improved aromatization of 3,4-Dihydro-5,6-dimethoxy-1(2H)-naphthalenone

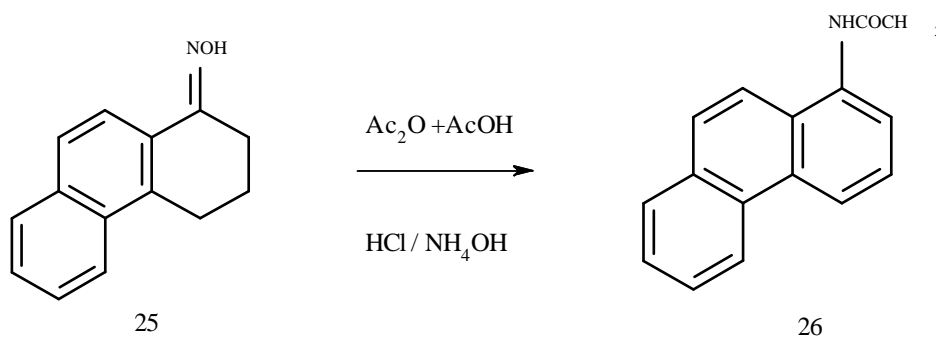
In 1973, Melwin S Newman and William M. Hung⁹ reported the improved aromatization of α -tetralone oximes to N-(1-Naphthyl) acetamides. The conversion of oximes of substituted cyclohexenones to aromatic amines has been carried out frequently by heating in acetic acid-acetic anhydride containing dissolved hydrogen chloride or hydrogen bromide. This reaction, originally discovered by Semmler, has been applied to methylated cyclohexenone α -tetralone and 1- and 4-lieo-1,2,3,4-tetrahydrophenanthrenes, although the yields rarely exceeded 50%. Because of the potential value of this type of intermolecular oxidation-reduction reaction for the synthesis of intermediates needed for the synthesis of polycyclic aromatic compounds, author developed an improved method for carrying out such reactions using acetic anhydride and anhydrous phosphoric acid at 80°C for the conversion of 7-methyl- α -tetralone, 7-chloro- α -tetralone and 4-keto-1,2,3,4-tetrahydrophenanthrene into the corresponding acetylamino compounds (Scheme-10) with above 80% yield.



Scheme 11: Improved aromatization of alpha-tetralone

3.2.4 Phenanthrene derivatives

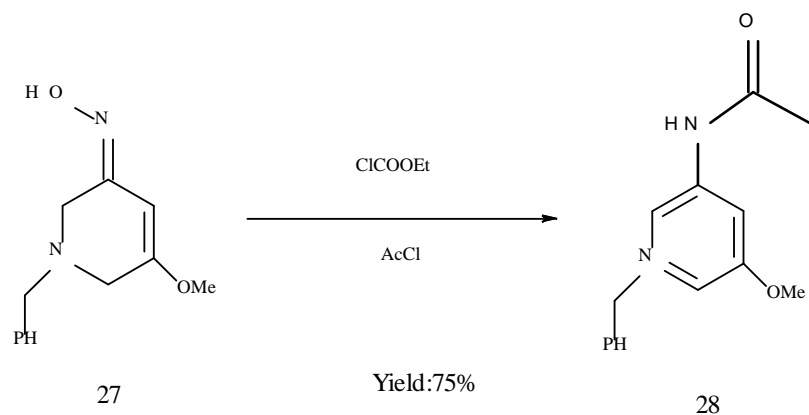
In 1992, Kenji Sasaki and Raymond Casatle¹⁰ aromatised 1-oxo-1,2,3,4-tetrahydrophenanthrene oxime to 1-aminophenanthrene using acetic anhydride, acetic acid. The acetylated compound was deprotected using hydrochloride and neutralised with ammonium chloride solution.



Scheme 12: Aromatization of 1-oxo-1,2,3,4-tetrahydrophenanthrene

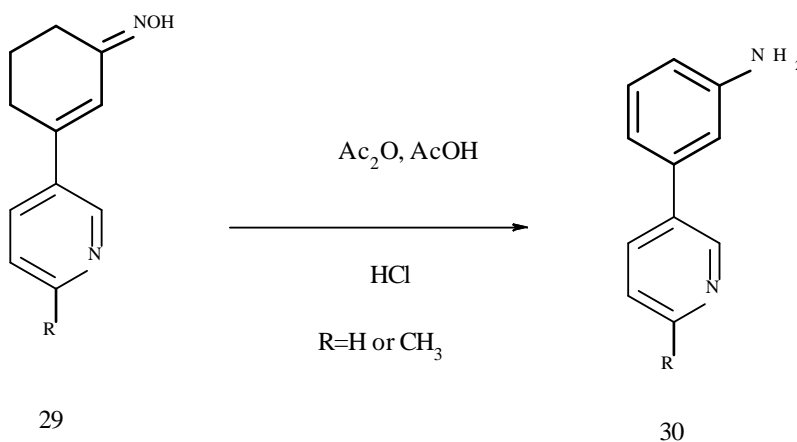
3.2.5 Pyridine derivatives

In 1981, Yasumitsu Tamura¹¹ et al developed novel and facile routes to 3-amino-5-hydroxypyridine derivatives through Semmler - Wolff aromatization of 1-benzyl-3-methoxy-5-oxo-3,4-dehydropiperidine oxime using ClCO_2Et -Pyridine and acetyl chloride.



