STUDIES IN THE SYNTHESIS OF FUROCOUMARINS

SUMMARY OF THE THESIS
SUBMITTED

by

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SUMMARY

CHAPTER I: Introduction

Coumarins are widely distributed in nature, either in the free state or in the combined state. These coumarins have attracted considerable interest due to their various physiological and biochemical properties. This chapter describes brief introduction about coumarin and its derivatives besides their occurrence, syntheses and properties.

CHAPTER II: Synthesis Of Furobenzopyrones By Claisen Rearrangement

Furocoumarins or furobenzo-α-pyrones form a class of compounds, of which only two i.e. furo(3,2-g)benzopyran-7H-one (linear form-psoralen) and furo(2,3-h)benzopyran-5H-one (angular form-angelicin) are found to occur in nature. Psoralens are found to possess remarkable skin photosensitizing activity causing phytophotodermatitis. Presently, psoralen, 5-methoxypsoralen (5-MOP), 8-methoxypsoralen (8-MOP) and 4,5′,8-trimethylpsoralen (TMP) are widely used in PUV-A (Psoralen UltraViolet-A) therapy for the treatment of dermatological disorders like psoriasis, vitiligo, atropic eczema and micosis fungoides in tumor stage. But these are reported to produce some unwarranted side effects, which are believed to be mainly due to the formation of diadducts with DNA. In order to minimize the side effects, furobenzopyrones containing an electron withdrawing group such as $-COOC_2H_5$, $-COCH_3$ and -CN at position 3 in the pyrone ring system have been synthesized, which are reported to produce monoadducts with DNA. Synthesis of furobenzopyrones reported in the literature involve multiple steps. In this chapter Claisen rearrangement is used as a key step to synthesize both angular as well as linear counterparts to study the chemistry and synthetic aspects of these compounds.

Claisen rearrangement of the following allyloxy derivatives were studied.

- ethyl-7-allyloxybenzopyran-2H-one-3-carboxylate
- ethyl-7-allyloxy-8-iodobenzopyran-2H-one-3-carboxylate

- 7-allyloxy-3-acetylbenzopyran-2H-one
- 7-allyloxy-8-iodo-3-acetylbenzopyran-2H-one
- ethyl-7-allyloxy-8-methylbenzopyran-2H-one-3-carboxylate
- 7-allyloxy-3-cyanobenzopyran-2H-one
- ethyl-2,4-diallyloxy-α-cyanocinnamate
- ethyl-2,4-diallyloxy-α-carboethoxycinnamate
- E, Z-ethyl-2,4-diallyloxy-α-acetylcinnamate

Synthesis of ethyl-2-methylfuro(2,3-h)benzopyran-5H-one-6-carboxylate was carried out from ethyl-7-hydroxybenzopyran-2H-one-3-carboxylate, which was obtained by Knoevenagel condensation, on allylation gave ethyl-7-allyloxybenzopyran-2H-one-3-carboxylate. Claisen rearrangement of this allyloxy derivative in refluxing DMA afforded a mixture of two products, alkali soluble and insoluble, which were separated and identified as ethyl-7-hydroxy-8-allylbenzopyran-2H-one-3-carboxylate and ethyl-2-methyl-2,3-dihydrofuro(2,3-h) benzopyran-5H-one-6-carboxylate respectively. The above dihydrofuro derivative when treated with NBS in the presence of benzoyl peroxide using CCl_4 as solvent under 200W tungsten lamp resulted in a mixture of two products, which were identified as ethyl-2-methylfuro(2,3-h) benzopyran-5H-one-6-carboxylate and ethyl-2-bromomethylfuro(2,3-h) benzopyran-5H-one-6-carboxylate.

Similarly Claisen rearrangements of ethyl-7-allyloxy-8-iodobenzopyran-2H-one-3-carboxylate, 7-allyloxy-3-acetylbenzopyran-2H-one, 7-allyloxy-3-acetyl-8-iodobenzopyran-2H-one, ethyl-7-allyloxy-8-methylbenzopyran-2H-one-3-carboxylate, 7-allyloxy-3-cyanobenzopyran-2H-one were carried out in boiling DMA to obtain the corresponding furobenzopyrones.

A facile synthesis of 9-allyl-6-cyano-2-methyl-2,3-dihydrofuro(2,3-h) benzopyran-5H-one was achieved by condensing a mixture of mono- and di-allyloxybenzaldehyde in dry pyridine with ethylcyanoacetate using piperidine as a base, produced a mixture of ethyl-2,4-diallyloxy-α-cyanocinnamate and 7-allyloxy-3-cyanobenzopyran-2H-one. Ethyl-2,4-diallyloxy-α-cyanocinna-

mate when subjected to Claisen rearrangement, afforded 9-allyl-6-cyano-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one. The formation of this product can be explained involving two simultaneous transformations during Claisen rearrangement: In the first step ortho migration of both the allyl groups from C-2 to C-3 and C-4 to C-5 take place, which is followed in the second step by the formation of pyrone ring, eliminating ethanol molecule and angular dihydrofuran ring due to regiospecificity. The above compound was then attempted for dehydrogenation with Pd/C (10%) in DPE resulting in the formation of an isomeric product 9-(1′-propenyl)-6-cyano-2-methyl-2,3-dihydrofuro(2,3-h) benzopyran-5H-one.

Similarly Claisen rearrangements of ethyl-2,4-diallyloxy-α-carboethoxy cinnamate and mixture of E and Z-2,4-diallyloxy-α-acetylcinnamate were studied to afford ethyl-9-allyl-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate and 9-allyl-6-acetyl-2-methyl-2,3-dihydrofuro(2,3-h) benzopyran-5H-one respectively. Ethyl-9-allyl-2-methyl-2,3-dihydrofuro (2,3-h)benzopyran-5H-one-6-carboxylate was refluxed in DPE containing Pd/C (10%) resulted in the formation of ethyl-9-(1′-propenyl)-2-methyl-2,3-dihydro furo(2,3-h)benzopyran-5H-one-6-carboxylate.

CHAPTER III:

Section 1: Synthesis Of Furobenzopyrones By Wittig Reaction

In the earlier chapter it was attempted to synthesize both angular and linear furobenzopyrones by Claisen rearrangement in refluxing DMA. The results were promising in the synthesis of angular counterparts but were not good in the case of linear furobenzopyrones. In this chapter Wittig method was planned to synthesize linear furobenzopyrones as Claisen rearrangement failed to give the linear product due to the presence of electron withdrawing substituent at position 3. Here Wittig method has been used to synthesize both angular as well as linear furobenzopyrones in good yields.

Ethyl-2-methylfuro(3,2-g)benzopyran-7H-one-6-carboxylate was prepared by condensing 2,4-dihydroxy-5-methylbenzaldehyde with diethylmalonate in the presence of pyridine and piperidine to give ethyl-7-hydroxy-6-methylbenzopyran-2H-one-3-carboxylate followed by acetylation and subsequent reaction with NBS in CCl_4 using benzoyl peroxide produced ethyl-7-acetoxy-6-bromomethylbenzopyran-2H-one-3-carboxylate. This bromomethyl derivative when reacted with triphenylphosphine in dry benzene gave its corresponding phosphonium salt, which on refluxing in dry toluene and triethylamine under inert atmosphere yielded ethyl-2-methylfuro(3,2-g) benzopyran-7H-one-6-carboxylate.

Similarly ethyl-2-methylfuro(2,3-h)benzopyran-5H-one-6-carboxylate, 2-methyl-6-acetylfuro(3,2-g)benzopyran-7H-one, 2-methyl-6-acetylfuro(2,3-h) benzopyran-5H-one were synthesized by taking appropriate starting compounds and then subjected to Wittig reaction.

Section 2: Synthesis Of Furobenzopyrones By Oxypalladation

This section mainly deals with the synthesis of furobenzopyrones using Wacker's oxypalladation technique. Two different approaches were followed: [1] $PdCl_2$ in combination with CuCl in the oxygen atmosphere as used in the Wacker method and [2] $PdCl_2$ with benzoquinone.