Scheme 13: Aromatization of 1-benzyl-3-methoxy-5-oxo-3,4-dehydropiperidine oxime

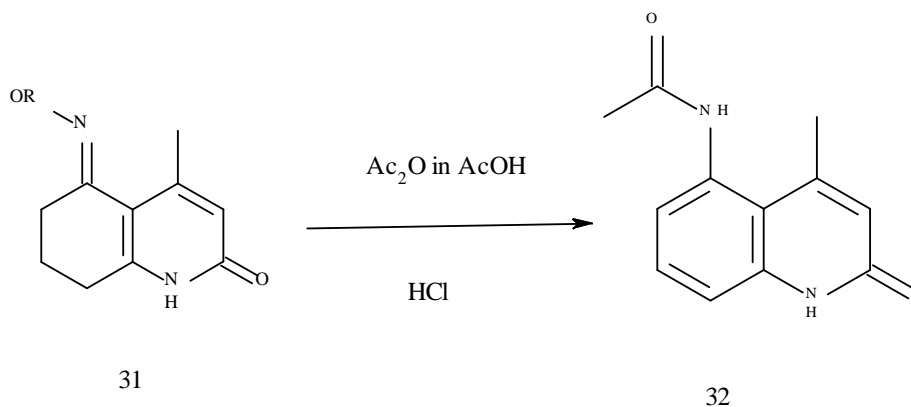
In 1984, Philip M Carbateas¹² et al developed a series of substituted 3- and 4-(3-aminophenyl) pyridines has been prepared as intermediates through Semmler Wolff rearrangement using acetic anhydride and acetic acid in the presence of hydrochloric acid for the synthesis of 1-alkyl-1,4-dihydro-4-oxo-7 pyridinyl-3-quinolinecarboxylic acids.



Scheme 14: Aromatization of 3-(2-alkyl-5-pyridinyl)-2-cyclohexene-1-one Oxime

3.2.6. Quinalone derivatives

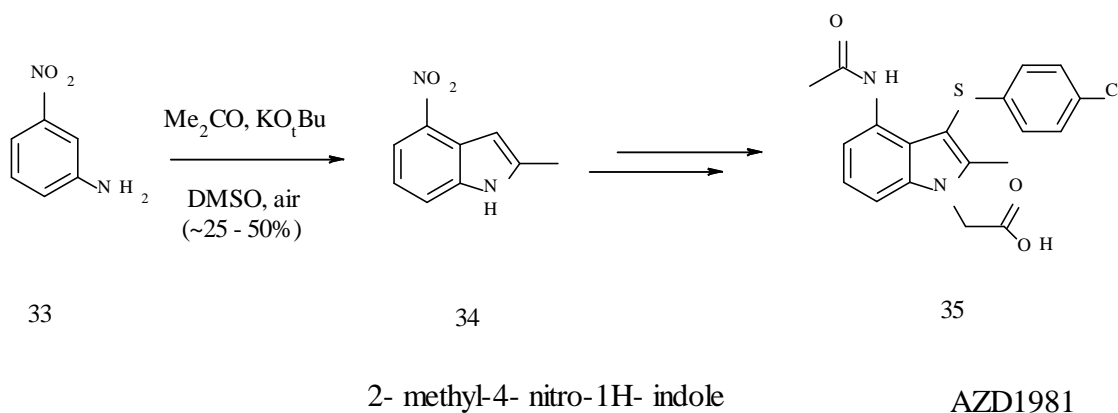
In 1980, Musta I. El-Sheikh and James M. Cook¹³ reported the conversion of 4-methyl-5,6,7,8-tetrahydro-5-(hydroxyimino)-2-hydroxyquinoline to 4-methyl-5-acetamido-2-quinolone with 53% yield under Semmler-Wolff



conditions. Scheme 15: Aromatization of 4-methyl-5,6,7,8-tetrahydro-5-(hydroxyimino)-2-hydroxyquinoline