The main endeavor of this work is to study the Wacker oxidation on different benzopyrones.

CHAPTER IV:

This chapter comprises of three sections, each dealing with different syntheses of furobenzopyrones.

Section 1: Synthesis Of Aminomethylfurobenzopyrones

In this section the methyl group of the furobenzopyrone derivative is transformed in to an aminomethyl derivative to enhance its hydrophilic

character. As a result, the penetration of the compound in to skin during topical application improves and efficiency of the therapy will be increased.

2-Piperidinomethylfuro(3,2-g)benzopyran-7H-one was prepared by allylating the 7-hydroxy-8-iodobenzopyran-2H-one followed by Claisen rearrangement in DMA, bromination and dehydrohalogenation with alcoholic KOH resulted in the formation of 2-methylfuro(3,2-g)benzopyran-7H-one, which on bromination with N-bromosuccinimide in CCl_4 using benzoyl peroxide as initiator gave a 2-bromomethyl derivative. It was then condensed with piperidine in boiling DMF gave on work up 2-piperidinomethyl derivative.

In a similar way 2-bromomethyl derivative was condensed with morpholine, N-phenylpiperazine, diethylamine and diethanolamine to obtain corresponding aminomethyl derivatives. Angular aminomethyl derivatives were also prepared by condensing 2-bromomethylfuro(2,3-h)benzopyran-5H-one with piperidine, morpholine, N-phenylpiperazine, diethylamine and diethanolamine in a similar way in refluxing DMF.

Section 2: Synthesis Of Schiff Bases

It was observed that the presence of azomethine (-CH=N) linkage in the Schiff bases is responsible for exhibiting or enhancing the antibacterial activity and also found that Schiff bases derived from 3-aminocoumarin possess antibacterial, antifungal and anthelmintic activity. Hence in order to have potent antibacterial agent, efforts have been made to prepare Schiff bases using furobenzopyrone system.

Synthesis of 3-phenyl-6-(4′-nitrophenyliminomethyl)furo(3,2-g) benzopyran-7H-one was carried out by condensing 3-phenyl-6-aminofuro (3,2-g)benzopyran-7H-one, which was obtained by condensing 2,4-dihydroxy benzaldehyde with acetylglycine followed by phenacylation, cyclization with alcoholic KOH and subsequent hydrolysis with H_2SO_4 to convert in to amino group, with p-nitrobenzaldehyde in dry benzene using piperidine as catalyst.

Similar condensations with other aldehydes such as p-vanillin, 2,4-dihydroxybenzaldehyde, 3,4-dichlorobenzaldehyde and p-methylbenzaldehyde were carried out to synthesize the Schiff bases, whereas Nitrogen mustard was prepared with p-[N,N-bis(2-chloroethyl)aminobenzaldehyde under the same reaction conditions.

Section 3: Synthesis Of Benzaldazines

Opening of pyrone ring is a well-known phenomena in the base catalyzed reactions. A number of reports shows that benzopyran-2H-one containing an electron withdrawing group at position 3 are good acceptors in Michael reaction. In this effort a novel cleavage in the pyrone ring is observed when such base catalyzed Michael type reaction was attempted with hydrazine, affording exclusively benzaldazine derivatives.

2,2′-Dihydroxy-4,4′-dimethyl-3,4,3′,4′-tetrahydrodifuro(2,3-f) benzaldazine was prepared from ethyl-2-methyl-2,3-dihydrofuro(2,3-h) benzopyran-5H-one-6-carboxylate (8) with hydrazine in refluxing ethanol. Its structure was confirmed by IR, PMR and mass spectral data. Similarly, reactions of ethyl-7-allyloxybenzopyran-2H-one-3-carboxylate, 7-allyloxy-3-cyanobenzopyran-2H-one, ethylbenzopyran-2H-one-3-carboxylate and 3-acetyl benzopyran-2H-one with hydrazine were carried out in order to understand not only the formation of such products but also to confirm with other electron withdrawing groups such as -$COCH_3$, -CN.