3.2.7. Indole derivatives

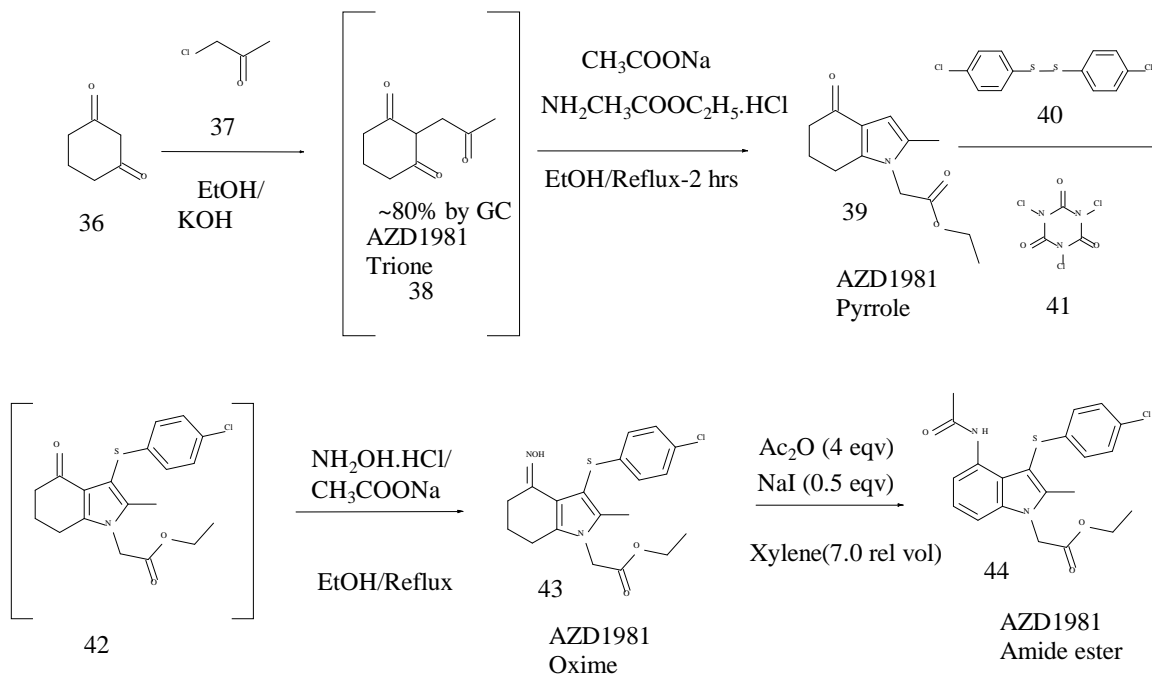
We developed a safe and efficient process for the synthesis of AZD1981, in which the indole-4 amide is formed by a Semmler-Wolff aromatization of a cyclohexenone oxime fused to pyrrole ring¹⁴. From the synthesis of AZD1981, the evolution of first generation route, which relied upon a sequential elaboration of 2-methyl-4-nitro-1H-indole, itself was prepared through Makoza reaction from 3-nitroaniline. Although this route proved robust and scalable in early development, we had concerns over the long-term economic viability of the route and certain aspect of process safety issues regarding specially the preparation and thermal stability of 2-methyl-4-nitro indole, which failed the koenen tube test. Moreover, Makoza chemistry for the synthesis of 2-methyl-4-nitro-1H-indole is carried out above the flash point of acetone in the presence of air which could be a potential safety issue. In addition to, there was inconsistency in the yield of 2-methyl-4-nitro-1H-indole (Scheme 16). So we developed



Scheme 16: Synthesis of AZD1981 from 2- methyl-4-nitro-1H-indole

alternative route through Semmler-Wolff aromatization, 1,3- cyclohexane dione 36 treated with chloro acetone in the presence of potassium hydroxide to form the trione 37, which is telescoped to next stage using ethyl glycine hydrochloride to form 38 . The 38

was thio etherified to form the 39, which is subjected to formation of Oxime 39. The Oxime 39 was subjected to Semmler-Wolff aromatization using acetic anhydride and sodium iodide good condition for aromatization.



Scheme 17: AZD1981 synthesis through 1,3- Cyclohexane dione

II. RESULT &DISCUSSION

In this research paper, a brief assessment on Semmler-Wolff rearrangement has been offered. It is used for synthesis of amine or its derivatives at specific positions in the presence of an acid condition. This rearrangement application is used for synthesis of aniline derivatives, o-phenylenediamine derivatives, α -naphthylamine derivatives, 1-amino phenanthrene derivatives, 3-amino-5-hydroxypyridine derivatives, 4-methyl-5-acetamido-2-quinolone derivatives and amino indoles derivatives.

In literature, a number of research groups have been reported application of Semmler-Wolff rearrangement. Previous applications to different types of molecules were discussed by providing schemes. Although reported routes would give the moderate to good yield, a number of challenges and some disadvantages still exist, such as tedious reaction conditions, usage of costly reagents/intermediates, poisonous reagents, explosive conditions.

CONCLUSION

we developed the safe and efficient process for synthesis of AZD1981 by using Semmler-Wolff rearrangement in this research paper. This rearrangement is more useful to design and synthesis of amino substituted indazoles and quinazoles,.

Acknowledgement

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